Medical Writing

Post-Approval Regulatory Writing

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Contents

Themes of upcoming issues of *Medical Writing*

March 2015: The theme will be '**Readability & plain language**'. Topics will include plain language, general fundamentals of good medical writing, how to target your audience, editing for clarity, and readability of patient materials, websites, regulatory documents, and more. *The deadline for this issue was 2 November 2014.*

June 2015: The theme will be '**Risk management**'. The issue will include articles on risk management strategies, writing risk management plans, and risk–benefit analysis. *The deadline for feature articles is 3 February 2015.*

September 2015: The theme will be '**Writing for lay audiences**'. The issue will include articles on writing for patients, medical journalism, and other forms of medical writing for the general public. *The deadline for feature articles is 2 May 2015.*

If you would like to submit an article, have ideas for issue themes or articles, or would like to discuss any other issues, please write to **editor@emwa.org**.

Post-approval regulatory writing

Lisa Chamberlain-James

Guest Editor

Editorial

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Very often in clinical development, we are focused solely on gaining marketing authorisation for our drugs – the scramble to be first to market, or to bring the next 'blockbuster' to patients. Phase I to Phase III is our primary goal. And to a large extent, this is how it should be – there's no point in spending millions on research and development if the drug is never given to patients.

However, what happens afterwards? As medical writers, does our job finish once we've written up the clinical study reports and dossiers, answered the regulatory authorities' questions, and helped a company gain approval? I'd like to think not – I'd argue that medical writers are needed just as much to keep a drug on the market as they are to get it there in the first place.

I'm not immune to the pull of a sexy CTD of course, and I find it almost impossible to refuse when a client calls for help with 'a new type of…' or 'the only treatment for…'. But is the rush to the altar of marketing approval where we should be putting ALL of our focus and energy? Isn't that like putting all of our effort into the birthing of a marketing authorisation and none into keeping the resulting infant drug alive?

Post-approval documentation has always 'been there' of course, but was perhaps seen as a necessary evil – a drain on resources with no return on investment. However, in the last few years it has undergone something of a renaissance; driven by the 2012 change in PV legislation and, I believe, the increasing thirst and demand for high quality information from patients, lobbyists, and support groups. The pharmaceutical industry has embraced these changes and is rising admirably to the challenge, but not without teething problems, and this is where the skills of a medical writer can really come to the fore.

This issue of *Medical Writing* is dedicated to post-authorisation documents and the medical writer's role in them. The first of our feature articles is from **Dakshayini Kulkarni** and discusses the pharmacovigilance system master file (PSMF). Her article gives a practical guide to handling and improving this constantly evolving document, based on findings from PSMF inspectors.

Sunil Modali explains the differences between and potential difficulties in writing pre- and post-authorisation documents; something that writers more used to pre-authorisation documents may not have considered. **Sarah Richardson** outlines the role of the strategic medical writer in post-authorisation documents and gives an outline of the legislation. The intricacies of writing non-interventional post-authorisation safety studies are described beautifully by **Greg Morely**, and finally, **Amy Whereat** looks at advisory boards specifically, and the issues and potential pitfalls in writing reports for them.

I thank all of the contributors for their willingness to share their knowledge and experience in this area, and for the hard work they have put into their articles. My thanks also to **Phillip Leventhal** for bravely dedicating a whole issue to this topic and for trusting me with his 'baby'. Finally – thanks to all of you, for reading this issue. Please do send me your feedback, and let me know if these articles have helped any of your 'infant drugs' survive!

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President's Message

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Dear medical writers

I can't believe that we are now at the end of 2014 – the ideal time to look back upon the achievements of the past year and opportunities for 2015. One of the greatest landmarks was the launch of the revamped EMWA website in March. With a new look and intuitive navigation, we now have a website to be proud of without double-login. Diarmuid De Faoite and Kieran Zealand, thank you for your remarkable efforts.

In May, we went to an unseasonal Budapest (oh for the sunshine we had in 2004 on our previous visit!). The conference was exceptionally well-supported and the number of delegates was the highest for a non-UK-based location. The EMWA Professional Development Committee, headed up by Jo Whelan and her successor, Barbara Grossman, delivered a comprehensive programme which ranged, as usual, from 'over-subscribed' to 'well attended'. We were treated to a full-day symposium on 'Transparency of clinical data – where does medical writing fit in?'. The educational value of the day has been prolonged by the publication of a post-meeting supplement, which includes papers from each of the speakers. Thank you to Kathy Thomas and Alistair Reeves for their immense efforts in bringing this initiative to fruition. Also, Sam Hamilton (Vice President) and Art Gertel (EMWA fellow) set up the EMWA Budapest Working Group, a collaboration of medical writers, professional associations, regulators, and industry experts, with the remit of reviewing the ICH E3 and E6 guidelines over the next 2 years.

Florence was the venue for our Autumn 2014 conference. Amazingly, 28 workshops were delivered over four sessions from Thursday until Saturday. Our past president, Andrea Rossi, welcomed EMWA to his stunning home town and Professor Fusco described *What scientific societies need from medical writers in the Mediterranean region*. In addition to Helen Baldwin's *Introduction to medical writing and the freelance business forum*, Sam and Art presented an update of the progress of the Budapest Working Group. The social programme encouraged us to explore the local sights and flavours. The continued success of our conferences is due to the hard work of many committee members, workshop leaders, and volunteers, as well as the Conference Directors (Alistair Reeves and Slavka Baronikova), Candi Bond Gunning, and the whole of the Head Office.

This is the fourth issue of *Medical Writing* in 2014. Phil Leventhal, his co-editors, and all contributors work ceaselessly to deliver our bespoke journal, with its unique and wide-ranging content. Previous issues in 2014 have presented journal software for medical writers, introduced the basics of regulatory writing, and have explored non-clinical health writing. The possibilities for writing on cosmetics, chemical products, and veterinary medicine indeed broaden the horizons for writers looking for new applications and challenges.

In between the conferences, the first EMWA webinars were delivered by Laura Collada Ali and her colleagues in the PR team; this initiative will be developed and expanded over the coming years. Executive Committee members attended careers events for post-graduate students, organised by Pharma Network and represented EMWA at meetings of related societies. In addition to the visible achievements, Sarah Choudhary as Honorary Secretary and James Visjani as Treasurer, with the capable support of Lynne Fletcher and the team at Kingston Smith, have maintained the constitution and finances of EMWA throughout the year.

In 2015, we will be visiting Dublin in May and The Hague in November. The Spring conference will see the launch of the EMWA expert sessions, complimentary groups which will offer experienced members the opportunity to learn about new areas and applications as well as sharing their experiences. Further progress with e-learning is anticipated and the new 3-year EMWA strategy will be in place. It certainly will be another busy year.

Finally, I would like to thank Head Office, our committees, volunteers, and our membership for all the success and achievements in 2014. I would like to wish you all Seasons' Greetings and look forward to seeing many of you in 2015.

Best wishes,
Julia Donnelly

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Responding to concerns over the PSMF: Inspectors offer key insights

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Abstract

The pharmacovigilance system master file (PSMF) is a detailed description of the pharmacovigilance system used by the marketing authorisation holder for their authorised medicinal products. The PSMF is intended to be a live, custom-made document that accurately reflects the pharmacovigilance system put in place for a given product. It is expected to contain meticulous detail so that the marketing authorisation holder's compliance with current good pharmacovigilance practices guidelines can be assessed. This article focuses on the feedback provided by the inspectors during their assessment of the PMSF with an emphasis on areas for improvement.

Keywords: PSMF, Inspection findings, Metrics

In July 2012, the Pharmacovigilance System Master File (PSMF) became a requirement for companies filing new marketing authorisation applications. The PSMF is a detailed description of the pharmacovigilance system used by the Marketing Authorisation Holder (MAC) for their authorised medicinal products.[1] It is intended to be a live, custom-made document that accurately reflects the pharmacovigilance system put in place for a given product. Since its introduction, many questions have arisen about its scope, purpose, and implementation.

Much needs to go into the PMSF to ensure that it meets the goals established by the EMA to improve oversight and accountability of pharmacovigilance data. When requested as part of the inspection documentation, the PSMF should be made available within 7 days. Competent authorities can also request immediate access to the document at any time during a product's life cycle.

The PSMF improves oversight of the existing pharmacovigilance system, identifies deficiencies in the system, and provides insights into risks in the conduct of specific aspects of pharmacovigilance. However, its implementation has posed several challenges: the PSMF includes extensive requirements that affect many functions and procedures; its maintenance is resource intensive; and adopting it has resulted in a steep learning curve for companies.

Today, with a growing number of companies implementing the PSMF, the issue is less about how to get started and more about how to overcome the problems that inspectors are pinpointing. Many companies are finding that they have to overhaul their PSMF because it lacks the details sought by the inspectors. Even though the PSMF guideline provides some details as to what is required, it is fairly open-ended, leaving a lot of room for interpretation.

Regulatory authorities at the Federal Institute for Drugs and Medical Devices in Germany and the Medicines and Healthcare Products Regulatory Agency in the UK have pointed out a number of gaps in the way the PSMF is being implemented. Their feedback has given MAHs certain insights into the regulators' perspectives on the guidelines and their expectations of the PSMF in practice. This article provides a practical guide on where and how the PSMF can be improved and what's been lacking – based on findings from inspectors.

Role of the qualified person for pharmacovigilance

Companies recognise that the PSMF is a valuable tool that enables oversight by the Qualified Person for Pharmacovigilance (QPPV), but the QPPV's involvement in dealing with major changes to the PSMF is not clearly understood. The QPPV must be informed of any content changes that fulfil the criteria for oversight of the pharmacovigilance system regarding capacity, function, and compliance. In addition, changes in the safety database,

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major contractual changes, and organisational changes should be communicated to the QPPV.

The addition of corrective and/or preventive actions to the PSMF – for example, following audits and inspections – must be reported to the QPPV, who should also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance. When an existing product requires a change or an increased workload with respect to any pharmacovigilance activity – for example, new indications, ongoing studies, or the addition of territories – the QPPV must be notified. Other areas that companies need to ensure the QPPV gets advised about are:

- Changes in arrangements for provision of the PSMF to competent authorities.
- Transfer of significant pharmacovigilance services to a third party – for example, the outsourcing of Periodic Safety Update Report (PSUR) production.
- Inclusion of products into the system for which the PSMF is responsible.
- Additions to or changes in the pharmacovigilance contact person nominated at the national level.

The QPPV must accept any such changes in writing.

Other findings involve proof of registration of the QPPV with the EudraVigilance database, the absence of details pertaining to the QPPV's backup arrangements, and contact information for the local QPPV nominated at the national level.

How much data?

One of the issues with the PSMF is that the guideline does not define boundaries covering data that should be submitted, which made it difficult for companies to determine upper and lower limits. If the PSMF lacked data, it raised flags, which often led to further document requests during inspection. The fact is that companies are reluctant to provide more data than required because they don't want to invest too much time or too many resources in including data that might not be needed. As a result, inspectors often found that the document lacked sufficient details.

The following aspects are expected to be included in the document:

- Description of the methods applied for monitoring pharmacovigilance system performance.
- List of performance indicators, including both performance measurements and targets.
- Matrix with pharmacovigilance activity versus Standard Operating Procedure (SOP) name.
- Description of risk-based approach to audit planning and/or audit frequency.
- Audit notes.
- Logbook to show individual changes to the body of the PSMF.

Clarifying metrics

Metrics or key performance indicators are central to the PSMF and must be included in the annexes together with the results of those measurements. The indicators used to monitor the pharmacovigilance system performance should, at a minimum, include timeliness of individual case safety report and PSUR reporting, quality of submissions, timeliness of safety variations, and overview of adherence to risk management plan commitments or other obligations or conditions for marketing authorisations.

Feedback from inspectors has defined the extent of some of the metrics. For example, compliance data for safety variations should include the following:

- Date on which the company decided that a safety variation was necessary – and the rationale for choosing that date.
- *Targeted* submission date and *actual* submission date (against internal timeline as per SOP).
- Date of approval by the Committee for Medicinal Products for Human Use at the EU level and at the national level, as applicable.
- Date of revision of the text of the summary of product characteristics, including questions around the 10-day timeline to update the electronic Medicines Compendium website.
- Date the patient information leaflet was introduced to product packs.

Annexes and logbook

The content of the annexes can undergo frequent changes; however, the changes do not have to be recorded in the logbook. Annex information can be managed outside the PSMF (independently versioned) but should be available on demand. Annex-related inspection findings include lack of details about worldwide agreements applicable to an EU-authorised product, including affiliate agreements (Annex B); incomplete list of countries in which the product is being marketed; and insufficient details surrounding the nature of the activity and site contact details (Annex C).

The logbook should reflect descriptive changes made to the main body of the PSMF. Changes to the PSMF annexes do not need to be recorded in the logbook; however, change control should be in

place. A frequent finding concerning the logbook is that it contains only generalised descriptions of the changes made to the main body of the document, for example, a major update to the section about the QPPV; the logbook should provide specific details regarding individual changes made to the body of the PSMF.

Recording deviations and corrective and/or preventive actions

Deviations from the quality system should be documented in the main body of the PSMF until they have been resolved. Although it is not expected that every unplanned SOP deviation will be recorded, the MAH is expected to demonstrate that assessments of the impact of such deviations were carried out. In addition, the logbook should contain information regarding the addition, amendment, and removal of notes concerning significant audit findings or quality system deviations.

Notes associated with significant audit findings are to be recorded in the main body of the PSMF. Cross-references to the associated audit report are to be avoided. The note should include a brief summary of the finding, a summary of the corrective and/or preventive actions, the date on which the finding was identified, and the anticipated resolution date. Only audits conducted or commissioned by the MAH are to be included in the PSMF.

Corrective and preventive actions associated with unresolved notes in the PSMF should be identified in the corresponding annex. Notes can be removed from the PSMF only when the proposed corrective and preventive actions have been fully implemented. Recording removal of the audit notes verifies that sufficient improvement has been demonstrated or independently verified.

Responding to the EMA's findings

Information from inspectors and assessors represents a useful guide to help companies improve the PSMF. Regulators have made it clear that it is not acceptable to simply list the MAH's documented procedures. Rather, the PSMF should contain a description of the processes of:

- Continuous monitoring of risk–benefit profiles
- Risk management systems
- Individual case safety report collection, collation, follow-up, and reporting
- PSUR scheduling, production, and submission
- Communication of safety concerns
- Implementation of safety variations.

Besides the safety database, any other systems or databases that are used to receive, collate, record, and report safety information must be described. These include medical information systems, product quality databases, clinical trial systems, and any other system important for the collection of safety data.

The MAH also has to provide proof that any delegated activities are performed in compliance with legal requirements. The PSMF should document deviations from pharmacovigilance procedures (including impact) until they have been resolved.

Implementation of the PSMF remains an immense and complex task, but the level of details that inspectors have started to provide in their feedback goes a long way to assist companies and their outsourcing partners in the preparation of a comprehensive document – one that will limit exposure to problematic inspections.

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Post-approval regulatory writing – How different is it from writing pre-approval documents?

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Abstract

Regulatory writing has various facets to it with good writing skills as a preliminary requirement. Well written reports form the basis of all regulatory submissions for marketing approval and its success largely depends on the research information presented to the regulators. Submission package should comply with the required guidelines and report structure. In addition, they should be written in a style that allows regulators easy access to the safety and efficacy information needed for making a decision on marketing the drug. Post-approval writing can present some interesting situations and challenges to the sponsor and the medical writer. It is important for a medical writer to be aware of these situations and make the necessary plans to surpass them, working with experts in different domains to ensure timely availability of the right drug to the right patients. The article describes in detail some of these situations.

Keywords: Pre-approval writing, Post-approval writing, Submission package, Sponsor, Guidelines, Regulatory agency

Background

Pharmaceutical regulatory writing involves writing documents, which provide information on research and development (R&D) conducted by a sponsor company, that are required by regulatory authorities to grant marketing authorisation for an investigational drug. Pharmaceutical companies create an extensive plan for the development of a drug. A typical drug development approach is to identify a potential drug candidate that would provide benefit for a particular medical condition, driven by an unmet medical need in the population. After the drug passes through laboratory and animal testing, clinical studies are conducted to answer important scientific questions – is the drug efficacious for the indication, and is it safe for use in the intended population?

The clinical development plan (CDP) document acts as a blueprint to help the sponsor plan and conduct R&D activities required for approval of the drug for a particular indication. The various clinical studies and analyses conducted as a part of R&D are parts of a complex jigsaw puzzle. The individual component becomes clearer when the development step is documented and a report is written. This role is usually accomplished by a regulatory medical writer working with others involved in R&D. Health authorities provide detailed guidelines on the templates and document structure in which information needs to be presented for the marketing application. For example, the European Union (EU), which is an ICH-compliant region, provides clear guidelines in its European Medicines Agency (EMA) website.[1] Regulatory medical writers are required to work in accordance with the regulations and guidelines provided.

Once substantial evidence for the safety and efficacy of the product is gathered from clinical and non-clinical studies, the product is eligible for an application towards its marketing approval for an unmet medical need. Drug development is not limited to all the activities conducted before a sponsor applies for approval of a drug for an indication; a large part of it continues after that. The sponsor develops the CDP to strategise and prioritise parts of R&D needed for the initial approval, while the other parts of R&D are planned later for the registration of other indications.

Summary of documents written by regulatory medical writers

The common technical document (CTD) is the prescribed format in which clinical submissions are

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made in the regions falling under ICH and also some other countries. The guidelines specifying details of the components of CTD exist on the regulatory websites (such as EMA for the EU region).[2] If a sponsor submits a CTD file to the regulator, writing of all the reports contained in that CTD file is called pre-approval documentation/medical writing. Document writing after the initial submission, in response to the assessment by the regulator[3] or as part of R&D for other indication(s), is called post-approval medical writing. Some examples of post-approval reports are:

(a) Reports for studies requested by the health authority (typical Post-Authorisation Safety Studies (PASS)), and safety-related reports such as Periodic Safety Update Reports (PSUR) and Risk Management Plans (RMP).
(b) Reports for studies conducted to extend the indication to other populations. For example, imagine that Drug X was initially approved for all adult patients with essential hypertension without any comorbid conditions. Other related populations in which the drug efficacy might be tried are – the paediatric population, hypertension due to secondary causes, hypertension in pregnancy, geriatric population, or patients with comorbid conditions (diabetes mellitus, heart failure, etc.).

Regulatory writing should be clear, evidence-based, well-organised, and complete taking into consideration the regulators who are the end users. Although regulatory writing needs to meet a lot of criteria to be seen as a neutral account of what was done and what the results say from the studies and analyses conducted, it would be fair to say that the 'art' of good writing enables presentation of the right information to the regulators such that they are not lost in a sea of information and have the right information needed for them to make the decision as to whether the drug works or not. Also, the structure of writing the reports should help them gather information for the questions they might have on the reports submitted to support them in making decisions on marketing the drug. Faster drug approval fulfils the unmet medical need and leads to its quicker availability to the needy patients.

Some examples of documents covered under regulatory writing are described in Table 1.

Sponsors typically approach regulatory writing by having writers within their organisations and also by utilising external support of writers with specialty in a particular type of regulatory writing. Usually the writers working in the organisation are well aware of the sponsor drug development strategy and are able to assign the priority and focus required for some of the regulatory documents. External writers, however, bring their expertise in a particular therapeutic area or a regulatory document. The sponsor is required to plan effectively on which writing task goes to whom and there is no 'right' approach.

Table 1: Examples of regulatory documents

Document category	Description
Clinical study report (CSR)	Guided by the ICH E3 guidelines,[4] it is a report of an individual clinical study integrating various components of the study conduct, results, and interpretation
Summary documents	These are documents that summarise the results from various parts of R&D, focusing on key areas like efficacy and safety. They form Module 2 of the CTD[3]
Investigators brochure	A compilation of clinical and non-clinical data that facilitates the investigator to conduct the clinical study[5]
Safety reports	Development Safety Update Reports (DSUR), Periodic Safety Update Reports (PSUR), and Risk Management Plans (RMP) are some of the safety reports prepared by sponsors as a regulatory requirement during development or marketing of the drug in the EU region[6]
Health authority questions (HAQ)	These are post-submission assessment reports from the regulators[3] requiring the sponsor to clarify the issues raised and hold a key role in approval of the drug by the regulatory authorities
Briefing book	These are documents created by the sponsor to engage in active dialogue with the regulator, cutting across the various modules of CTD to bring together all the key information required by the regulator for their assessment

Preapproval regulatory writing

The focus of regulatory writing prior to marketing approval is to ensure the results of drug R&D activities are presented in the correct format within the template guidance provided by ICH. It accounts for answering the questions that were the objectives of the studies conducted and builds comprehensively on the information that has become available from all the research done on the molecule. It has to be comprehensive to ensure that all the relevant information generated, reaches the regulators in the most organised fashion. It should deter regulators from rejecting the application merely due to missing key information. Health Authorities usually come back with questions that need to be

addressed appropriately using tactful writing skills. The end result of a poorly written marketing application for a genuinely beneficial drug is delayed drug availability to the patients.

The skill sets required to write the different documents can vary substantially.

- Writing a Clinical Study Report needs a good understanding of research methodology and basic statistics to interpret the results and give a clear account of study conduct, results and the conclusions drawn from them.
- Writing summary documents and briefing books for the regulatory authorities require a far more impactful approach. The writer should have a good understanding of the drug development process. The writer should know how reports from various departments impact the decision by regulators for marketing the drug. The art of simplifying and presenting the key information is hard to master; however, that is exactly what the writer has to do – take the huge amount of information generated over years of research on the molecule, and present it in a way that helps the regulators make their decision. A lot of effort goes into data mining for the right information. Also, knowledge over various domains is required, such as regulatory requirements of the region where the submission is planned, what the regulators expect from the submission, and whether all the key questions with regard to safety and efficacy of the product are addressed adequately. Incomplete information can result in rejection of an application or further questions from health authorities for clarity. Some of these questions might require further studies to be conducted, thus pushing back the target approval of the drug by years.

Post-approval regulatory writing

Post-approval writing for any research is conducted, as described above, to augment the approval provided by the health authority or to apply for marketing of the drug in a new indication based on additional R&D. If the writing is for studies mandated by the health authority as a condition to give approval, it has to reach the regulators within the stipulated time to avoid delay in the planned marketing of the drug to patients.

If a writer is involved with writing a report for a study that was conducted for an indication other than the one the drug is approved for, the writer has to think carefully about the following points while drafting the report:

(a) All the relevant efficacy and safety data is presented well, without allowing a chance for interpretation that some of the information is missing in the documentation. This can impact the marketing status of the drug for the primary indication.
(b) The report writer should evaluate (along with the other authors of the report) how the information generated from the study fits with the information covered in the preliminary submission that is available with the regulators. Also, whether the information is contradicting with, or is in line with the results achieved from pre-approval studies, needs evaluation. This is extremely challenging because the report should always be written to avoid any scope of misinterpretation, even if the new information generated puts the marketing status of the drug for the primary indication at stake.

A lot of interesting and unique situations arise in post-approval writing. This is because the sponsor wants to ensure that they are able to identify other unmet medical needs which can be fulfilled by the drug which has received an initial approval. The sponsor might approach filing for approval for the claims for benefits in another indication immediately following initial approval or it might require a longer duration of R&D and experience from marketing of the drug before being able to file for additional claims.

Some interesting facets of post-approval writing are described below.

Engaging writers for post-approval writing

Once a submission is done, the team including the writer(s) involved in submission activities usually get reassigned to other tasks. For post-approval writing, should the sponsor engage the same writer(s)? Reassignments are part of business today as sponsors try their best to manage the resources and manage the risk associated with some of these reassignments.

A new writer like any other new team member would need time to start contributing effectively. This means that it would take time for the writer to do their homework on the reports written in the past and the influence they have on the writing task at hand.

A writer who was involved right from the start can help bring perspectives from previous documents and ensure that the post-approval documents

are in sync with the previous documents submitted. A new writer brings in a new perspective, experience, and strategies from other submission documents they have written in the past. The sponsor has to decide on resource optimisation and priority of the project, which determines who ends up writing the regulatory documents.

Duration between initial approval and post-approval writing

Writing regulatory documents in continuity after the initial submission, works well for the sponsor as long as other claims from the drug are planned. However, there could be situations when new studies are conducted a long time after the initial submission with the drug already in the market. In this case, it is not always possible to have the same team that worked on the initial submission to be part of the new R&D and writing requirements. Challenges faced by this team would be to ensure that the data on the initial R&D is supplemented with the marketing experience, and the safety and efficacy data is based on its use in the population.

Safety reports post-approval

Safety takes a special focus when the drug is marketed in the population. While R&D is conducted prior to submission, only a small portion of the population who were enrolled in the studies is exposed to the new drug. With marketing approval, larger populations get exposed to use of the drug and adverse effects not evident from the early clinical trials may become more apparent. From the regulatory writing point, writing periodic reports such as Periodic Safety Update Reports (PSUR) presents to the regulators the safety profile of the drug and reasons why the drug should be marketed further. The RMP document is written to ensure that the adverse events related to the medication are well managed by various modes such as label information, education of patients, use of social media, etc. As long as clinical drug development is continuing post-approval, a Development Safety Update Report (DSUR) is mandated, with the focus to communicate to the authorities what is the drug benefit–risk profile for continuing drug development.

Writing follow-up reports for reports in the submission package

There can be further challenging situations while writing documents post-approval. Imagine a case where results of an interim analysis of a study were submitted to substantiate the claim of the drug for approval. When the whole study gets completed, well after the approval for the drug, the writer might find a situation where the results can vary from the interpretation made at the interim analysis. This could be because the data generated from the site was ongoing and follow-up information might impact the interpretation made for interim analysis. In this case, what should be the approach? We are bound by ethical standards to ensure that the health authorities are aware of this situation and only drugs with the right benefit–risk ratio reach the patients. But imagine the pressure the writer has to face to ensure that the results are presented in a fashion such that there is no room for misinterpretation!

Conclusion

Regulatory writing is an extremely specialised job that is done by individuals with a capability of depicting information in both, concise and precise format. It requires a lot of cross-functional interaction, planning and influencing to ensure the right message is presented in the reports. Writing documents pre- and post-approval has its own set of challenges. The examples illustrated above point towards the expertise needed and the strategic approaches required to plan and execute regulatory writing pre- and post-approval. From a writer's standpoint, it is important to understand drug development and the challenges that come up as a part of the process, and the constant push to get the right drug to the right patients. A lot of thought process goes into writing regulatory documents and the role of the medical writer is key to substantiate that the right drug should reach the right patient population and the regulators are convinced to make this decision.

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Errrors and corrrections

We all make mistakes, right? I once spotted an error in the title of a scientific paper some colleagues had got published. Instead of *Familial* they had written *Familiar*, the reason being that the Swedish word *familjär* can have both meanings and they picked the wrong one. Quite how this got past the editor and reviewers I do not know. But anyway, the authors published an erratum and got the title corrected.

While unfortunate, this mistake was relatively trivial. It did not lead to data being misinterpreted or erroneous conclusions being propagated. Noting that 'Errors serious enough to invalidate a paper's findings may require retraction', the International Committee of Medical Journal Editors (ICMJE) includes guidelines on errata in its Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals.[1]

To assess, among other things, whether the ICMJE guidelines are being applied, a group of researchers from St. Louis searched for and analysed errata published in 20 leading journals (10 in general medicine and 10 in cardiology) over an 18-month period.[2] They found 557 published errata, nearly 40% of which appeared in the *New England Journal of Medicine* or *The Lancet*. Erratum rate was positively correlated with journal impact factor. Alarmingly, only half of the errors classified as 'major' had been corrected.[2] This in spite of the fact that 540 (94%) of the articles requiring errata were published by signatories to the ICJME guidelines, according to which 'The journal should post the new article version with details of the changes from the original version and the date(s) on which the changes were made'.[1]

The St. Louis team call for a 'consensus about errata reporting'.[2] Well, what are the ICMJE guidelines if not some kind of consensus? Rather than lack of a consensus, the problem seems to be the inevitable failure of authors, reviewers, and editors to spot every error, and the non-inevitable failure of journals to adhere to existing guidelines concerning corrections.

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Strategic medical writing in the post-authorisation phase

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Abstract

This article outlines the latest legislation for some of the most common post-authorisation documents (Risk Management Plans, Periodic Safety Update Reports, and Post-authorisation Safety Studies) and explains the role of the strategic medical writer. The strengthening of post-authorisation legislation has led to documents with new and improved formats. At the same time, the strategic medical writer's role has evolved almost in parallel with these legislative changes. The strategic medical writer contributes document and scientific expertise, writing skills, and project leadership through effective communication, and also provides an invaluable link in the team in the development of post-authorisation documents by anticipating problems, managing the review process, advising on data presentation, and ensuring compliance with guidelines. This process results in the production of high-quality documents, makes the submission process smoother, promotes the strengthening of the pharmacovigilance system, and ultimately contributes to patient safety.

Keywords: Post-authorisation documents, Legislation, Medical writing, Pharmacovigilance

Introduction

Thalidomide was marketed following tests carried out in animals and was sold without prescription. The first child affected by thalidomide was born in the late 1950s,[1] but it was not until 1960 that neuropathic side effects were first reported, in the UK.[2] In 1961, following a sudden increase in cases of phocomelia, a German paediatrician noted that 50% of these patients had been exposed to thalidomide. It was not until 2 months later that the drug was withdrawn from the market, and the UK Ministry of Health issued a statement warning patients to stop taking the drug. However, the drug was not removed from sale. At this juncture there were up to 5000 reported deformities in the UK and 10 000 worldwide.[3] There was a flaw in the system and it was clear that legislation was required to ensure patient safety and regulate the pharmaceutical industry. Proposals for new legislation to control medicines in the UK were published in 1967 and the outcome of these proposals was the Medicines Act 1968.[4] The Act established legislation that required all medicines already marketed to undergo peer review and subsequent approval or withdrawal. In addition, the Act required that from 1971 all new medicines underwent a pre-marketing assessment for safety, quality, and efficacy by the licensing authority.

The history of thalidomide emphasises the vulnerability of patients. In addition, it highlights the requirement to understand the mechanism of action of a drug and its related toxicities,[5] in conjunction with the necessity for legislation, not only before authorisation but also in the post-authorisation phase. The post-marketing arena is vital to ensure the safety of patients and the effectiveness of medicines in real-life settings. This is achieved by monitoring adverse events, and evaluating the benefit–risk profile of a medicine. This process includes the production and submission of documents such as Risk Management Plans (RMPs), Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports (PSURs/PBRERs), and Post-Authorisation Safety Studies (PASSs) to the authorities by the marketing authorisation holder (MAH). The medical writer can play an important role in the preparation of these documents. However, recent legislation and the new and more complex format of the documentation demand more than just organising and formatting data. This provides an ideal opportunity for the strategic medical writer to add value to the documents by developing 'effective communication, arising out of the teamwork between the authors and the medical writer',[6,7] to produce high-quality post-authorisation documents and ensure a smooth submission process.

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This article outlines the latest legislation and explains the role of the strategic medical writer in some of the most common post-authorisation documents.

Legislation

Historically, the EMA has been criticised for its deficiencies. These have included inconsistency and a paucity of robustness in information and assessment, as well as insufficient transparency.[8,9] However, the regulatory environment is changing. In 2012, the biggest change to human medicine legislation since 1995 was instigated. This resulted in the strengthening of pharmacovigilance legislation and demand for increased transparency of regulatory decision making. The key changes to the legislation are shown in Table 1.[10]

The changes impact the entire product lifecycle and will take time to fully implement.[10] Amendments made to Directive 2001/83/EC (the community code relating to medicinal products for human use)[11] and Regulation (EC) No 726/2004 (laying down community procedures for the authorisation and supervision of medicinal products for human use and establishing an EMA)[12] have improved and generated changes in the pharmacovigilance system. These include risk evaluation and harmonisation of regulatory action on drug safety.[13] The new legislation defines the roles and responsibilities for key responsible parties, rationalises EU decision making on drug safety issues to prevent unwarranted patient exposure to risks, increases transparency and communication of medicine safety, and strengthens companies' pharmacovigilance systems. The legislation ensures structured risk management procedures and data collection, and makes companies legally liable to perform PASSs as well as post-authorisation efficacy studies. In addition, new EU pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) amending Regulation (EU) No 726/2004 (pharmacovigilance of medicinal products for human use) increases the level of transparency of safety information. Submissions of PSURs are required more frequently and are required to assess product safety through the assessment of the benefit–risk profile of the drug.[14–17]

As a result of the new legislation a Pharmacovigilance Risk Assessment Committee (PRAC) was established at the EMA in July 2012. The main responsibility of the PRAC is to provide recommendations relating to pharmacovigilance activities, including risk management systems. It is responsible for assessing all aspects of the risk management of medicines, including the risk of adverse reactions, while considering the therapeutic effect of the medicine. The establishment of the PRAC strengthens the regulation of medicines, improves transparency and communication in pharmacovigilance, and contributes to the risk management process.[18,19]

The role of the medical writer has evolved almost in parallel with the changing legislation. In the 1960s medical writing began to be formalised with the publication of style manuals and by the late 1990s guidelines were published to improve the quality of the reporting of randomised trials (the CONSORT Statement).[20,21] Today the medical writer has a multi-faceted role, described by Limaye[22] as the 'four pillars of medical writing' (document expertise, scientific expertise, writing skills, and project leadership), a role that reaches beyond an editorial function. The strategic medical writer fulfilling this multi-faceted role has a key position in the production and submission of the new post-authorisation documentation. This is because the new documentation has more complex data in larger amounts, and requires greater detail, additional analysis, and input from different specialities. In addition deadlines remain tight.

The changes in the legislation have major implications for post-marketing documentation (described in the following sections). In the past, the European Commission's pharmacovigilance guidelines were drawn up in accordance with Article 106 of Directive 2001/83/EC, known as volume 9A,[23] and PSURs were based on the guidance document ICH E2C. The application of the pharmacovigilance legislation (as of July 2012) has been replaced with the good pharmacovigilance practice (GVP) guideline.[24] The significant changes in post-authorisation documentation provide the opportunity for the strategic medical writer to become an invaluable link in the team.

Risk Management Plan

When an initial authorisation is obtained, the benefit–risk is considered positive for the target population for the specified indication. Post-marketing data are essential as the drug has not been used in the 'real-life setting'. Therefore, there will be potential risks that have not been identified, and there may be additional or greater risks for subsets of patients outside of the target population. Risk management involves risk detection, risk assessment, risk minimisation, and risk communication and should consider both the individual patient and the public health impact.

Risk management is an important part of post-marketing documentation. The strategic medical writer can anticipate problems, provide a central

Table 1: Key changes to human medicine legislation instigated in 2012

Areas of change	Measures	Key implications
Coordination of lists of medicines	• Controlled lists of all EU products will be created to support EU medicines databases • Coordination of safety monitoring	• Reports of suspected adverse drug reactions (ADRs) will be more effective at identifying safety issues • Identified safety issues will be published and accessible
Authorisation requirements	• Marketing authorisation (MA) dossiers submitted to the EMA will change: pharmacovigilance system description will be reduced • A pharmacovigilance system master file (PSMF) that can be requested or inspected will be maintained by all companies	• Less variations to authorisation (a new process to coordinate assessment and processing of applications to change MA, meaning multiple submissions are no longer necessary) • The marketing authorisation holder (MAH) has the responsibility to maintain an accurate PSMF
Reporting of ADRs	• Patients in the EU have the right to report suspected side effects • From 2016: legal endorsement of the use of International Organization for Standardization (ISO) standards • ADR reports will come only from industry and national agencies	• All patients can report a suspected side effect • Centralised reporting will allow the EMA to report suspected ADRs to the WHO on behalf of 30 member states
Signal detection	• New legal obligation for the EMA, national regulatory agencies, and industry to analyse data to detect new or changing safety issues	• New or changing safety issues should be detected more quickly • New advice and warnings will reach patient information leaflets more rapidly • ADRs should be minimised
Inspections and audits	• Strengthened EU coordination of inspection • Regular audits of the EMA, national authorities, and industry	• Greater assurance of the quality of pharmacovigilance performed by industry and regulators
Risk Management Plan (RMP)	• All new products will have an RMP that will include a safety specification, a pharmacovigilance plan, and risk minimisation safety and efficacy studies • Post-Authorisation Safety Studies (PASSs) will be legally binding • Studies will be monitored to ensure high quality	• Post-authorisation surveillance will be risk proportionate and robust • High-quality information on the benefits and risks of medicines will be generated post-authorisation and the results shared
Effectiveness of risk minimisation	• Monitoring of effectiveness is a new legal obligation for industry and regulators	• Specific studies will be done to ensure understanding of safety messages • This will change prescribing and dispensing behaviour of health professionals • ADRs will be reduced
Periodic Safety Update Report (PSUR)	• Content changes to Benefit Risk Evaluation Report • No routine reports for generic products; timing of submission will be risk proportionate • The EMA has published a legally binding list of birth dates and submission dates • Eventually, the EMA will process all reports for the EU and all assessments will come through EMA Committees • There will be binding/legal outcomes, e.g. variation, suspension, revocation	• Benefits and risks are re-examined regularly post-authorisation • Negative assessments will change rapidly to warnings • Opportunity for international harmonisation between the EU, Japan, and the USA
Scientific committee	• Formation of the Pharmacovigilance Risk Assessment Committee (PRAC) • All key safety issues will pass through this committee	• High-quality benefit–risk assessment • Legally binding outputs for product reviews • Fast, efficient updates to all product information
Transparency and communication	• Major increase in publically available documents • Public hearings at the EMA • EMA communication coordination for nationally authorised products • EU and national medicines web-portals that will include agendas, minutes, recommendations, and opinions • Companies to keep product information up-to-date with the web-portal	• Increased and improved information on the benefits and risks of medicines • Expeditious information on new safety issues, new advice, and product information updates • Coordination of information between Member States
Fees charged for pharmacovigilance	• New fees will be charged to industry (European Commission consultation recently closed and legal proposal awaited)	• Adequate resources should be available to ensure robust public health protection

link for all members of the team, manage the review process, advise on data presentation, and ensure compliance with guidelines, ultimately facilitating the aim of ensuring patient safety.

The Medicines and Healthcare Products Regulatory Agency describes risk minimisation activities for an MAH as 'ensuring that it constantly monitors the risks of its medicines in compliance with relevant legislation and reports the results of this, as required, to appropriate Competent Authorities. Taking all appropriate action to minimise the risk of the medicine and maximise the benefits, including ensuring the accuracy of all information produced by the company in relation to its medicines, and actively updating and communicating it when new information becomes available'.[25] The strategic medical writer has a significant responsibility in ensuring accuracy of information and compliance with the regulations, as well as data interpretation and project management. A problem frequently encountered in the production of post-authorisation documents is the late arrival of essential data, or incorrect data (i.e. data that does not entirely encapsulate what is required in a particular section of the document), which puts extreme pressure on the team to meet the submission deadline. Through collaboration, support, and coordination with the team, the strategic medical writer can pre-empt this by producing a list of data required and the time scales involved as far in advance as possible. Then, through regular communication with the different departments and team members involved, the medical writer can check the progress of data production, thereby reducing the likelihood of late or incorrect data.

The RMP consists of seven parts and the safety specification section is subdivided into eight modules. The new requirements have presented a challenge for the industry in preparing a superior document that incorporates all of the required legislation.[26–29] The strategic medical writer can help with this challenge by advising on templates and ensuring that the chosen template meets the required legislation.

The RMP assesses the product in the context of benefit–risk analysis in order to prevent or minimise the medicine's risk in patients. Producing a RMP requires the input of different specialists (e.g. pharmacologists, clinical research physicians, pharmacovigilance experts, and toxicologists). The strategic medical writer's role includes coordination of the team and management of the review cycles. This includes ensuring that the correct data is received on time, and that the specialists input is received, reviewed, and included in the document appropriately.

Periodic Safety Update Report

A PSUR (formerly known as the PBRER) is a document used for post-authorisation evaluation of a product at defined time points. The document provides a concise, critical analysis of the medicine. It includes a summary of the benefits and risks, new or emerging information on benefits and risks, and the results of all studies of both authorised and unauthorised uses. Cumulative data from previous reports are also incorporated in the benefit–risk evaluation. The legal requirements for submission of PSURs are established in Regulation (EC) No 726/2004, and Directive 2001/83/EC, and in the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities, provided for in Regulation (EC) No 726/2004, and Directive 2001/83/EC. The new required format of the PSUR for the EU is based on the PBRER described in ICH-E2C (R2) and replaces the format previously described in ICH-E2C (R1). PSURs provide an opportunity for the MAHs to review the safety profile of their products and ensure the summary of product characteristics and package leaflets are up-to-date. Due to the extent of the changes to the format of the PSUR, significant changes are being made to production, review, and assessment processes by the MAHs.[30–34] The new format PSUR includes larger and more diverse populations than pre-authorisation documentation and requires the inclusion of a larger amount of data due to the required cumulative analysis and benefit risk evaluation. The strategic medical writer can assist the MAH by being involved at the very beginning of the process, advising on the problems that may arise, such as late data or essential information not being available at the required time, and the impact this has on the very tight timelines.

The new format PSUR is intended to be a common standard for periodic benefit–risk evaluation of marketed products[35] and is believed by regulators to meet the national and regional requirements for periodic safety reporting. The objective of the new format PSUR is to provide a critical analysis of new or emerging post-authorisation information on the benefits and risks of a medicine presenting an overall benefit–risk profile that includes cumulative information. The evaluation of benefit is a new facet of this document and unless the safety or benefit–risk profile has changed during the reporting period a concise discussion of benefit is usually sufficient. In the context of efficacy and effectiveness, the new format PSUR

must contain the evaluation of the medicine from the International Birth Date, include relevant new safety information and cumulative knowledge, and focus on new information. It should provide information on all approved indications, dosage forms, and regimens for the active substance. The full ICH E2C (R2) guideline specifies the required format for new format PSURs including table of contents and section numbering, and Section 3 of the guideline gives specific guidance on content.[36,37] The strategic medical writer can also add value by advising on interpreting the guidelines to produce the template and suggesting the best format to present data.

Post Authorisation Safety Study

A PASS is any study relating to an authorised product that quantifies potential or identified risks, evaluates risks in populations where there is limited or missing safety information, provides evidence relating to the absence of risks, confirms the safety profile of the product, or measures the effectiveness of risk management measures (Directive Art 1 [15]). A PASS may be a clinical trial or a non-interventional study. A non-interventional study should meet the requirements of Volume 10 of The Rules Governing Medicinal Products in the European Union.[38] The purpose of a non-interventional PASS is to generate data of clinical or public health importance. If a PASS is a clinical trial, Directive 2001/20/EC details the legal obligations relating to the implementation of good clinical practice in the conduct of clinical trials.[38] Companies are required to provide a written study protocol before commencement of the study (details of the format and content are presented in Module VIII of the guideline on GVP[39]). Pharmacovigilance data and new information generated should be monitored and the benefit–risk balance considered. Information from the PASS should be included in PSUR and RMP updates. The final study report should be submitted as soon as possible after finalisation and within 12 months of the end of data collection, and should include a publicly available abstract (details of the format and content are presented in Module VIII of the guideline on GVP[39]). For the medical writer, this is where pre-authorisation meets post-authorisation: the skills required are similar to those needed for the production of a pre-authorisation clinical study report.[40]

Conclusion

The strengthening of post-authorisation legislation has instigated documents with new and improved formats. The focus has changed to include a much stronger assessment of the benefit–risk profile of the product, the aim being to improve patient safety and avoid disastrous events like those seen with thalidomide. To this process the strategic medical writer contributes document expertise, scientific expertise, writing skills, and project leadership[22] through effective communication. In addition, the strategic medical writer provides an invaluable central link in the team in the development of post-authorisation documents by anticipating problems, managing the review process, advising on data presentation, and ensuring compliance with guidelines. This results in the production of high-quality documents, ensures a smooth submission process, facilitates the strengthening of the pharmacovigilance system, and ultimately contributes to patient safety.

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Non-interventional Post-Authorisation Safety Studies (NI-PASS): A different type of report

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Abstract

Although Post-Authorisation Safety Studies (PASS) have been around since 2001, most regulatory writers would have been unaware of their existence until the recent changes in European regulations, which include mention of these studies as part of general strengthening of pharmacovigilance procedures. Interventional PASS will largely adhere to International Conference on Harmonisation requirements, but non-interventional (NI) PASS should be reported according to a particular mandated format, which may appear strange to writers used to drafting clinical study reports for interventional trials. Given their novelty, there is no consensus as to how these reports should be drafted. This article addresses the structure of NI-PASS reports and provides an interpretation, albeit preliminary, of the corresponding European Medicines Agency guidance text.

Keywords: Post-authorisation safety studies (PASS), Non-interventional (NI), Pharmacovigilance Risk Assessment Committee (PRAC), Risk Management Plan

Background

A clinical development programme, however exhaustive, will always be subject to certain limitations. For example, the number of patients exposed may be insufficient to detect small but significant safety signals. In addition, the controlled setting of clinical trials may not adequately reflect clinical practice in that real-life patients may, for example, be multi-medicated or have more concurrent illnesses. In this context, the regulations in the European Union have recently been changed to enable more proactive assessments of approved drugs (see Sarah Richardson's article on p. 267 for a good overview of these changes). Notably, a body dedicated to post-authorisation assessment known as the Pharmacovigilance and Risk Assessment Committee (PRAC) has been set up.

Post-Authorisation Safety Studies (PASS) are one of the tools available to PRAC for monitoring approved drugs.[1] However, the concept of a PASS predates the PRAC by more than a decade. According to Directive 2001/83/EC (DIR) Art 1(15),[2] a PASS is defined as 'any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.' In particular, these studies are conducted to quantify potential or identified risks, fill gaps in existing safety data, further define risks (or absence thereof), for example after long-term use, or assess the effectiveness of a risk minimisation activity. As such, they may form part of a Risk Management Plan (RMP).

PASS can be divided into interventional and non-interventional studies. Interventional PASS will, by and large, be conducted and reported in accordance with familiar International Conference on Harmonisation (ICH) guidance and are not discussed further here. In non-interventional observational studies, treatment is assigned by decisions guided entirely by clinical practice and administered according to approved labelling, with no additional protocol-mandated procedures or tests. Non-interventional (NI) PASS studies can include, for example, literature reviews or retrospective analysis of registry data, in addition to observational studies, and cohort studies. The rest of this article will focus on non-interventional observational studies, as these are the ones that regulatory writers will most likely encounter. A NI PASS should, like an interventional

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study, also be conducted largely in the general spirit of ICH and Good Clinical Practice, but certain aspects may differ. In particular, a final study report for an NI-PASS (note the guidance refers to 'final study report' rather than clinical study report [CSR]) should be based on the guidance issued by the European Medicines Agency[3] and differs in many features from a typical CSR for interventional trials (hereafter referred to as 'ICH-based CSRs'). The following sections discuss various aspects of NI-PASS reports, with reference where appropriate to familiar ICH-based CSRs.

EU PAS registry

Methodological details of all PASS studies should be posted to the EU PAS registry, which is run by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, see http://www.encepp.eu/). Much has been made about the need to disclose interventional trial protocols and results, and this analogous requirement for NI-PASS is presumably a further effort to increase transparency and strengthen pharmacovigilance procedures. The study results should also be posted to the website within 2 weeks of submission of the final study report (usually submitted within 1 year of completion of data collection). Some companies post the entire report (with redactions and stripped of the appendices) while others opt for posting the report abstract.

Guidance for posting to this registry is available.[3] Nowadays, most pharmaceutical companies have groups dedicated to posting details of interventional trials on sites such as clinicaltrials.gov. Observational studies, however, may have slipped under the radar and when drafting a report it is worth checking early on that the study has been registered on the ENCePP website and hence has an EU PAS registration number. Note that a final study report for an NI-PASS cannot be completed without this registration number.

Structure of NI-PASS reports

A guidance document covering the format and content of the final study report of NI-PASS was issued in 2013.[4] The guidance document suggests that the table of contents of the guidance document itself can be used to build a template for the NI-PASS report (see Table 1). If this table of contents is not used directly, it would still seem advisable to stick as closely as possible to the structure provided by the guidance. A sensible approach might be to keep the headings of the structure given in the guidance with 'not applicable' if appropriate, and add extra headings and subheadings if necessary. By analogy with ICH-based CSRs, sections covered by the guidance do not have to be considered as separate numbered sections in the report. Thus, the abstract does not necessarily need to be numbered as Section 1.

Table 1: Suggested structure of NI-PASS according to the EMA guidance[4]

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

Cover page and EU PAS registry

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

Abstract

Unlike the synopsis of an ICH-based CSR, an NI-PASS report has a structured abstract, in some ways similar to a journal abstract but with more subheadings. The structure of the abstract is defined by the guidance and, in addition to the title and key words, includes rationale and background, research question and objectives, study design, setting, subjects and study size, variables and data sources, results, and discussion. The guidance actually states that the word count (excluding the title and certain other administrative details) should not exceed 500 words. With so many subheadings, and for a study of any complexity, this will be challenging. As far as I am aware, this word count can be exceeded (in the same way that the synopsis of an ICH-based synopsis should not exceed 3 pages, but is subject to some flexibility). Sensible advice here would be to keep as close to 500 words as possible without omitting any important features, results, or conclusions of the study, particularly if the abstract is to be used for disclosure of the results.

Administrative sections and methodology

As with an ICH-based CSR, the first part of an NI-PASS report has sections covering administrative aspects (investigators, other responsible parties, milestones) and research methods. In the case of protocols written according to the latest NI-PASS guidance,[5] the methodology sections can be adapted from the corresponding sections in the protocol. The correspondence is not exact; report subsections such as 'Bias', 'Subjects', and 'Sensitivity analyses' do not have an exact counterpart in the protocol, although issues such as bias and sensitivity analysis may be addressed in protocol sections such as 'Data analysis' and 'Limitations of the research methods'. With a view to facilitating drafting of the NI-PASS report further down the line, it might be helpful to have the guidance for final study reports to hand as well as the protocol guidance when writing an NI-PASS protocol.

For an ICH-based CSR, it is generally considered good practice to extensively cross-reference the protocol. In the case of an NI-PASS report, however, the protocol may not necessarily be appended to the CSR (or it might be redacted during disclosure). In general, the methods section of an NI-PASS report should perhaps be more stand-alone than an ICH-based CSR counterpart. If the NI-PASS study was initiated prior to 2012 (when the PRAC became operational), then it is unlikely that the study was conducted with a protocol drafted according to the latest guidance and it will not have been submitted PRAC. In some cases, studies intended largely as marketing exercises may have subsequently been designated as an NI-PASS. The original protocol of these studies may therefore not resemble the mandated protocol format and the methods section will require more thought and work. The writer will have to refer to the guidance text to ensure that the content is appropriate, especially as some sections will be unfamiliar to someone used to writing ICH-based CSRs.

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

Results

The structure of the report as presented in the guidance has six sections. The 'Participants' section is self-explanatory. The next section 'Descriptive data', according to the guidance text, refers largely to patient characteristics. As NI-PASS are by definition non-randomised studies, it is important to have a good understanding of the baseline characteristics of different patient groups in order to assess potential biases when making group comparisons. The 'Outcome data' section should include, according to the brief guidance text for this section, the 'numbers of subjects across categories of main outcomes'. In some of the few examples of NI-PASS reports available, these have been interpreted as referring to outcomes such as pregnancies. However, when the guidance text says 'numbers of subjects' this perhaps suggests that patient results *per se* should not be included here (contrary to what the heading implies). Moreover, there are other sections where outcome results can be included (e.g., 'Main results' and 'Other analyses'). So another interpretation would be that this subsection could be used as the equivalent of the section 'Analysis populations' in an ICH-based CSR.

The last subsection of the Results section is 'Adverse events/adverse reactions'. Detailed guidance is given for this particular subsection. A clear, well-structured subsection here will, for example, enable ready incorporation of data into a Periodic Safety Update Report. This section will likely closely resemble the adverse-event-reporting section of an ICH-based CSR.

Discussion

For many ICH-based CSRs, the standard advice is to keep the discussion section brief and fairly non-committal, the argument being that higher level documents such as the clinical overview are more appropriate places to relate the study findings to the rest of the clinical development programme and the literature. However, an NI-PASS report does not form part of a clinical development programme and so may be more likely to be read in isolation. Moreover, in the case of NI-PASS reports, the discussion section is structured into four subsections (key results, limitations, interpretation, and generalisability). It is thus more difficult to avoid involved discussion.

As with the results section, this part of the final study report will be easier to write if the protocol has been written in the NI-PASS template. For example, the 'Limitations' subsection can largely be based on the 'Limitations of the research methods' in the protocol, embellished with *post hoc* knowledge and understanding gleaned from the results. Most observational studies will be subject to similar limitations (e.g., bias) and similar strengths as well (greater applicability to clinical practice, a point that is specifically addressed in the 'Generalisability' subsection).

Appendices and annexes

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

NI-PASS: past, present, and future

When the PRAC was established, NI-PASS were plucked from relative obscurity and given a much more prominent role. At present, the reporting of these studies according to the mandated format is still a relatively new undertaking for many companies. The guidance is also evolving, so it is advisable to check the EMA website occasionally (Home>Human regulatory>Pharmacovigilance>Post-authorisation safety studies at http://www.ema.europea.eu) for new developments. With time, a consensus will likely emerge as to how to approach NI-PASS reports, although the wide range of possible study types may slow this process down. I emphasise that my interpretation for the particular case of observational studies here is just that, an early take on how to best follow the guidance when reporting an NI-PASS. For the most part, common sense, along with drawing on analogies from ICH-based CSRs, should be sufficient to produce a report that is fit for purpose.

Author information

Greg Morley A chemist by training, but starved of career opportunities in Spain, Greg Morley made the switch first to translation and editing, and then medical writing. He now has more than 15 years of experience as a medical writer. He is currently working as an embedded contractor with a major pharmaceutical company.

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Writing publications for advisory boards

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Abstract

Medical communication publications are designed to raise awareness of medicines, cosmetics, and technology. These publications ensure that doctors are informed about the role of new and existing medicines and the literature concerning appropriate prescription for specific patient groups. With the increasing choice of medicines available today, practical guidelines and recommendations are increasingly needed to help practicing clinicians to choose the most appropriate product for their patients. Advisory boards, consisting of clinicians, with a solid experience in a specific therapeutic domain, are well placed to provide this advice. The pharmaceutical industry often supports independent advisory boards to consider current issues in patient care and communicate their opinions on how to best deal with these problems. Medical writers are well placed to be involved in advisory board management. They ensure the quality of this type of communication as they have a solid understanding of science and the ethics, standards, and regulations required for medical publications.

Keywords: Medical communications, Advisory boards, Product lifestyle management, Publications

Medical communications publications are peer-reviewed articles meant to communicate specific clinical experience and recommendations about the use of different medicines, cosmetics, medical techniques, or technologies. Once the registration studies are published and a product or technology is launched on the market, many sponsors continue to publish studies and guidelines to support their product throughout its 'life cycle'.

These publications are one of many tools used to implement medical communication (medical marketing) strategies. The publication may be promotional, or it may seek to change prescribing habits or improve clinical management for patients. For example, a sponsor may wish to support the use of their product in a combined treatment regimen. An advisory board publication may extend what is provided in the clinical trial publications and may suggest the use of a product or technique in a specific clinical setting or patient population.

Communicating recommendations or guidelines can also be a useful tool for changing prescribing habits and improving treatment practices when newer more effective products exist or when different products or practices vary between countries or regions. Patient outcomes can also be improved by harmonising the treatment of specific patient groups or the appropriate use of different products, techniques, and local practices. Medical communication publications thereby add clinical experience to the bank of clinical or epidemiological data in a given field.

Advisory boards

An advisory board is composed of a group of experts in a given field from one or several countries. These experts are also often referred to as key opinion leaders (KOLs). KOLs are usually practicing clinicians with a significant level of research experience who like trying new ideas, techniques, or technologies to improve the treatment of their patients. Therefore, KOLs are often involved in international trials and regularly attend and speak during international conferences. In their country or region, KOLs are seen as leaders. They willingly share new ideas or their experience within their own hospital but also are called upon to speak locally or internationally.

Advisory board publications

Manuscripts produced by advisory boards are often sponsored by industry. Although their primary objective is to communicate a given scientific or medical opinion about a product or therapeutic class, they may also have an element of promotion or be related to a particular stage in a product's lifecycle. Following registration, a board may be asked to discuss their local experience or to suggest appropriate use in a multiproduct regimen with locally registered products, which may differ between

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countries. Later in the product lifecycle, an advisory board may be asked to discuss their 'off label' experiences and suggest further studies for other patient groups or the combined use of a given product with other marketed products. Often, advisory board members have had considerable experience with a given treatment and may be asked to reflect upon better or different ways of using these products. In some cases, they may even go as far as suggesting that an older therapeutic class or practice be stopped or replaced by more effective treatments. Sometimes an advisory board may be asked to consider the management of known side-effects associated with a therapeutic class. Also, they might be interested in sharing specific local knowledge or practice with the international community.

The role of the medical writer in preparing advisory board publications

Medical writing for advisory board publications requires not only solid knowledge about the clinical trial process but also a feeling for pharmaceutical marketing strategy and product lifecycle management. Therefore, medical writers who do this kind of work must keep up to date with competitors in a field and must constantly be on the lookout for partnerships and positioning opportunities for their clients. In addition to professional medical writing skills, the medical writer must be comfortable communicating with KOLs and with medical and marketing managers from pharmaceutical companies. They also need to be good public speakers because they may be called upon to lead a group through an agenda to reach a consensus or to work with the board to define the most appropriate kind of publication to meet their needs.

Although advisory board meetings are often industry-sponsored, the board members' opinion should always remain *objective* and be based, where possible, on the published literature or solid clinical experience. Should there be a lack of data in a particular area, it is acceptable to make reference to the consensus based upon the group's experience. The medical writer or the medical communications team will need to communicate with both medical experts and the sponsoring client to produce a fair and balanced manuscript, fit for a peer-reviewed publication. The medical writer must also ensure that the manuscript is produced in line with good publication practices.

In Europe, medical writers who are multilingual are at an advantage because, during advisory board meetings, local experience and medical culture and practices may be discussed in the local language. A multilingual medical writer can understand the discussions and later transpose the results into English for communication to the international medical community.

The activities of the medical writer may differ according to their level of experience and according to whether they work within an agency, as part of a consulting network, or independently as a freelancer. Below is an outline of some activities that a medical writer could consider when involved in writing publications for advisory boards.

Before the meeting

- In collaboration with the client, organise the literature review and define the search strategy, key words, and so on. Identify key references and recognised authors in the field. *It might be more important to listen to your client carefully than impose your opinion.*
- Define the consensus methodology. Some standardised methods exist for developing a consensus, such as the DELPHI process, but the group can choose or define their own voting method, as long as the decision-making process is clearly defined in the methods.
- Define the key messages and key data to be communicated in the article. *Consider why and for whom you are writing.*
- Invite the board members, book the meeting room, and discuss with the client the appropriate internal people to invite. *Try to keep the number of sponsor-related personnel in the room to a minimum to ensure that the discussion remains objective.*

During the meeting

- The medical writer or representative may be asked to co-chair the meeting. This can be useful to ensure that the agenda is followed, that the meeting remains on time, and that the key points are addressed and conclusions reached.
- Capture key action points for each board member and define their roles and responsibilities in the project.
- Capture key messages for the experts who wish to communicate on the topic. *Listen to the 'story' they want to tell. This will form the backbone of the publication. Usually advisory boards know what story they want to tell!*
- Check that there is a literature or defined 'experience' to support each key message.
- Suggest a draft title for the article.
- Suggest a name for the group, particularly if they will continue to publish on the same topic. *Having a name for the group makes it easier to recognise them later.*

- The medical writer may also be asked to write up minutes or action items from the meeting, particularly when key action points need to be followed up.

After the meeting

- Write up the minutes or key action points. Ensure all board members know what they have to do … and when!
- Communicate with each member to follow-up on action points and timelines.
- Prepare a detailed outline with key references for each point.
- Obtain agreement for the outline from both board members and the client.
- Start writing the first draft of the publication.
- Manage the various rounds of changes and cope with the client's opinion. *Sometimes it is important to be thick-skinned and let your work be pulled apart by the client, and sometimes the client needs your lead to get the publication up to standard. It is the medical writer's responsibility to ensure that the client and authors are aware of Good Publication Practices.*
- Assist the corresponding author to ensure that all necessary documentation is available for article submission (e.g. conflict of interest forms, etc.).

Conclusion

Writing medical communication publications is a challenging and rewarding speciality. These publications, which are based on advisory board meetings, ensure that practicing clinicians around the world are kept up to date with recent medical literature combined with the benefit from years of practical experience from experts. Medical writers who do this work act as an interface between the forefront of science and talented professionals from all walks of medical science. This specialty requires creative thinking, strong professional and interpersonal skills.

Author information

Amy Whereat Having both health science and marketing qualifications, Amy Whereat has pursued a career in medical affairs and international product management for the pharmaceutical industry, first in Australia, later in France. Amy is based in Paris, where she is a medical writer and communications consultant for industry and research partners worldwide.

AIDS researcher charged with fraud

A 2010 article in *PLoS Medicine* called for guest authors of ghostwritten articles to face fraud charges.[1] While it is uncertain whether that will ever happen, the summer of 2014 did see the arrest and prosecution of a US-based researcher for scientific fraud.[2]

Korean-born Dong-Pyou Han is alleged to have faked experiments on a new HIV vaccine at Iowa State University.[3] The experiments, which seemed to show a strong antibody response to part of an HIV glycoprotein, raised hopes of a breakthrough in the fight against HIV infection. Though Han resigned from his university post in autumn 2013 and entered into a voluntary exclusion agreement barring him from receiving federal funding for 3 years, he denies the charges against him.

The case has provoked debate as to whether scientific fraudsters should face legal proceedings. It also raises other interesting questions. Should perpetrators be banned from research? Should they repay any funding awarded based on fake findings? Should their institutes be held financially liable?

The answer to some of these questions would appear to be 'Yes'. The National Institutes of Health (NIH) paid out a total of $5 million based on a grant application and progress reports that partly relied on data Han is alleged to have falsified. Of this amount, Iowa State University has agreed to repay nearly $500 000 that went towards Han's salary.[4]

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Peer review fraudster busted

What's the best way to ensure your manuscript gets a favourable review? Do the review yourself, of course. Just don't get caught.

In a case that saw SAGE Publications retract 60 articles published in *Journal of Vibration and Control*,[1] Taiwanese researcher Peter Chen suffered the consequences of being found out. In 2013, SAGE and then Editor-in-Chief of *JVC* Professor Ali H Nayfeh became aware of irregularities surrounding a number of articles, two thirds of which were co-authored by Chen. Specifically, they found evidence that Chen had created multiple accounts with different email addresses in SAGE's online submission system. This enabled him to review his own papers under false identities.[1]

SAGE and Professor Nayfeh confronted Chen and, unsatisfied with his response, contacted his institute, the National Pingtung University of Education (NPUE) in Taiwan. NPUE began to investigate Chen, who subsequently resigned. It is not known how many other people were involved or who they are. SAGE was unable to verify any of the 130 email addresses implicated in the scam.[1]

The Chen case follows a similar saga in which South Korean scientist Hyung-In Moon had 35 articles retracted for much the same reason.[2,3]

The opportunity to cheat the peer review system in this way arises from journal editors asking authors to nominate peer reviewers. This in turn is a consequence of the difficulties many editors face in finding people to review submitted manuscripts. While I do sympathise with the editors, the onus is on them to verify the identities of the reviewers they enlist.

The Chen and Moon cases were both reported by Retraction Watch,[4] a truly fascinating blog dedicated to exposing researchers who break the rules to get ahead. Among other malpractices, it presents disturbing yet instructive cases of ghostwriting, plagiarism, data fabrication, and image manipulation. Anyone looking for a disincentive to cheat need look no further than this catalogue of ruined careers and damaged lives.

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The EMWA Budapest Working Group: A 2-year collaboration to make recommendations for aligning the ICH E3 guideline with current practice and developing clinical study protocol guidance

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Abstract

International Conference on Harmonisation (ICH) E6 and ICH E3, developed nearly 20 years ago, are the current regulatory guidance documents for developing clinical study protocols (CSPs) and clinical study reports (CSRs). Ambiguity in the guidelines, and recent public disclosure requirements mean that review and revision of these guidelines is warranted. In May 2014, EMWA assembled a group of experts, called the Budapest Working Group (BWG), and initiated a 2-year collaboration with a variety of stakeholders to review the two guidelines. The resulting recommendations should address the needs of the widest possible community; incorporate developments since the guidelines were first issued; and facilitate responsible clinical trial data sharing. In this first of three planned open-access publications, we explain the objectives of this project, present our 2-year project plan, and report on progress to date.

Keywords: Budapest Working Group, Clinical study report, Clinical study protocol, ICH E3, ICH E6, Regulatory guidance, Reporting, Responsible clinical trial data sharing

Nearly two decades have passed since the International Committee on Harmonisation (ICH) issued regulatory guidance documents for developing clinical study protocols (CSPs) and clinical study reports (CSRs), respectively ICH E6 and ICH E3. Since then, the evolving context of global pharmaceutical research and development and their applications means that review and revision of these guidelines is now required.

Public disclosure and transparency of clinical trial data

Despite the global drive towards public disclosure of clinical trial results,[1–3] underreporting of trials registered on the US FDA's http://www.ClinicalTrials.gov occurs.[4] For the 53 new medicines approved by the European Medicines Agency (EMA) in 2009–2011, nearly three-quarters of the related results were disclosed within 1 year of trial completion or regulatory approval, and nearly 90% by 31 January 2013.[5] Voluntary publication of trial data, combined with publication of summary clinical trial results on the EMA's EU Clinical Trials Register (http://www.clinicaltrialsregister.eu), has undoubtedly enhanced public disclosure and transparency in the EU. The EMA policy on publication of clinical data for medicinal products for human use, effective 1 January 2015,[6] will strengthen this trend by mandating stepwise disclosure of clinical data submitted under the centralised marketing authorisation procedure in the EU.

Current guidance for developing clinical trials and reporting results

The topics for inclusion in a CSP are described in Section 6 of the ICH Guideline for Good Clinical Practice E6 (ICH E6)[7] and more recently in the SPIRIT (Standard Protocol Items: Recommendations

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for Interventional Trials) initiative,[8] and the 2014 EU Clinical Trials Directive No. 536[9] (effective May 2016) Annex I section D, both of which provide a more extensive list of contents. The regulatory and ethical basis for writing CSRs is grounded in Section 5.22 of the ICH E6 guidelines, and authoring guidance is given in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).[10] Although ICH E3 and ICH E6 were developed simultaneously and were issued in 1995 and 1996, respectively, certain sections of the two documents conflict and some parts of ICH E3 are ambiguous. As a result, information necessary for reporting a clinical trial may not be adequately captured at the beginning of the study and the guidelines are often interpreted when the results are reported. Brevity in current E6 guidance means there is potential for developing more detailed interpretational CSP guidance that will better support CSP preparation as well as subsequent clinical study reporting.

Since 1995, there have been isolated and incomplete attempts to clarify reporting guidance for CSRs, both regionally, through EMA's 2004 guidance on adapting appendices for CSRs included in marketing authorisation applications (MAAs),[11] and globally, through ICH's 2012 supplementary questions and answers document.[12] Furthermore, a consolidated presentation of updated CSR authoring requirements was published in 2014.[13] The 2014 EU Clinical Trials Directive No. 536[9] Annex IV, Section A lists items to be included in publicly posted results summaries which, if integrated into CSR synopsis guidance, could create efficiencies. No formal revision and reissue of the original ICH guidance documents for developing CSPs and CSRs has occurred to date.

Considerations for the next 20 years and beyond

Regulatory and technical developments over the past 20 years, combined with recent initiatives to enhance the transparency of clinical trial data, mean a review and possible revision of the existing ICH guidelines for CSPs and CSRs are necessary.

Objectives

Review and suggest adaptations to existing guidance text in ICH E3 and develop recommended detailed guidance text for CSPs

ICH E3 is a guidance document, not a template. It should be interpreted flexibly to produce a CSR tailored to the individual study.[10] ICH E3 provides a framework for distilling voluminous study data into comprehensible CSRs that integrate with other documents in the full dossier submitted to regulatory authorities for review. Although regulatory reviewers may be most interested in the summary and overview documents derived from the CSRs, the dossier must be based on well-prepared individual CSRs. However, some aspects of the ICH E3 guidance are ambiguous. This leads to varying interpretations and, ultimately, different ways of reporting the data.

A *de novo* review of ICH E3, conducted by current end-users, will provide recommendations to minimise ambiguity. The end product should not be a complete rewrite of the ICH E3 guideline because it generally suits its intended purpose. As ICH E3 links to many other guidance documents, including ICH E6 and other industry processes and procedures, the recommendations must anticipate a possible 'domino effect'. Oversight review of the *de novo* review recommendations will ensure appropriate handling of broader issues with collateral impact. Ultimately, stakeholder evaluation and support of the combined *de novo* and oversight reviews will ensure that the final recommendations address the needs of the widest possible community. As CSP guidance must address some CSP components that ultimately feed into ICH E3, a project to develop recommended CSP guidance will also be undertaken.

Consider the increased access to CSPs and CSRs

Historically, the primary audience for CSPs and CSRs comprised investigators, industry insiders, and regulators. The Pharmaceutical Research and Manufacturers of America (PhRMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA) jointly developed Principles for Responsible Clinical Trial Data Sharing, which were implemented on 1 January 2014.[14]

In addition, the EU's recently introduced disclosure and transparency policy (EMA policy effective 1 January 2015[6]) increases the traditional audience for CSPs and CSRs. Academic and research groups can request access to datasets to attempt to reproduce study results, or they may perform their own analyses. In anticipation of this change, many pharmaceutical companies created websites for requesting clinical study data and established independent adjudication panels to assess the requests and ensure appropriate disclosure.

Public access to CSPs and CSRs requires, above all, that individual study participants cannot be identified from published information. Developing targeted treatments, which focus research efforts on genetically suitable populations – effectively 'personalised medicine' research – will present

challenges. Patients with rare conditions enrolled in small numbers at a particular site may be relatively easy to identify from their data. If an individual's pre-existing conditions are disclosed, this could preclude their eligibility for health insurance cover in some countries. Potentially, clinical trial data could also be used to influence reimbursement decisions in countries with 'free at the point of access' healthcare services or to exclude entire populations from health insurance coverage or state medical aid based on genetic predisposition.

Science and medicine are evidence-based disciplines, where peer-reviewed publication is held in high regard. Cited publications support fact and develop and inform scientific discussion. Professionals, who have Internet, library, and financial resources at their disposal, rarely have difficulties accessing the actual publications from a simple bibliographic reference. To aid transparency and to prevent exclusion of those without institutional resources, the wider audience for CSPs and CSRs must have access to the literature at little or no cost.

Finally, CSRs and CSPs that ultimately progress into a filing within a submission dossier must also continue to meet electronic data standards.[15]

Align CSP content and ICH E3 (CSR content)

ICH E6 and ICH E3 are inextricably linked, so a review of one requires a review of the other.

Currently, ICH E6 guidance for CSP development is minimal and open to interpretation. Detailed CSP guidance needs to be developed to improve reporting, optimise reproducibility, enhance transparency, and protect participants.

Currently, study objectives are often not clearly linked to endpoints. This not only raises issues of reproducibility but also confounds statistical analysis planning and reporting.

There is also no requirement that the rationale of the study design is documented. This is best captured when the protocol is being developed. Protocols are usually developed rapidly, so the responsible multidisciplinary team inevitably focuses on producing a final protocol in the shortest possible time. Recording how and why a particular aspect of a study design develops may be a low priority, but if not captured, can lead to reverse engineering when producing the CSR. A requirement to include rationale for design elements in the protocol will increase reporting accuracy and enhance transparency.

Steps must be taken early in the project lifecycle to meet the requirement for disclosure-ready CSRs. Patient identification numbers must not include a centre identifier that could enable individuals to be identified. Sponsors should be prompted to consider fundamental study set-up issues during protocol design because they lay the foundation for creating a disclosure-ready CSR.

Facilitate clear, fit-for-purpose information sharing

Since ICH E6 and ICH E3 were developed, unwieldy paper-based systems have given way to multiple electronic systems. Information is electronically accessible and shared through professional and social media platforms. Subsequent interpretation and dissemination of resulting insights falls outside the remit of current statutory regulation. Clinical study data must be summarised with absolute clarity and at a level appropriate to support informed interpretation and minimise aberrant claims or criticisms.

To present high-level summary data for regulatory review, detailed data from constituent 'building block' CSRs are typically abstracted and repurposed for regulatory submission summary documents, which include the MAA in Europe, the New Drug Application in Japan and the USA, and the US biologic and device equivalents (Biologic Licensing Application and Product Marketing Application, respectively). The CSR must, however, completely summarise within-study data to allow later simplification. The widespread lack of understanding about this can complicate creation of a CSR. For example, although adverse effects are of ultimate regulatory interest in a submission summary document, the actual numbers of patients experiencing adverse events must first be summarised in the CSR. Ambiguity in ICH E3 guidance about displays of adverse events can lead to CSRs that summarise and report only the numbers of patients experiencing the events without detailing the actual events. This confounds the identification of patterns in event frequencies and compromises the description of individual laboratory abnormalities in the context of adverse events. Upcoming transparency regulations mean that incorrect interpretation of this guideline must come to an end; the guideline must include clear, directive language devoid of ambiguity.

Encourage a streamlined process for disclosure-ready CSRs

Publicly disclosed integrated CSRs will include the CSR text portion (Sections 1–15 in the ICH E3 guideline numbering system), Appendix 16.1.1 (protocol and protocol amendments), Appendix 16.1.2 (sample case report form), and Appendix 16.1.9 (documentation of statistical methods). Patient data listings (Appendix 16.2) will not be disclosed.[6] The summarised data in Section 14 (tables, figures and graphs referred to but

not included in the text) do not typically include individual patient data, although there are some exceptions, namely, listings of death, other serious, and significant adverse events (Section 14.3.2), narratives of deaths, other serious, and certain other significant adverse events (Section 14.3.3), and abnormal laboratory value listing (Section 14.3.4). The data listings to be included in the disclosed sections should conform to current standards for anonymisation[16] with the understanding that these will inevitably continue to develop. Narratives should be moved to a non-disclosed appendix.

Industry is currently debating a two-step process for submitting and then publishing clinical study results. The two-step process involves producing a submission-ready CSR that may contain data that must be removed after submission to produce the final disclosure-ready CSR. We propose that the CSR should be as disclosure-ready as possible from the outset to safeguard against inadvertent identification of participants, assure optimally timed public disclosure of clinical trial results, and be as cost efficient as possible.

Facilitate – not hinder – the process of licensing medicines

Getting safe and effective medicines to market is in the best interests of all parties. The global population needs medicines and their approval should not be hampered by suboptimal data presentation. Regulatory reviewers appreciate clearly written and well-presented documents; clearly presented information helps them better understand the data and may ultimately streamline the regulatory review processes. Optimisations may include tabulating selected data currently presented in narrative form and increasing the use of graphs over summary tables to illustrate trends.

The Budapest Working Group: Methods for reviewing and developing the ICH E3 guideline and developing CSP guidance

In May 2014 EMWA assembled a group of experts, called the Budapest Working Group (BWG), and initiated a 2-year collaboration with a variety of stakeholders to review the ICH E3 and CSP guidelines (including E6). The roadmap for the BWG and stakeholder reviews resulting in final content recommendations are summarised in Figure 1. Briefly, the project comprises four stages.

- Stage 1: Existing ICH E3 guidance will be reviewed and recommended updates developed. New recommended CSP guidance will be developed and then reviewed. These tasks will be performed separately by an EMWA BWG *de novo* review and development team.
- Stage 2: The results of each *de novo* work exercise will be assessed by an EMWA BWG oversight evaluation team to ensure that it meets Good Clinical Practice requirements; transparency/disclosure requirements including responsible clinical trial data sharing; is aligned with the other relevant guidance documents; meets the needs of the international medical writing community; and is globally acceptable and in agreement with industry trends.
- Stage 3: Stakeholders will review the recommendations.
- Stage 4: Comments from stakeholders will be consolidated and integrated into the recommendations.

The outcomes of the stakeholder consultation will form the basis for the second open-access publication originating from this project, which will be published in *Medical Writing* in late 2015. Final content recommendations for ICH E3 and for CSP guidance, agreed by majority consensus with stakeholder parties, are expected to be published in the second-quarter of 2016 in a prominent open-access journal, such as *BMJ Open*. The update and reissue of ICH E3 and the issue of detailed ICH guidance for CSPs including any public consultation processes, are outside the scope of responsibility of the BWG.

Composition of the Budapest Working Group

The BWG collaboration includes professional associations, regulators, and key industry participants with expertise in ICH E3 and ICH E6 guidelines, CSP and CSR templates, and disclosure and transparency issues. In addition to the two main teams (*de novo* review and development team and oversight evaluation team), the BWG also includes a strategist who is working with the partner and stakeholder organisations and an experienced medical writer who is providing administrative support at all stages of the project.

Composition of the de novo *review and development and oversight evaluation teams*

The E3 *de novo* review team comprises five members:

- Two freelance expert end-users of ICH E3 and ICH E6 (SH and DJ) who have a total of 36 years of regulatory medical writing experience and have written for large and small European, American, and Japanese sponsors,

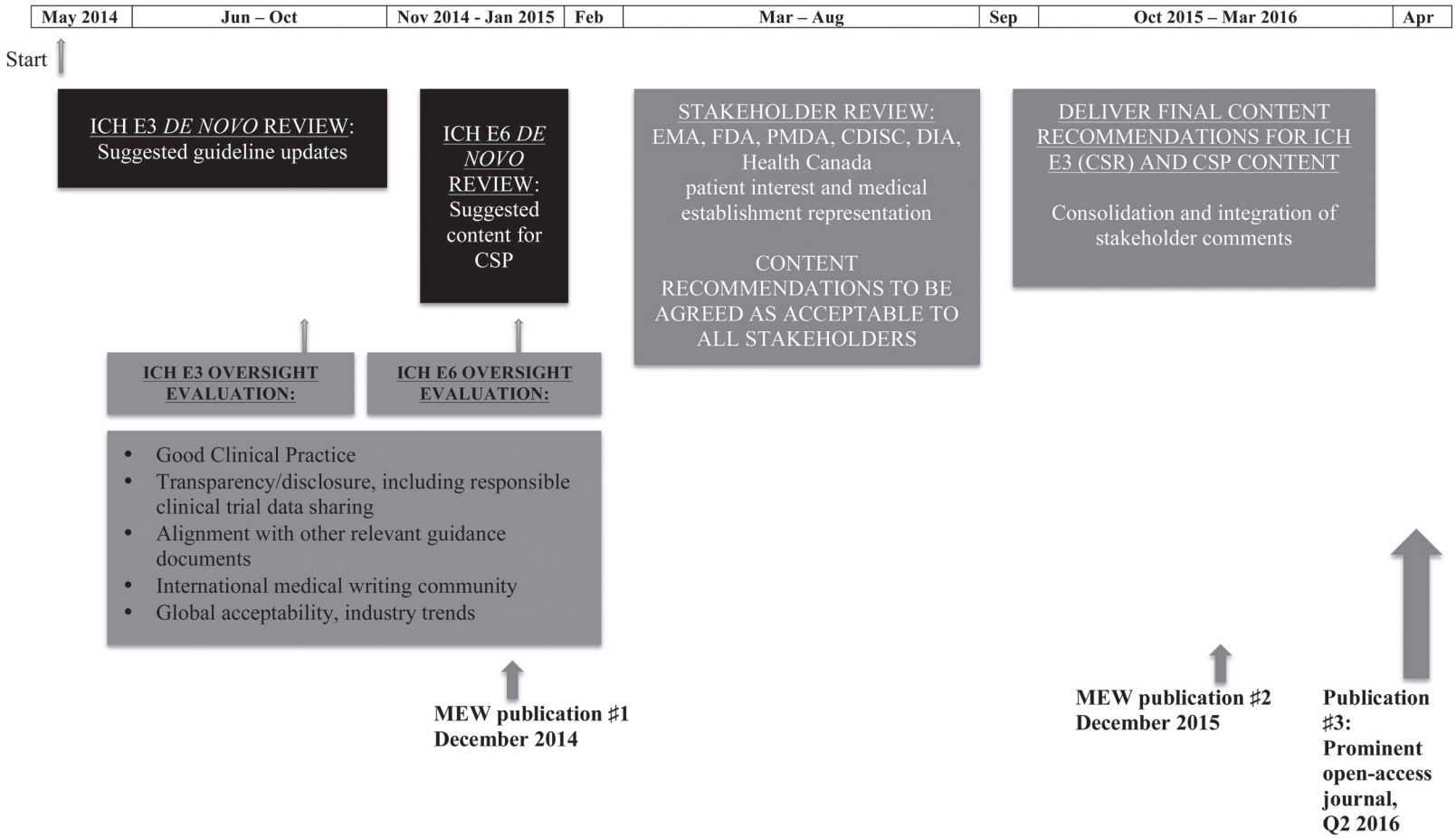

Figure 1: A 2-year roadmap for the EMWA Budapest Working Group *de novo* review and oversight evaluation; stakeholder review; and developing final content recommendations of the ICH E3 (clinical study report) guideline; and developing recommended clinical study protocol guidance.
CDISC, Clinical Data Interchange Standards Consortium; CSP, clinical study protocol; CSR, clinical study report; DIA, Drug Information Association; ICH E3, ICH guideline for clinical study report (CSR) authoring; ICH E6, ICH guideline for Good Clinical Practice, including guideline for CSP authoring; EMA, European Medicines Agency; FDA, (US) Food and Drug Administration; MEW, *Medical Writing*; PMDA, Pharmaceutical and Medical Devices Agency (Japan).

Table 1: Composition of the Budapest Working Group

Name	Affiliation(s)	*de novo* Team Member	Oversight Review Team Member	Position in Budapest Working Group	Focus of Expertise in Budapest Working Group
Sam Hamilton	Sam Hamilton Medical Writing Services Limited (UK) EMWA Vice President	■ E3	■ CSP	Chair Project manager ICH E3 *De novo* reviewer ICH E3 Oversight reviewer CSP guidance	ICH E3 and CSP guidance end user Project management Association perspective – Europe
Debbie Jordan	Debbie Jordan Limited (UK) EMWA member	■		*De novo* reviewer ICH E3 and CSP guidance	ICH E3 and CSP guidance end user
Vivien Fagan	Quintiles (UK) EMWA member	■		*De novo* reviewer ICH E3 and CSP guidance	CSR and CSP reviewer
Anna Shannon	Quintiles (UK)	■		*De novo* reviewer ICH E3 and CSP guidance	ICH E3 and CSP guidance biostatistical sections end user
Graham Blakey	consult2deliver (UK) EMWA member	■		*De novo* reviewer ICH E3 and CSP guidance	ICH E3 and CSP guidance pharmacokinetic sections end user
Tracy Farrow	PPD (UK) EMWA member		■	Oversight reviewer ICH E3 and CSP guidance	Global transparency and disclosure perspective
Walther Seiler	Bayer (Germany) EMWA member	■ CSP	■ E3	Oversight reviewer ICH E3 Project Manager CSP guidance *De novo* developer CSP guidance	Global CSP and CSR templates perspective
Aaron Bernstein	Synchrogenix Information Strategies Inc. (USA) EMWA Past President AMWA member		■	Oversight reviewer ICH E3 and CSP guidance	International medical writing community Association perspective – US
Art Gertel	MedSciCom, LLC (USA) EMWA & AMWA Fellow Think Tank Fellow		■	Oversight reviewer ICH E3 and CSP guidance	Global strategic perspective Regulatory Ethics
Tania Kotsokechagia	Lexis Comms Limited (UK) EMWA member			*Ad hoc* support	Administrative/medical writing project support

including pharmaceutical companies, contract research organisations (CROs), biotechnology companies, and academic institutions
- One member (VF) experienced in reviewing CSRs and protocols from a medical writing CRO perspective
- An experienced biostatistician (AS) working for a CRO responsible for statistical authorship and review of CSPs and CSRs
- An experienced freelance clinical pharmacologist (GB).

The E3 oversight evaluation team includes:

- A pharmaceutical company CSR and CSP template expert (WS)
- A CRO transparency and disclosure expert (TF)
- A consultant with expertise in global regulatory standards and industry trends (AG)
- Representation from the American Medical Writers Association (AMWA) (AB).

Teams will remain the same for the CSP project, except for SH and WS who will exchange roles, SH to the oversight evaluation team and WS to the *de novo* development and review team. WS will develop the CSP guidance that will be subsequently reviewed by DJ and VF. The members of the BWG are listed in Table 1.

Status of the review

Oversight evaluation is now complete for the ICH E3 review and is ongoing for the CSP content recommendations. A package of introductory material has been delivered to the stakeholders. The BWG anticipates completing its review and development work in January 2015. Stakeholder review of both documents will begin in March 2015 and will include:

- Regulators in all three ICH regions – EMA, the US FDA, and Japan's Pharmaceutical and Medical Devices Agency (PMDA)
- Regulator outside the ICH region – Health Canada
- Clinical Data Interchange Standards Consortium (CDISC)
- Drug Information Association (DIA)
- Patient interest representation
- Medical establishment representation.

In addition, a number of stakeholders hold cross-organisational positions and contribute expertise and insights from three large pharmaceutical companies; the ICH E3 2012 question and answer working group; and TransCelerate Biopharma Inc. transparency effort.

Declarations

All BWG team members provided their time and expertise on an entirely voluntary basis. EMWA and AMWA generously contributed funding for team meetings throughout the duration of this project. EMWA funded the open-access of this publication.

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Author information

Sam Hamilton, PhD, is a freelance regulatory medical writer with 21 years of experience in clinical and medical writing roles in the pharmaceutical industry. Sam has written numerous protocols and CSRs for all phases of studies for European, American, and Japanese CROs, pharmaceutical sponsors, biotechnology companies, and academic groups over the past 16 years. Sam is currently Vice President of EMWA.

Walther Seiler, PhD, ELS, is a regulatory medical writer with more than 20 years of experience in an international CRO and a global pharmaceutical company. His current responsibilities include the maintenance of his company's templates for CSRs and CSPs.

Art Gertel, BA, BS, MS, PhD, has more than 35 years of increasingly senior-level positions in the pharmaceutical industry and leadership roles in professional organisations, as well as with collaborative efforts focusing on the improvement of the research, development, review, and approval of new therapeutics and diagnostics. He is the Past President of AMWA; a Fellow of both AMWA and EMWA; recipient of AMWA's Swanberg Award; a member of CDISC's Glossary and Protocol Modeling groups, and serves on the Advisory Boards of The International Publication Planners Association (TIPPA) and Hummingbird IRB. Art is a Registered Agent with the FDA, a Senior Research Fellow with the Centre for Innovation in Regulatory Science (CIRS), and has recently established a strategic regulatory consultancy – MedSciCom, LLC.

Profile

An interview with Esther Moreno Barriuso: On some fundamental concerns of medical interpreting

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Interpreting has had a fundamental role in the history of medical knowledge – it calls directly on such concepts as cultural displacement, originality, and orality.

Esther Moreno Barriuso has a deep understanding of medical interpreting concerns. She studied physics at the University of Cantabria (core courses) and Zaragoza (specialty in Optics) in Spain, and at the University of Saint-Étienne in France (as an Erasmus student). She holds a PhD in physics from the Optics Institute (Spanish Research Council, CSIC) and the University of Cantabria and has completed several medical translation and biomedicine courses to enhance her knowledge in this field. In 2011 she obtained a degree in English <> Spanish simultaneous and consecutive interpreting from the Sampere School of Translators and Interpreters, which included several interpreting assignments. She is a member of the Spanish Association of Translators, Copy editors and Interpreters (ASETRAD). We turned to her to address some of the most interesting issues in this field.

Medical Writing (MEW): We tend to speak of written words as 'fixed' or 'stable', even if we know translations may change in time. This concept seems to be not applicable to interpreting, given the oral characteristic of its main process. What are the consequences of this ephemeral output for interpreters at work?

Esther Moreno Barriuso (E.M.B.): Being a translator, aside from being an interpreter, is an added value since the research process and the resources I use in my assignments are basically the same. However, one has to learn to slightly lower one's expectations when it comes to achieving 'perfection' in interpreting: translations can be reviewed, polished up, and improved, but in interpreting there is no second chance: you cannot re-interpret a sentence unless you have made a clear mistake; you have to move forward. Overcoming that sense of frustration is hard at the beginning, especially when you feel ready to produce a good speech but the speaker doesn't cooperate as much as desired. So it is crucial to set for yourself attainable goals and make sure they are achieved: speak in full sentences without hesitation, and convey a clear message, even if something is missed along the way.

An interpreter's duty is to help the audience understand as much as possible, so finding the perfect and most accurate word for a given term is not worth it if it entails underperforming for the next three sentences. You have to keep calm and be practically minded.

MEW: You have worked in a myriad of different situations, including liaison, consecutive*, and simultaneous* interpreting in different fields, such as health economics, haematology, prosthesis, and neurology. In a more challenging setting, you have also interpreted during a coronary artery bypass graft (CABG) surgery procedure. What has been your most challenging assignment and how have you prepared for it?*

E.M.B.: Interpreting inside an operating room during a CABG procedure was certainly one of the most interesting and rewarding situations I have experienced as an interpreter, but it wasn't the most challenging one (the surgery's outcome didn't depend on my interpreting, thank goodness!). If I had to pick the most complex overall scenario, I would choose the November 2013 Conference on West Syndrome (a rare and serious epileptic encephalopathy affecting children characterised by infantile spasms and arrest of psychomotor development). Neurology is for me the most complex medical specialty. The conference brought together the top specialists in the field with parents of children with this disease who were eager to learn about the latest research findings and the therapeutic approaches under development. Bridging these two groups was a huge responsibility for us interpreters. We were only given the abstracts but not the presentations themselves, and our interpreter's booth was located on stage but behind the curtain. We saw what was happening on stage through a low-resolution CCTV monitor, which meant that in those cases where the slides' font were not big enough, we didn't even get to make out what was written on them.

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The way I prepared for this assignment was similar to any other interpreting project: do as much advance research and reading on the subject as possible, from patient guides to medical publications, create a comprehensive glossary on the condition, do a web search for videos of the speakers – so as to get familiar with their accent, cooperate with your booth partner* using a team effort approach and make the most of the breaks during the conference talking face-to-face with the specialists who are attending, so as to get a deeper understanding of the current status of the disease. Being curious and being 'nosy' are key for this job!

MEW: What is the most difficult part about the medical interpreting profession in general?

E.M.B.: For me the biggest challenge is always to interpret a speaker who doesn't string his/her ideas together and jumps from one concept to the next one, leaving the previous sentence unfinished. This is certainly challenging and frustrating at the same time, because it prevents the interpreter from wrapping up the speech in a nice manner and from conveying a clear and helpful message.

Regarding specifically the medical interpreting profession, the lack of material to prepare for the assignment makes things much more complicated, since the speakers usually rely heavily on graphs, data, and other visual elements contained in their slides to explain their research's main findings. Moreover, in medical presentations, the slides are usually riddled with acronyms, so having the presentation beforehand becomes even more important. But of course, ideal world scenarios hardly ever happen, so an interpreter needs to learn to calm down and do their best with the resources they have been given without panicking. In this respect, booth mate support and help are also key for the success of the interpreting.

MEW: Would you mind sharing some of the reasons why you enjoy working as an interpreter?

E.M.B.: There are so many of them! It may sound like a trite remark, but the satisfaction of becoming a bridge between people who would otherwise not understand each other is one of the main reasons. And this feeling is most intense when doing consecutive or liaison interpreting, although I know many interpreters don't agree with me. Moreover, to have the chance to peek into worlds I didn't even imagine existed and to learn with each assignment about a new topic is also utterly fulfilling. The social side of interpreting is also an appealing balance for the lonely days I spend translating at home, and its human component is one of the most gratifying aspects of this profession: meeting interesting people who leave a deep impression on you, getting to know excellent booth mates from whom I have learned an awful lot – I haven't really had any terrible experiences in this respect – and being thanked for the work you have done; that is something that seldom happens when you are a translator. And to top it all, the thrill that precedes the microphone turning red (i.e. ON) is something I also enjoy.

E.M.B. has given us a broad view of what medical interpreting entails, and it really seems to be a demanding – but also very rewarding job. We thank her for this contribution!

Esther Moreno Barriuso can be contacted at interpretando@moreno-barriuso.com; http://about.me/esthermoreno

Definitions of terms

Simultaneous interpreting
The interpreter works in a booth in turns with at least one colleague. The speaker in the meeting room speaks into a microphone, while the interpreter renders the message into his/her microphone almost simultaneously.

Consecutive interpreting
The interpreter sits or stands together with the delegates, listens to the speech and renders it in a different language after the speaker has finished, generally with the aid of notes.

Liaison interpreter
Liaison interpreting is one mode of interpretation where the interpreter enables fluid communication between two parties. This technique is less formal than consecutive interpretation and is best suited to casual business meetings, working groups, and other dynamic events where there are no more than two working languages, as it provides a greater level of reactivity.

Booth partner
Interpreting is a very demanding task and this is why typically two interpreters work as partners in a single booth and take turns every 30 minutes or so; the one who is not interpreting doesn't simply rest, but helps his/her booth partner with glossary searches, figures, particularly complex terms, etc.

English Grammar and Style

Revising medical writing
Backtracking, pronoun-induced
Part 1 – Semantic revision

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Introduction

Pronouns are useful referents (i.e. the thing doing the referring) to avoid repetition of words (usually nouns). Although personal pronouns (he, she, and I, in particular) are infrequent in medical writing, the neutral 'it' and the demonstrative pronouns (singular, 'this and that'; plural, 'these and those') are common. However, the personal pronoun 'it' and the demonstrative pronouns invariably cause us to backtrack: to refer back to previous textual information (an antecedent) to find out what the pronoun is replacing. Backtracking impedes immediate comprehension of the text, especially when the antecedent is an entire sentence.

There are techniques for eliminating the personal pronoun 'it' and the demonstrative pronouns. These techniques may be semantic, syntactic, or both. Eliminating the neutral and demonstrative pronouns will help the reader by improving clarity, thereby eliminating a distraction to immediate comprehension.

There are four main techniques for eliminating personal and demonstrative pronouns: semantic revision, single syntactic unit revision, double syntactic unit revision, and syntactic position revision. In the first of three articles on backtracking pronouns, we examine semantic revision, i.e. replacement of pronouns by words with explicit reference to an antecedent. The examples are from graduate student writing in the course 'Systematic research writing'.

Example 1: 'It' in the subject position of a contiguous sentence

The example is taken from an Introduction section, research problem context:

> *The Dynamic Marble Size (DMS) algorithm is a market-inspired distributed algorithm for solving difficult combinatorial resource allocation problems.* ***It*** *represents both tasks and resources as agents.*

The personal pronoun 'it' could refer back to 'Dynamic Marble Size algorithm' but 'it' could equally refer to 'a market-inspired distributed algorithm' without changing the meaning. We can assume that 'it' cannot refer to 'difficult combinatorial resource allocation problems' because the plurality of the statement excludes the singular 'it' as the referent. The suggested revision is an already stated abbreviation of the antecedent. The suggested revision is:

> *The Dynamic Marble Size (DMS) algorithm is a market-inspired distributed algorithm for solving difficult combinatorial resource allocation problems.* ***The DMS algorithm*** *represents both tasks and resources as agents.*

Note also that by using an abbreviation, we avoid monotonous repetition of 'Dynamic Marble Size'.

Example 2: 'It' in the subject position of an independent clause of a complex sentence

This example is from a Discussion section, limitation-counterargument:

> *Although this* ***sample survey*** *of current physical therapy outpatients may not translate to the general population,* ***it*** *does support development of such a service.*

The backtracking introduced by 'it' can be avoided by repeating the antecedent as an attenuated form:

> *Although this* ***sample survey*** *of current physical therapy outpatients may not translate to the general population,* ***the survey*** *does support development of such a service.*

Example 3: 'This' in the subject position of a contiguous sentence

This example is from the Introduction section, justification for hypothesis and hypothesis:

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These infants are less likely to engage in object manipulation, body exploration, midline activities, and upper extremity weight-bearing postures. ***This*** *may affect neural connectivity.*

It is not clear what ***this*** refers to. The intention of the author was to refer to the lower likelihood of infants engaging in all four of the activities in the list. Therefore, replacing 'This' with 'These decreased engagements' eliminates any doubt about the antecedent of 'this':

These infants are less likely to engage in object manipulation, body exploration, midline activities, and upper extremity weight-bearing postures. ***These decreased engagements*** *may affect neural connectivity.*

Notes

(a) We need to use the word 'these' rather than 'this' because there are several antecedents.

(b) The expression of 'these' in the present is dictated by the context of the present tense of the predicate ('are less likely') in the first sentence.

Summary

Three semantic revision options are useful for revising sentences containing the backtracking personal pronoun 'it', and the demonstrative pronoun 'this': (1) an abbreviation, (2) an attenuated antecedent, and (3) a term that renames the antecedent(s).

The next article will examine four options for revising 'Backtracking, pronoun-induced' sentences by a single syntactic unit revision.

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News from the EMA

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The articles included in this section are a selection from the EMA's news and press release archive for March–June 2014.
More information on the work of the EMA can be found on its website: http://www.ema.europa.eu.

European Medicines Agency agrees policy on publication of clinical trial data with more user-friendly amendments

12 June 2014 – The European Medicines Agency Management Board on 12 June 2014 agreed the policy on publication of clinical trial data, together with more user-friendly amendments proposed by EMA Executive Director Guido Rasi, that will not only allow the Agency to proactively publish clinical trial data that are submitted as a part of marketing authorisation applications, but also give the possibility to download, save, and print the trial data for academic and non-commercial research purposes.

In light of discussions at the Board, the wording of the policy, including practical arrangements for academic and non-commercial research users, will now be finalised with a view to its adoption by the Board through written procedure by mid-July 2014, and will be effective from 1 October 2014. Importantly, the Agency will ensure that the policy will not prejudice citizens' rights under existing access to documents legislation and the new clinical trials regulation.

Since embarking on its plans for the proactive publication of clinical trial data, the Agency has aimed to achieve the broadest possible consensus among its stakeholders and their often competing views and interests. After an extensive consultation phase that took place between June and September 2013, the Agency carried out a second round of targeted consultation in May 2014 that showed broad support for the policy, but highlighted concerns over the proposed view-on-screen-only access.

The Agency's policy is an important step forward towards achieving increased transparency in the regulation of medicines in Europe. It takes the Agency beyond its legal obligations and provides an unprecedented level of access to clinical trial data that are used as a part of decision making for new medicines.

Regulatory information – Companies now required to update, complete, and improve quality of information on authorised medicines submitted to the European Medicines Agency

16 June 2014 – From today, the European Medicines Agency requires marketing-authorisation holders to update the information on authorised medicines that they have submitted in accordance with Article 57(2) of the 2010 pharmacovigilance legislation.

This includes completing previously submitted information with additional data elements included in the new data-submission format, bringing medicine information up-to-date, and checking that the quality of the information is in line with the updated reporting requirements.

Companies need to complete this process by the end of 2014.

The additional elements that are now required include:

- the details of the legal basis of the marketing authorisation;
- a description of the medicinal product type based on controlled vocabularies;
- information on the authorised pharmaceutical form and before reconstitution into the 'administered' pharmaceutical form;
- a description of the size of the marketing-authorisation-holder company.

From today, the data submission system will only accept submissions that are in line with the updated data-submission format. From July 2014, the Agency is planning to begin a systematic review of the quality and integrity of the information submitted, to ensure that it is accurate and up-to-date.

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This information on medicines is being used to support pharmacovigilance data analysis, to facilitate medicines regulation and fulfil regulatory actions and legal obligations, and to strengthen communication with the Agency's stakeholders and partners. By streamlining the identification of products relevant to pharmacovigilance procedures, this database is expected to simplify adverse reaction reporting for marketing-authorisation holders and ensure that fees are calculated accurately.

Since January 2014, the Agency has been releasing guidance documents to support marketing-authorisation holders in these tasks. These include updates to the legal notice, detailed technical guidance, a data quality control methodology, and controlled vocabularies.

The Agency has also published two new guidance documents today concerning the splitting of the full presentation names and substance names best practice.

In addition to completing previously submitted information, marketing-authorisation holders need to continue to submit information on new marketing authorisations within 15 calendar days from the date of notification of the granting of the marketing authorisation by a regulatory authority. If companies using the EudraVigilance Gateway to submit data cannot provide this information within this timeframe because of the schema changes, they should inform the Agency of their expected submission plan by emailing art57submissionplan@ema.europa.eu and provide their name, headquarter ID, volume of data, and timeline for submission.

The Agency has been working closely with representatives of European pharmaceutical industry associations on the development of these measures through the Joint Implementation Working Group. The Group has endorsed all of the aspects related to the planning of and guidance on the data maintenance submission process.

In line with Article 57(2) of the 2010 pharmacovigilance legislation, all holders of marketing authorisations for medicines in the European Union (EU) must submit information to the European Medicines Agency on all medicines authorised for use in the EU and keep this information up-to-date. This includes:

- nationally authorised medicinal products (NAPs);
- centrally authorised medicinal products (CAPs);
- mutually recognised medicinal products (MRPs);
- decentrally authorised medicinal products (DCPs).

Marketing-authorisation holders are also required to submit to the Agency information on all medicines for which they hold a marketing authorisation in European Economic Area (EEA) countries outside the EU (i.e. Iceland, Liechtenstein, and Norway) since the pharmacovigilance legislation has been incorporated into the EEA agreement.

Marketing-authorisation holders were initially required to submit information on all human medicines authorised in the EU by 2 July 2012. Since July 2012, marketing-authorisation holders have also had to submit information on new marketing authorisations granted after 2 July 2012.

Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014

19 June 2014 – As of 21 July 2014, it will become mandatory for sponsors to post-clinical trial results in the European Clinical trials Database (EudraCT), managed by the European Medicines Agency (EMA). This date corresponds to the finalisation of the programming of the database as referred to in a European Commission guideline, in application of the current clinical trials Directive 2001/20/EC and the Paediatric Regulation. Under these frameworks, since the result-related information is fed into the publicly accessible European Union Clinical Trials Register, summary results of clinical trials will become available to the public as sponsors start to comply with their legal obligations.

What this means for clinical trial sponsors

Sponsors will now be obliged to post results in EudraCT for any interventional trials registered in EudraCT and that have ended within a certain period of time:

- For any interventional clinical trials that ended on or after 21 July 2014, sponsors will have to post results within 6 or 12 months following the end of the trial, depending on the type of trial concerned;
- For trials that ended before that date, sponsors will need to submit the results retrospectively, in accordance with the specific timeframe laid out in the above-mentioned European Commission guideline on the posting and

publication of result-related information on clinical trials.

EudraCT already contains protocol-related information submitted by sponsors for interventional clinical trials conducted in European Economic Area (EEA) countries, as well as clinical trials conducted in third countries, when the clinical trial is part of an agreed Paediatric Investigation Plan (PIP). Information on these is already made public in the European Union Clinical Trials Register.

Clinical trial sponsors were encouraged to start uploading summary results on a voluntary basis, when new functionalities were made available in EudraCT in October 2013. This was intended to enable them to get used to this new feature and be ready to comply with the legal requirements.

A further iteration of EudraCT was launched at the beginning of May 2014 with improved functionalities. The scope of the information to be posted in EudraCT has also been extended to include marketing-authorisation holder sponsored clinical trials conducted in third countries that involve the use in the paediatric population of a medicinal product covered by an EU marketing authorisation.

As of 21 July 2014, with the launch of a final iteration of EudraCT, all functionalities will be in place to enable the posting of results by sponsors on a compulsory and systematic basis.

What this means for public access to information on clinical trial results

A subset of the data included in EudraCT is made available to the public in the European Union Clinical Trials Register. The content and level of details of these summary results are set out in the European Commission guideline and in its technical guidance. A number of summary results can already be viewed on the European Union Clinical Trials Register website. A typical set of summary results provides information on the objectives of a given study, explains how it was designed, and gives its main results and conclusions.

In addition, information on paediatric studies that ended before the Paediatric Regulation came into force in 2007, which used to be accessible through the EMA website, is now available through the European Union Clinical Trials Register. This improvement allows a greater and richer approach to the search and greater public access to clinical trial-related information.

It is foreseen that access to summary results will be an essential feature of the European Union Clinical Trials Register for interventional clinical trials conducted in EEA countries, as well as clinical trials conducted in third countries which are linked to European paediatric drug development.

Outcome report on first European collaboration between regulators and HTA organisations: improving the contribution of regulatory assessment reports to health technology assessment

25 June 2014 – The report of an initiative undertaken jointly by the European Medicines Agency (EMA) and the European network for Health Technology Assessment (EUnetHTA) to make regulators' reports about scientific assessments of medicines better usable by health technology assessment (HTA) bodies has been published in *Value in Health*, the Journal of The International Society for Pharmacoeconomics and Outcomes Research.

The article, entitled 'Improving the contribution of regulatory assessment reports to health technology assessments – a collaboration between the European Medicines Agency and the European network for Health Technology Assessment',[1] is authored by staff members of the EMA and representatives of EUnetHTA. This work was the first joint project between regulators and HTA bodies on a European level and is part of their ongoing dialogue to support policy-maker decisions in the future.

Clinical data generated by pharmaceutical companies during the development process of a medicine is the basis for the evaluation of the benefit/risk balance of a medicine for the purpose of marketing authorisation. The same data informs the assessment of the effectiveness of the new medicines compared to existing therapies, as part of the HTA process to support decision making on appropriate utilisation, price, and reimbursement in EU Member States.

The joint EMA-EUnetHTA project responded to a political recommendation to consider how the assessment of the favourable and unfavourable effects of a medicine as contained in the EMA's European Public Assessment Reports (EPARs) can best be used to inform the assessment of the relative effectiveness of new medicines for HTA purposes in EU Member States. As part of this project, the EMA and EUnetHTA developed an improved structure and presentation of key information with the view to increase clarity and transparency of the outcome of the scientific-review process as reflected in the EPARs.

'With the improved presentation of data and information in the EPAR it is envisaged that this

regulatory document through harmonised efficacy data presentation will be more useful in the context of rapid relative effectiveness assessments by HTA bodies when they inform policy makers and healthcare decision makers in the future', explained the authors.

Beyond the EPARs project, the EMA and EUnetHTA are continuing to explore other areas of collaboration or exchange of information. These include ways for sponsors to obtain scientific advice or early dialogues with regulators and HTA or payer bodies, discussions and exchange on scientific and methodological guidelines, exploring opportunities of exchange on regulatory assessments in view of subsequent HTAs, post-licensing data generation and the specificities of orphan medicinal products. Regular meetings are held between EMA and EUnetHTA, most recently on 15 May 2014. Minutes from these meetings are made available on the websites of both the EMA and EUnetHTA, as is the joint 3-year work plan.

The value of cooperation between regulators and HTA bodies has a real potential to reduce the time for a medicinal product to reach patients. It also has potential to reduce development costs for sponsors by shaping medicines development programmes so that they generate data relevant for the needs of both regulatory authorities and HTA bodies.

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Management Board delays formal adoption of European Medicines Agency publication of clinical-trial-data policy to October 2014

9 July 2014 – The Management Board of the European Medicines Agency (EMA) has postponed formal adoption of the policy on publication of clinical trial data to its 2 October 2014 meeting. Further clarifications on wording and practical arrangements will be discussed by Board members, who have confirmed their general support to the overall aims and objectives of the policy, including the more user-friendly amendments proposed by EMA Executive Director Guido Rasi that would allow data to be downloaded, saved, or printed for academic and non-commercial research purposes.

Further to the agreement reached with the European Commission in accordance with Article 80 of Regulation (EC) No 726/2004, the Board was not able to conclude on the final wording of the policy through a written procedure. Members of the Board have offered additional valuable contributions which will now be considered and addressed in the next few weeks, with a view to reaching final agreement at the next Management Board meeting in October.

The Agency welcomes this additional round of joint reflections and respects all opinions, as well as the views expressed by several Member States, which largely reproduce the complexity of the debate on both political and technical aspects which have emerged during the previous general and more targeted consultation phases. In the last 12 months, the Agency has attempted to strike a balance between proactive data disclosure, the absolute need to protect personal data, and the concerns relating to the protection of commercially confidential information.

The Agency management remains committed to introducing this additional measure towards transparency as soon as possible, so as to enhance citizens' awareness and confidence in the EU authorisation system for medicinal products. The Agency has also underlined several times that the new policy, if approved, will be without prejudice to the provisions of Regulation (EC) No 1049/2001 on access to documents and the new clinical trial Regulation (EC) No 536/2014, which will become applicable in 2016 at the earliest and, as also noted during the debate, will apply to clinical trials conducted in the European Union.

The Agency management is conscious that any delay prevents citizens, and in particular academics and non-commercial researchers, from enjoying the benefits of proactive publication of clinical trial data for a further period. The Agency will continue to work with the Management Board and the European Commission ahead of the 2 October meeting to ensure that members receive the clarifications requested and to facilitate the adoption of the policy.

Guide on methodological standards in pharmacoepidemiology revised to include pharmacogenetic studies

14 July 2014 – The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), coordinated by the European Medicines

Agency, has revised its guide on methodological standards in pharmacoepidemiology and added a chapter on the design and analysis of pharmacogenetic studies.

These studies aim to investigate how individual genetic variations determine the response to a medicine, both in terms of therapeutic effect and adverse drug reactions. They help optimise the prediction of treatment response leading to a better use of medicines.

The new chapter on pharmacogenetic studies provides a comprehensive overview of all relevant methodological guidance for the conduct of pharmacogenetic studies, from the identification of genetic variants through to study design, data collection, analysis, and reporting.

Like the other sections of the guide, this chapter contains web links to internationally agreed recommendations and key points from important guidelines, published articles, and textbooks. It also highlights good practice guidance for the conduct of these studies.

ENCePP is a network of over 170 research centres, existing networks, and providers of healthcare data, whose aim is to strengthen the post-authorisation monitoring of medicines by facilitating the conduct of multicentre, independent, and scientifically robust studies focusing on the safety and balance of benefits and risks.

By offering a single and comprehensive overview of all relevant methodological guidance for researchers in pharmacoepidemiology and pharmacovigilance, the ENCePP guide is a key tool in supporting high-quality post-authorisation studies.

Users can view the guide as HMTL webpages with links to each chapter and section and also as a consolidated PDF version for download.

The guide is updated annually to ensure that all developments in the field are incorporated.

New in *European Science Editing*

Writing in the May 2014 issue of *European Science Editing*,[1] Ernesto Galbán-Rodríguez and Ricardo Arencibia-Jorge take a fascinating look at editorials. Noting their often attractive titles, exciting content, and ability to boost journal impact factors (IFs), the authors also highlight a number of potential cons: lack of peer review, risk of publication bias and editorial conflicts of interest, and excessive self-citation. In a second article,[2] Frank-Thorsten Krell focuses on this last problem, pointing out that Thomas Reuters now excludes any journal it finds guilty of self-citation abuses from its Journal Citation Reports for 2 years. This denies the journal an IF. Krell explores the possibility of journals being unfairly excluded and describes some of the dubious ways in which IFs can be boosted.

Elsewhere in the same issue, EASE (European Association of Science Editors) President Joan Marsh highlights the under-representation of low- and middle-income countries on the editorial boards of psychiatry journals.[3] Journal editor Denys Wheatley draws attention to some of the writing problems faced by non-native English users, bemoaning the lack of courses in scientific writing.[4] And Matko Marušić adds to the ongoing debate about whether to refer to 'gender' or to 'sex'.[5]

Lastly, freelance medical writer Richard Clark tackles the apostrophe, lambasting the European Medical Writers Association for the lack of an apostrophe in its name,[6] a point that was recently addressed in *Medical Writing*.[7]

As well as *European Science Editing*, EASE also produces *Guidelines for Authors and Translators of Scientific Articles to Be Published in English*, which it updates annually. The 2014 update[8] incorporates the recently amended ICMJE (International Committee of Medical Journal Editors) statement regarding what constitutes authorship[9] and the San Francisco Declaration on Research Assessment.[10] Impressively, the guidelines are available in 21 languages. Volunteers are sought for translation into as yet unrepresented languages!

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The Webscout

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The language of marketing

For this Webscout, I decided to leave the path of scientific writing and enter the land of marketing, which goes overall with the theme of post-approval medical writing. However, I will not limit this Webscout to medical marketing and instead take a more general view on language and writing in a marketing context.

Of course, there are numerous examples of marketing-specific terms or words common to marketing with a very specific meaning. The marketing dictionary on the website **Common Language in Marketing: The Global Resource for Defining Marketing Terms and Metrics**

http://www.marketing-dictionary.org/

is a good place to start. It is an open-source encyclopaedia that includes the most important terms used in marketing and is intended for 'anyone interested in the exciting world of marketing'.

But marketing is not solely the terms and definitions. Language is powerful and is exploited to convey marketing messages and influence people. A brand-specific language and tone can be more than helpful to differentiate a product from competitors as described in an article on the website **Marketing Week**

http://www.marketingweek.co.uk/analysis/essential-reads/whats-the-language-of-your-brand/4007277.

According to **Wikipedia**, 'brand language is the body of words, phrases, and terms that an organisation uses to describe its purpose or in reference to its products.'

http://en.wikipedia.org/wiki/Brand_language

'Brand language is used in marketing to help consumers connect specific words or ideas to specific companies or products'. An article on the website **brandchannel**

http://www.brandchannel.com/features_effect.asp?pf_id=281

states that the tone of voice should be consistent not only in marketing messages targeted at customers but also in internal communications.

Sometimes, or rather quite often, marketing messages are completely overblown and rather turned into a meaningless nonsense. The website **Corporate Gibberish Generator™**

http://www.andrewdavidson.com/gibberish/

lets you create your own marketing messages. Sure, this is just fun but, honestly, advertising texts like the rubbish it creates really exist. So how do you know whether your marketing message works? Take the 'Aunt Agnes test' as suggested on the website **MindShare Consulting**

http://mindshareconsulting.com/behind-your-marketing-language/.

Which terms and phrases should be avoided in order not to alienate but rather attract potential customers? An article on **greatwriting blog**

http://blog.greatwriting.com/2013/11/bad-marketing-language.html

gives specific examples of bad marketing language. And which should you use? As explained on the website **about money**

http://advertising.about.com/od/copywriting/a/The-10-Most-Powerful-Words-In-Advertising.htm,

the 10 most powerful words include 'health', 'results', and 'safety'.

But effective marketing writing is not only about the words you use. According to an essay on the **University of Mississippi** website

http://home.olemiss.edu/~egjbp/comp/ad-claims.html,

adwriters usually use a basic set of techniques. When you are able to identify the technique in a claim, you can get an idea of how much truth lies in it. The examples given look quite familiar – you can find claims like them every day. Try out their technique on some of the claims that come to mind. You will never look at advertisements the same way.

Did this Webscout section help you or do you have any questions or suggestions? Please feel free to get in touch and share your thoughts.

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New in *European Science Editing* 2

The August 2014 issue of *European Science Editing* contains a couple of interesting articles on plagiarism. Plagiarism expert Miguel Roig reports the findings of his own analysis of 63 editorials on plagiarism published between 2008 and 2012.[1] Plagiarism was defined in 41% of the editorials, but its definitions varied greatly. Self-plagiarism was frequently covered, but there was no real consensus as to how much recycling of one's own text is OK. Roig identifies two main themes across the editorials: (1) warnings about the consequences of plagiarism and (2) the use of plagiarism detection software. He concludes that journal editors are very concerned about plagiarism and rightly calls for universal guidelines for what should be considered acceptable text recycling.

Roig's piece is complemented by an essay from regular contributor Denys Wheatley, who addresses various aspects of plagiarism.[2] He highlights the contribution of cultural factors to plagiarism; describes the roles of referees and publishers in identifying and dealing with plagiarists; and points out the shifts in writing style that often bring plagiarism to the reader's attention. He ends by offering a potential solution to the problem: better education and training of researchers.

Elsewhere, Karen Shashok explains how authors' editors (editors who help authors to get their work published) can help to reduce wastage in terms of peer reviewers' time and unwarranted publication costs.[3] She further lists ways in which publication officers, journal editors, and publishers can help to streamline the publication process. Finally, Eva Baranyiová uses instructive examples to explore some of the more easily missed referencing errors in draft manuscripts, errors she blames on excessive haste.

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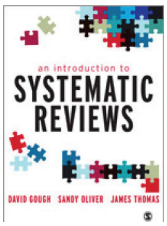

An Introduction to Systematic Reviews
by David Gough, Sandy Oliver, and James Thomas;
SAGE Publications Ltd, 2013.
ISBN: 978-1-849-20181-0.
26.99 GBP. 304 pages.

An informative guide to ensure your systematic review is transparent, repeatable, and accountable

The Cochrane Collaboration (www.cochrane.org) is recognised as a leading organisation promoting evidence-based health decision making through researching and producing independent systematic reviews based on primary research.[1] The authors of *An Introduction to Systematic Reviews* recognise the influence of the Cochrane Collaboration but have developed and extended their own methodology to address what they call participative research, 'where evidence-informed decision making meets stakeholder involvement'. In this book, stakeholders are defined as 'people having some self-interest in a piece of work because they might use the findings, or because decisions made by others in light of the findings may have an impact on them'.

The three authors and nine other contributors of *An Introduction to Systematic Reviews* are based in the Social Science Research Unit (SSRU) at the Institute of Education, London and as such the content of the book is principally aimed at those working in the field of social sciences. However, much of the information in the book is applicable to the systematic review of evidence in health and social care.

The 11 chapters represent the research methods that have been developed and applied by the SSRU over a period of many years when conducting their own systematic reviews. To improve understanding, a useful glossary is provided at the end of the book together with a substantial number of supporting references for the preceding chapters.

A well-structured overview of the common stages required of a systematic review is provided as an introduction and summarised in a flow diagram. The seven stages outlined in the flow diagram then form the basis for the arrangement of the information presented in the remaining chapters of the book. These chapters address formulating the review question and methodology to be used in the systematic review, defining a search strategy, describing study characteristics, assessing study quality and relevance by applying appraisal criteria, undertaking a synthesis of findings from studies to answer the original review question, and finally communicating the findings to stakeholders. The importance of preparing the equivalent of a protocol stating the approach and methods to be used, and producing it before starting a systematic review, is discussed and stressed.

To obtain a meaningful systematic review, the research question, and how to answer it, has to be clear from the beginning. Hence, Chapter 4 of the book describes in detail how to build what is called a 'conceptual framework', which enables several key components to be considered at the beginning of the research. In reviews of medical treatments, this is often achieved via a PICOT framework (an acronym of Population, Intervention, Comparison, Outcomes, and Time) and enough time should be included in the process to ensure that the correct framework has been achieved. The authors point out that only by doing this will the criteria for inclusion and the relevant search strategy be properly developed.

One chapter is dedicated to the importance of information management systems when huge amounts of information are being generated, managed, and accounted for, and another to developing and implementing a correct search strategy. As expected the correct processes need to be in place to allow transparency, accountability, and repeatability, and the authors provide comprehensive information and guidance on how this might be achieved. Critical appraisal of the literature is also addressed and several examples of detailed critical appraisal tools are provided.

Multiple stages are involved when undertaking a synthesis of (or combining) the results. The preliminary stages involve selecting the studies to be included, extracting data, and describing key features of the studies in a well-defined and transparent way. Several approaches for achieving these early stages are discussed in detail.

Once the initial stages have been completed, the selected data from individual studies can then be

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combined. According to the authors, combining the results of the individual studies is achieved by using two main 'modes': configuration and aggregation. The appropriate mode broadly depends on how much the studies differ from each other, i.e. whether they are heterogeneous or homogeneous, which in turn is heavily dependent on the type of question being put forward. Each systematic review has common stages of synthesis but how these are ordered is again dependent on the type of synthesis being pursued and several examples are illustrated. A range of non-statistical and statistical methods for synthesis are presented and discussed.

As a medical writer you will probably work as part of a team involving a statistician to tackle this part of the systematic review. However, it is important to understand the concepts employed if you are going to write about them at a later juncture. This chapter is not for the faint-hearted because, although written to be accessible to a non-statistician, the methods under discussion are not simple, and some prior knowledge of the concepts presented and examined will pay dividends.

Clearly, generating the systematic review is not enough and the best way to communicate the results to a wider population is addressed. How the information is used and what it is used for is discussed and several methods of 'turning knowledge into action' are presented, namely linear push–pull models, relationship models, and system models. Some useful tips on how to communicate with the media are also presented, e.g. include fact boxes and avoid jargon by writing in plain English.

As outlined by the authors, the main audiences for this book are (1) those undertaking reviews; (2) those funding, planning, or undertaking primary research to identify what information is already known and where research needs to be better targeted; (3) those using reviews to better inform decision making; (4) those putting research findings into practice; and (5) stakeholders who are directly affected by research outcomes.

This is not an undemanding introduction to the subject, and readers will need a degree of knowledge or appreciation of this area to fully understand the concepts discussed. However, the book does emphasise what needs to have taken place to result in research deserving of the title 'systematic review', and will be a useful resource for medical writers involved in this specialised area of medical writing.

You might also want to take a look at a workshop presentation on YouTube by Professor David Gough, similarly entitled *Introduction to systematic reviews (I)*, which can be found at http://www.youtube.com/watch?v=apWAql2TQKM.

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Opportunity

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Editorial

In these dark winter months, how many of us have day-dreamed about moving to an exotic, sunny location? Janet Davies describes how she did exactly that when she resigned from her job in Holland and moved to the Azores to start a new life as a freelancer. Alistair Reeves and Suzanne Geercken provide more useful language resources for non-native speakers in the final part of their series, which has filled our bookshelves with many helpful references.

To ensure the long-term success of our businesses, marketing is a fundamental skill that freelancers need to establish early on to attract potential clients and contracts. Following on from his recent webinars, Matt Craven from The CV and Interview Advisors will share his top tips for writing effective CVs. In this the first of a series of articles, Michelle Storm Lane gives her advice on how to build our business profiles, and Fiona Higgins describes how to use social media to our advantage and improve our online presence. Finally, if you're feeling over-worked as you desperately try to deliver pre-Christmas deadlines, take a short break and have a chuckle at our Freelance Foraging photo taken by Kathryn at an equestrian event where they clearly think horses can read.

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Calling all freelancers!

Don't miss this issue in the main journal:

Sam Hamilton's article describing progress to date on the EMWA-initiated 2-year forensics project on ICH E3.

Out on the ocean: Freelancing in the Azores

I live and work on a volcano in the middle of the North Atlantic Ocean. Well, not exactly in the middle, but almost. Check it out on Google Earth, or an old-fashioned globe if you prefer: coordinates 38°35′5″N, 28°48′34″W. There you will find the Azores, a dispersed group of nine volcanic islands – each consisting of several volcanoes – that emerge above sea level where the North American tectonic plate meets the Eurasian tectonic plate at the Mid-Atlantic Ridge.

Rather unimaginatively, I called my business Atlantic Medical Writing. I suppose I could have gone for Volcanic Medical Writing, but then I'd be at the bottom of all alphabetical listings! Here I share with you my experiences of setting up business as a freelancer in a new country.

How did I come to be working as a freelance medical writer here?

The dream began some 7 years ago when my husband and I were pondering our next move. We wanted space, land, better weather than is generally available in Northern Europe, and a good internet connection. We had been looking at central and northern Portugal, then we went on holiday to the Azores. We didn't visit all nine islands – just Faial, one of the central group of five. There we saw houses and ruins for sale, with land and a

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Figure 1: Pico from Faial.

sea view. Prices were a little higher than those on mainland Portugal, but still pretty low compared with anywhere else we had considered. The Azores are part of Portugal, but they are governed autonomously and are in the Eurozone (Figure 1).

Finding our dream home and office

Although we didn't see the house for us on that first visit, we decided that this was where we wanted to be. On our return to the Netherlands, where I was working full time as an Editorial Project Manager for a medical communications agency, we put our house on the market.

Within a week we had a buyer. Within a month the sale had fallen through. Then the financial crisis kicked in, and it took until October 2013 to sell the house.

In the meantime, we had obtained our Portuguese fiscal (tax identification) numbers, which are required for buying property in Portugal, and opened a Portuguese bank account. We kept looking at (and coveting) several houses on Faial, while we were there house- and pet-sitting and meeting lots of new people, building our circles of friends and acquaintances.

Then we saw our house: a ruin (walls mostly intact, no roof) with 8000 m^2 of land, overlooking the sea. We purchased the house and land at the end of 2011 and, early in 2012, employed a local builder to start clearing the debris (and more than 30 years' growth of brambles) from inside the house, rebuild part of one wall, and install steel and concrete reinforcement to keep the house standing during earthquakes. (Did I mention the earthquakes? All part of living on a convergence of tectonic plates. Ours are still moving apart.) Our savings were now all gone and our Dutch house was still not sold (Figure 2).

Setting up the business

In February 2014, we finally moved into a rented cottage on the island, just a minute's walk from our property, so I can work while we establish the kitchen garden and keep an eye on the house renovations. Our ruin now has a roof (Figure 3). I made it clear to our new landlady that the internet must be up and running by the time we arrived, because I already had work booked from my previous employer. So, I plunged straight into freelancing during our first weeks on the island. At that time, storms were battering most of Europe, and many parts of the UK were being flooded. Our weather was just as bad, if not worse, and not conducive to internet connection or even electricity! We got to know our telecoms technician, Antonio, quite well, and amazingly we managed to communicate despite my limited Portuguese vocabulary. Yes, we should have learned Portuguese a long time before we arrived!

Figure 2: The ruin.

Figure 3: The ruin acquires a roof.

More language challenges

In a brief break between projects, I took a Portuguese-fluent friend with me to the tax office to register my business. The tax official referred us to an accountants' office, where we were told I could register as a straightforward single-person business or as a single-shareholder society with 'limited' status. After much deliberation and calculation, I chose the latter option, and my business is officially called Janet R Davies Unipessoal, Lda. I think Atlantic Medical Writing has a better ring to it, but that wasn't allowed by the Portuguese business registration authority. Still, I could register it as my trade name – for an extra fee.

In Portugal, you must specify your business activity precisely, choosing from a long list of possible activities. 'Medical writer' is not one of them. After some discussion, we chose a definition incorporating science, editing, research, and consultation, given that the only 'writer' options come under the 'arts' category. Now that wouldn't do, would it!

My Portuguese-speaking friend was essential at this point because neither the tax official nor the accountant (Sandra) spoke English. The consultation with the accountant was quite a challenge: my friend's Portuguese doesn't stretch to financial jargon, but I suspect I would not have understood any better had the meeting been conducted in English! I was left feeling that I had placed a great deal of trust in people I barely knew. Still, so far – so good.

Paperless office, anyone?

My business was registered through the use of an efficient online system. This was done by a solicitor. The next step in the process – registering at the social security office – was very much less efficient. I went there with Sandra and waited patiently as the guy at the desk used one finger to type in my information. He entered the same information three times. He then photocopied the business-registration document printed out by the solicitor, and finally, once the computer had generated the required social security number, he printed that out and then photocopied it. One for the file and one for me. I discovered later that, despite using an efficient online invoicing system, I too have to print out my invoices and keep the paperwork for 10 years.

Next, off we went to the stationery shop, fiscal and social security numbers in hand, where Sandra instructed me to buy a hardcover, bound notebook (livro de actas) in which she proceeded to write four pages of text, which I had to sign. Apparently, this is some kind of legal declaration about how my business runs – Sandra will have to update it (by hand) every time I make a change to my business (for example, if I decide to give myself a pay rise). Another job done, and I rely on trust yet again. But Sandra is a gem. Our communication is aided by Google translate, and that way I get to spot typos in her Portuguese!

So the administrative aspects of setting up the business have been quite trying. Not only tricky to understand, but also a very slow process involving an odd mixture of old and new technologies and of flexible and totally rigid attitudes of government officials. Perhaps it is the same everywhere.

Still, I am up and running, work is coming in, and I am now in the throes of designing a website and updating my Linked In profile. Although I am not at all confident about marketing my business (and I confess this activity is often pushed to the bottom of my to-do list), I do know one thing – I am probably the only freelance medical writer based on a mid-Atlantic volcano. Could that, perhaps, be my unique selling point?

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A writer's 'best friends' – Recommended language resources for (medical) writers (3)

Admittedly, a self-employed medical writer's job mostly consists of spending hour after hour in the relative isolation of his or her office trying to make sense of puzzling data and converting them into an easily comprehensible, readable (English) text. In the previous contributions in the 'best friends' series, we recommended resources that help you achieve this goal. There are, however, occasions when 'knowing the language' alone will not be enough. What if you have to attend a meeting with your business partner or need to negotiate a contract? In these situations knowing the local rules of conduct, your business partner is likely to observe will be as important as fluency in English.

Susanne remembers, for instance, a situation at her very first EMWA conference:

We were having lunch and the conversation at the table naturally started with people commenting on

the food that was served. This gradually evolved into a discussion about food and cooking in general. The Italian lady I was sitting next to and I as well as several other people at the table got quite involved in the subject, exchanging recipes and calling up memories of fine dishes we had cooked and enjoyed. When I later shared my satisfaction with this inspiring lunchtime conversation with an English colleague, she replied something like: 'Well yes, but I don't actually understand why people in Europe always make such a fuss about food'. This remark made me feel quite self-conscious – since the English colleague had apparently not shared our enthusiasm at all – maybe talking about food and cooking was not as suitable subject for small talk in a multicultural context as I had thought.

In today's instalment of the best friends' series, Susanne would therefore like to entice you to go beyond language alone and explore some of the aspects of intercultural interaction:

To be consistent with the 'best friends' format, restricting my choice of recommended books on intercultural awareness to the English and US cultures is necessarily subjective and prejudiced. Suggestions for further reading involving other cultures are more than welcome.

Watching the English. The Hidden Rules of English Behaviour[1]

Watching the English was recommended to me some years ago by a fellow German translator who is married to an Englishman. Since I am more familiar with US than English culture, I found the book to be very helpful in understanding the English and to appreciate the cultural differences between the UK and the US.

Watching the English is intended to provide us with what the author and anthropologist Kate Fox calls 'the "grammar" of English behavior' (*Watching the English*, p. 2. To be consistent with Kate Fox, I also use the term 'English' rather than 'British' or 'UK' culture. As to a rationale for her choice, please see *Watching the English*, pp. 20–21).

In the introduction, she explains that her analysis of English culture is based on a research method called 'participant observation, which essentially means participating in the life and culture of the people one is studying, to gain a true insider's perspective on their customs and behaviour, while simultaneously observing them as a detached, objective scientist' (p. 3). This method is usually applied to the study of alien cultures, but Kate Fox uses it 'at home'. The result is a charming and highly entertaining mixture of fond personal involvement paired with a well-structured, detailed analysis of English behaviour in everyday situations. She covers every aspect of social life – rules of introduction and of saying good bye, pub talk (quite a long chapter), rules of humour (of course, a must for any foreigner trying to understand English culture), dress codes, rules at work, and everything in between. If this sounds like dry reading, believe me, it is not. Despite her scientific background, Kate Fox's style is unpretentious and entertaining; her vivid descriptions of typical everyday English social interactions make you smile or even laugh out loud. At the same time, she successfully teaches us to deeply appreciate this unique phenomenon called Englishness.

I, for my part, have taken away valuable learnings from reading this book: in the chapter on Weather Talk, for example, Kate Fox explains that blunt disagreement with any statement about the weather or even open criticism of the English weather is considered a breach of etiquette – I blush: unaware of this rule, how many times have I broken it? In the section on rules of introduction, she mentions that there is a certain reluctance in the English to readily give their name when first introduced (this cultural peculiarity, by the way, is also corroborated in Jane Walmsley's 'Brit-Think, Ameri-Think' described below). This fact may be useful if you want to avoid uncomfortable situations at your next business meeting.

Not surprisingly, there is also a chapter on food rules in the book, where we read: 'Food is just not given the same priority in English life as it is elsewhere'… 'No-one wishes to be seen as too deeply fascinated by or passionate about food' (pp. 296–97). I suppose this helps in explaining what happened at the EMWA lunch table all those years ago.

Brit-Think, Ameri-Think – A Transatlantic Survival Guide[2]

Non-native speakers of English often tend to forget that the British and Americans, while they share a – largely – common language, differ greatly in their cultural attitudes and customs. Jane Walmsley's *Brit-Think, Ameri-Think* is an eye-opening book about this cultural divide. Jane Walmsley was born and raised in the US but moved to Great Britain as a student, married an Englishman, and stayed on to live in the UK. Being familiar with both US and UK thinking, she often found herself taking the role of a translator or mediator trying to bridge the transatlantic cultural gap. In *Brit-Think, Ameri-Think*, she presents her experiences with this 'translator' role; the book impressively juxtaposes US and

UK attitudes towards fundamental issues like choice, money, consensus, perception of heat and cold, business attire, success and failure, goods and services, and humour. Walmsley's descriptions of the cultural peculiarities of both nations are interesting, succinct, and funny. Unlike Kate Fox's more scientific style, this book uses informal writing including jargon and cartoons. *Brit-Think, Ameri-Think* is a valuable resource for medical writers dealing with business partners from the UK or the US, since it helps them recognise and avoid potential transatlantic cultural blunders. The book is instructive, entertaining, and also relatively short so that I would even recommend it as a light read on your next holiday or business trip.

Alistair's selection this time covers three books that are also not language works: *Harrison's Principles of Internal Medicine, Goodman and Gilman's The Pharmacological Basis of Therapeutics*, and *How to Report Statistics in Medicine* by Tom Lang and Michelle Secic.

Harrison's Principles of Internal Medicine[3]

It is not a language work, but one of the foremost textbooks on medicine in the World in the English language. And that is where the 'language resource' comes in: If you don't know *Harrison's* as it is known throughout the world, you should, and if you have it on your bookshelf but don't often take it down, then you should try doing so a little more. Unless, of course, you use only electronic resources – but even then, that doesn't prevent you from using *Harrison's* these days.

Harrison's has been a valued companion throughout my entire, now almost 40-year career in medical translation, writing, and editing. I am not ashamed to admit that I am old-fashioned enough to still prefer the paper version, now in its 18th edition. Sticking to a few reference books on paper gives you valuable respite throughout the day from the monitor, Wikipedia, and other exclusively electronic resources. I remember in the first few years in this business, when we were still using electric typewriters, I used to sit and read *Harrison's* for hours with great enjoyment to familiarise myself with terminology and style. It was obligatory reading every time I was faced with a new indication. And an obligatory reference work together with medical dictionaries when looking for the exact meaning of a word or term in a particular context. The search for a single word sometimes used to take hours, but that didn't matter, along the way you came across all sorts of other fascinating terms, definitions and turns of phrase that meant that the time was not wasted – and this contributed to your general knowledge of medicine too!

The contributions to *Harrison's* are, quite simply, a delight to read, and gave me a real feel for what you can do with language in our context: especially indication-specific terminology, plain medical English, collocations, the correct choice of verb for different medical and surgical procedures, avoidance of distraction, and how to compose paragraphs in medical texts. Like all medical textbooks, *Harrison's* is not cheap. If language is your prime concern, however, you don't need to have the most up-to-date edition, and second-hand copies are very reasonably priced.

Things have changed as far as reference works are concerned, and users now expect answers at the click of a mouse or at the most after a few keystrokes. *Harrison's*, unlike me, has moved completely with the times and for US$220 (about €160) you can subscribe to *Harrison's Online* which makes this possible: 'Backed by the authority of *Harrison's Principles of Internal Medicine*, 18e, the world's most trusted medical text, [it] delivers information on the diagnosis and treatment of more than 4700 diseases and disorders', is continually updated, and is fully searchable. It also offers a drug database, videos and animations, and 'much more'.

This is a staggering resource that every medical writer, editor, and translator should be familiar with, whether you work primarily as a regulatory writer or in medical communications.

Susanne would like to add that the book has also been translated into many languages (she has a copy of the German translation in her office). Together, the English and the translated versions provide an invaluable source of high-quality, closely reviewed translations covering the full array of medical indications.

Goodman and Gilman's The Pharmacological Basis of Therapeutics[4]

This has been one of my favourite reference works for the past four decades, now in its 12th edition. While *Harrison's* focuses on the disease entities and their various treatments, *Goodman and Gilman's* focuses on drug classes and treatments, and the disease entities they are used for. They therefore complement each other perfectly. With its 'landmark text', it falls into the same category as *Harrison's* for me: an indispensable reference work that I also used to sit and read, sometimes with a specific term in mind, sometimes just to fill in a quiet half hour, always learning something on the way, about language, pharmacology, or medicine. And one I still often refer to today, again, as

far as I am concerned, preferably on paper. A rewarding resource to any medical writer, editor, or translator, and those working in the area of clinical pharmacology will find it especially useful, if not indispensable. As a language reference work, I have learned as much from it as from *Harrison's*.

It is an expensive book, but again, unless you really do need the latest information, you don't need the latest edition and can go for a second hand (earlier) edition. If you need the latest information or prefer staying at the monitor, you will probably be interested in an online version, but as far as I can see, this is only available as part of a very expensive package (more than US$800 [€590] per year or US$50 [€37] to use it for 48 hours). So I expect most of us, especially freelancers, will be sticking to the paper version.

How to Report Statistics in Medicine[5]

What is a book on statistics doing in an article about language resources for medical writers? Quite simply, you can find a definition and explanation of any statistical concept you will come across in medical writing in this brilliant book by Michelle Secic and Tom Lang. And the title says it too – how to *report* on statistics … in other words, how to *write about* statistics, which means it is a very worthwhile investment at about €30.

Most medical writers have no special qualifications or training in statistics and find it difficult to penetrate the baffling terminology of statistics. It is not easy to find simple, straightforward explanations of basic concepts that we need to understand in our everyday work. Michelle and Tom have put together a book that you can sit down and read to learn from, or use as a reference work from time to time. While reading, you learn the *language* of statistics, and that is what we writers are interested in: only if we ourselves understand the terminology we use than we feel confident that the reader does too. This book is a must for newcomers to the profession because, as a non-statistician, you can actually understand what the authors are talking about.

The book finishes with a 43-page guide to statistical terms and tests as a quick reference to what can be found in greater detail in the earlier chapters, which are prefaced by a detailed consideration of the differences between clinical and statistical significance. We all know the blurred line that often exists between the two in reports and publications – and this is usually because the implications of the concepts themselves have been misunderstood, not a deliberate attempt to misrepresent an outcome. This difference is explained using simple language, which is the hallmark of this entire work.

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Treating your CV as a living and breathing document

So your contract or project is soon to end; the PC gets switched on, the lamp fired up, the coffee maker is set to 'constant' and off you go, CV writing in earnest! You say to yourself, 'I'll get this done tonight and I'll start applying for roles tomorrow'; then you realise, it's not a quick job; writing a list of duties and responsibilities is one thing but conjuring up a powerful professional summary that is going to sell your services is another. Writing case studies is definitely not easy; thinking about your value proposition and your brand takes some serious grey matter, and writing a series of tangible and measurable achievements involves recalling all sorts of information long forgotten – and that's before you start worrying about key skills, education, professional development, publications, articles, and the rest.

The point I am trying to make is that a high-impact CV takes a lot longer than a few hours. From my experience, as a one-off task, I would suggest it's at least 15 hours' work. Yes, you can conjure up a basic CV in a couple of hours, but something truly worthy of a professional medical writer is and should be a much bigger undertaking.

Having said all this (and for the purpose of this article), there are some ways to reduce the late nights and coffee sweats: it's all about keeping a chart of your tasks and achievements *During* your contract so that when you get round to writing your CV, you have all the raw material to hand. This is also a great strategy for interviews or client pitches. Inevitably you will be asked a number of situational or comoetency-based interview questions, and recalling key events from your career is pretty tough if you haven't thought about these in advance.

We recommend something called the Career Autobiography Approach© which is all about getting into the autobiography mind-set. As a point of interest, let's just pontificate about how long it would take to prepare the raw material for an autobiography. Let's say that you've been offered €60k plus royalties and all you need to do is to furnish your manuscript with some interesting significant events from your life, sufficient to fill a 300-page book. How long is that going to take? Many hours I would suggest! Preparing for the freelance market is no different; to be effective, you need to know the main important events that have happened in your career. If you are able to recall things that have happened in your career, then handling interviews is so much easier. Questions like 'Give me an example of when you have handled conflict in the workplace' or 'Tell me about a situation when you introduced an idea that resulted in significant business benefits' become much easier to answer than trying to think of them 'off the top of your head'.

Now, the same applies to writing your CV. The more information you have at your fingertips when you start writing about each of your freelance contracts, the better your information is going to be. If you have documented your successes and the business benefits that have occurred as a result of your endeavours, then it's much easier to sell yourself when the time comes to create this all important document. Scrabbling around for some kind of tangible and measurable outcome from something you did 18 months ago is not easy, but referring back to an up-to-date and reasonably detailed career chart makes it easier.

A simple career chart consists of several columns, each with key nuggets of information. Start by identifying the skills and competencies that are important to your profession and future roles, and make sure that you have evidence that you have demonstrated these skills. Then start mapping out events including major projects and achievements. Make a note of the situation or challenge that your client faced; make a note of the circumstances surrounding your involvement (your task); note down the key actions that you took and the reasons why you took them; and finally, make a note of the outcome, focusing on providing tangible and statistical evidence that you succeeded. What I have described here is STAR (Situation, Task, Actions, and Results), which is a fantastic tool for preparing, writing, and talking through pieces of work.

This living breathing document (career chart), over time, is going to become substantial; there may be as many as half a dozen achievements from each assignment, but what a great resource to refer back to when writing and updating your CV, or preparing for an interview. It's a very simple solution and if you can make a habit of noting down these nuggets of information, I guarantee you will find it much easier to effectively sell yourself next time you need to apply for a position.

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Ways to boost your medical writing income

Marketing – love it or loathe it, your medical writing business can't flourish without it.

Marketing isn't just about getting more work; it also enables you to land better work. If you can incorporate some simple marketing techniques into your working life you are more likely to have a greater range of projects to choose from, which puts you in a stronger position to turn down any that could prove to be stressful and unprofitable.

Freelancer Mike Symes says he treats his own business as if it were one of his clients. If he has four clients, his own business counts as the fifth, so he will spend one-fifth of his time on marketing and improving his business.

The key is to make it as targeted as possible to make the best use of your time and resources. Here are some ideas to give your freelance medical writing businesses a boost:

Use a recruitment agency

If you feel daunted by the idea of prospecting for clients yourself, you can 'outsource' the task to recruitment agencies specialising in Pharma, Biotech, Life Sciences and Medical Communications (for a list of IPSE Accredited Agencies, please see

www.ipse.co.uk/supplier-directory). The larger agencies have branches all over the world.

It is worth bearing in mind that agencies charge the end-client a commission on top of your fee, which usually means you have to work for a slightly lower rate than if you were engaged directly by the client. However, the upside is that agencies are often best placed to know where the opportunities are and can therefore provide you with a steady stream of work – this means that in the long run you could actually be better off by not having too many gaps between projects.

In addition, some large companies appoint agencies to handle all their talent requirements and refuse to deal directly with freelance contractors. Therefore, if you want to work with one of those companies, going via an agency is the only option.

When dealing with an agent, remember that they are salespeople, working in a highly competitive environment to earn their commission. Don't give away more information than is necessary for you to win the project – some agents under pressure to hit their sales targets may ask who else you have worked with or been interviewed by. Be wary of revealing your entire professional network or you could find agents using the information to promote their own business instead of yours! Additionally, try to find out as much as you can about the project from the agent before you give permission to send your details to the client.

Despite these caveats, if you do your research you will be able to find reputable agencies who take the time to get to know you so they can sell you effectively. It is worth registering with several agencies to increase your chances and it is important to meet each one face to face. Be sure to return their calls promptly and to follow up on every single project for which you have been put forward (for further tips on working with agencies, visit www.ipse.co.uk/advice/working-agencies).

Spread the word

Many freelance medical writers enjoy years of profitable work by using nothing more than the time honoured word-of-mouth technique. Relying on your network is one of the most effective ways of reaching end-clients directly, with no recruitment agency in between. This simplifies the relationship and gives you more control over your rate.

To fuel the word-of-mouth effect, make sure you tell everyone you know that you are working as a freelance medical writer, even your family and friends. Describe your areas of scientific interest in ways that a layperson can understand – leads can come from the most unexpected sources.

How else can you keep in touch with your network? 'Easy one. Christmas cards', says freelancer Kelvin Prescott. 'It just has to say best wishes and remind them that you still exist. Sounds too simple? It is, but the returns on investment are fabulous'.

You could also ask any past colleagues, employers, or clients to write you a short recommendation to use on LinkedIn or on your CV – people who respect you are usually very happy to do so. It also has the advantage of reminding them why they enjoyed working with you.

To go one step further, you can ask your existing contacts to introduce you to someone who has a need for your services. John Niland, patron of the European Forum of Independent Professionals, feels that too many freelancers miss prime opportunities to gain valuable referrals because of fear. 'Some of these fears do possess certain plausibility', he says. 'The usual excuses range from "good referrals come to me" to a genuine concern about not being seen to be too commercial in a trusted-adviser relationship. Nevertheless, it's useful to challenge ourselves here: are we acting out of genuine concern on the client's part, or out of sophisticated procrastination on our part? Do we simply lack the courage to ask?' (for more advice on how to pluck up the 'courage to ask' and an illustration of an effective referral conversation, please visit www.ipse.co.uk/advice/referral-conversation).

With all business conversations, it is important to remember the human angle. Ask the person about their holiday, their personal life, and their interests. One freelancer recounts how he noticed a replica sailing boat on the desk during a meeting with a prospective client: 'When I asked about it we both realised we shared a huge passion for sailing. At that point I knew the contract was mine!'.

Rethink your CV

If you work in a competitive field, your CV can be the deciding factor that gets you through the door to discuss a potential project.

The standard way of presenting a CV is to have a 'career history' section, showing your employment record in reverse chronological order. However, for freelance medical writers this presents a challenge: how do you convey the breadth of projects you have worked on?

Matt Craven, founder of The CV and Interview Advisors, recommends that freelancers should take a slightly different approach:

> Write each major project you have done as an evidence-based case study and create a section

titled 'Portfolio'. This is the most effective framework for freelancers to write their CV – it breaks your career down into individual pieces of work. You may identify 30 pieces of work and decide that 15 of them are up to date and relevant. Once you have identified the key pieces of work, write them as short case studies, no more than six lines long, ideally using the STAR methodology (Situation, Task, Actions, Result).

The CV then becomes a portfolio of case studies and you are able to change the order around depending on what roles you are applying for. Of course, recruiters will still want to see your dates of employment or contract engagement, so put a career chronology section after the case studies with the date, company name and your job title. This framework will provide you with much more flexibility and allow you to tailor the CV to the roles you are applying for in a much more effective way. (Matt Craven runs regular free online workshops on honing a freelance CV – if you wish to receive event updates, please sign up to the IPSE newsletter at www.ipse.co.uk/events.)[1]

Increase your rate

Ruth Adams says, 'I enrolled on a marketing course in which the presenter, Chris Cardell, suggested to the assembled crowd that we should double our rate the next time we were asked to quote. It seemed outrageous at the time, but I tried it anyway. To my surprise, the client didn't bat an eyelid and it led to a lucrative year-long contract. The client was delighted with my work and renewed the contract the following year'.

Of course, there will be times when a client decides not to go ahead due to price. However, it is important to experiment by trying out different price points, because your perception of what is expensive can differ radically from your prospective client's view. A popular rule of thumb is that you should be losing around 20% of your work due to price. If nobody ever challenges your rate, it suggests that you are at the bottom of the market.

Build your online presence

Do you need a website? Many business advice articles would have made you believe that it is an absolute must, but a surprising finding in a IPSE survey showed that clients ranked a website and/or online presence as the least important factor when selecting a freelancer. The top three things they look for are qualifications, price, and evidence of training (attitudes to freelancing: freelancers versus business leaders, 2010, www.ipse.co.uk/research/freelance-sector-research).

Therefore, it may not be worthwhile investing large amounts of time and money on a website at the expense of the previous approaches discussed here. However, there are cost-effective ways to increase your web presence in order to enhance your professional reputation and build a thriving market for your services.

Some freelancers use their LinkedIn page instead of a website – you can set up a custom URL for your profile and publish the URL on your business cards and email signatures. You can also create a 'company page' on LinkedIn, which provides a powerful way to serve specific updates to selected audiences.

A free blog platform such as wordpress.com can also be used to create a simple website. If you are able to spend some time writing blog posts on your chosen therapy area, it helps to attract the attention of your network – whenever you create a new blog article be sure to publish a link to it on your LinkedIn page.

Another excellent way of signalling your expertise in your field is to include white papers on your blog, website, or LinkedIn page. If you have written a doctoral thesis, perhaps there are elements of this that could be adapted to create a white paper, or report that addresses particular scientific angles that your prospective clients are interested in.

Blog articles and white papers provide you with valuable and relevant content that you can use to email prospective clients (according to the EU anti-spam rules, it is ok to send unsolicited email to business owners and company employees without their prior consent, as long as you don't conceal your identity, you provide an easy (free of charge) way for the person to opt-out of receiving further communications and you provide a valid address for opt-out requests.). It is far more powerful to approach someone with a 'you may find this useful' message than with an email asking for work (if you need a list of potential prospects to email, you can find wide range of 'useful links' in the resources section of www.emwa.org.).

This article has been adapted from guidance provided in the IPSE Guide to Freelancing. For more information please visit www.ipse.co.uk/guide.

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What is search engine optimisation and how can it improve visibility?

For most businesses, a highly visible presence online is increasingly important, and investing in the right search engine optimisation (SEO) techniques can go a long way towards achieving this. We asked HMA Digital Marketing, a top digital agency in the North of England, to share its top tips.

What is SEO?

SEO is the process of improving your website's visibility in search engines such as Google, Yahoo, and Bing. SEO affects only a search engine's 'organic' results. 'Sponsored' results, where a company pays to have its organisation featured in a listing, e.g. Google Adwords, are separate.

Why is SEO important?

A website enables you to stay in touch with your customers and prospects 24 hours a day, 365 days a year, whether they are placing an order or simply finding out more about you or what you offer. However, in today's competitive landscape, having an online presence isn't enough, you need the right search engine strategy so that customers can find you. Around 75% of users never scroll past the first page of search results (source: MarketShareHitsLink.com), therefore, businesses that dominate the first page of results are much more likely to gain exposure to potential customers than those further down.

How does it work?

Quite simply, the content of your website is ranked according to what the search engine considers to be most relevant to the user's search query. Therefore, the way in which you create, manage, and update your content has an important impact on website traffic and a business's visibility online. This in turn may influence the number of enquiries, leads generated, sales conversions, and so on.

Top tips for SEO

To implement a successful SEO strategy and improve the visibility of your business, we've put together our top tips on how any business – large or small – should be considering SEO in everything they do online.

Key phrases

Begin from the customer's perspective: why is a potential customer visiting your website, what are they trying to find, and what search terms would they use to find it? By looking through the customer's eyes, you will discover the key phrases that generate traffic to your website. These key phrases can then be applied to page titles, descriptions, URLs, and page content to improve your website's visibility. However, be careful not to over insert the same key phrases, known as keyword stuffing, as this can go against your ranking.

Create valuable content

Pay attention to writing high quality, original content around the search terms you want to be found for. Search engines will only list your site for information which closely matches your searcher's query. This means that if your website content is irrelevant and doesn't add value for your audience, you are far less likely to occupy a high position in search engine results.

Keep it fresh

Stay on top of news and take this as an opportunity to publish up-to-date, relevant information for your customers. The more regularly you update your content, the more frequently it will be crawled and indexed by search engines and, therefore, ranked more highly. Blogs are an excellent way of keeping your website content fresh and, in addition to improving your ranking, they help to build relationships and encourage social sharing. Go one step further and set up Google authorship, allowing you to link your blog content to your Google+ profile and stand out more in search engine results.

Don't forget to optimise images

Images are often overlooked in SEO, yet they are increasingly important to the customer experience and provide another opportunity for your business to be found. Choose a relevant image file name and caption as well as using ALT and Title tags. The ALT tag (ALTernate text) is a text description that can be added to the HTML tag that displays an image. When the cursor is moved over the browser, the ALT text appears. A title tag is an HTML tag used to define the title of the web page.

Don't forget the social network site, Pinterest. Make your images pin-able by adding Pinterest's 'Pin-It' button. With 70+ million users, Pinterest is one of the fastest growing social networks and one of the top social media traffic referrals to websites (source: Shareaholic Jan 2014 stats).

Build links

Link building is the process of generating quality inbound links to your website from other websites and remains one of the most important indicators to determine site relevancy and importance. Plan

your link building strategy carefully and select a handful of relevant trusted sites rather than lots of links on poor quality sites as this will work against you. Marketing applications such as Group High can help you identify influential bloggers to generate more word of mouth buzz, increase trust, and empower your biggest advocates. Furthermore, creating unique and compelling content will encourage others to link to your website naturally.

Social media sharing

When website content is shared on social media, this sends a strong message to both visitors and Google that your content is valuable, especially when it is shared a lot. Make sure that all of your website pages, news, and blog articles are easily sharable by implementing a sharing plugin. Most of these are free (e.g. ShareThis) and easy to set up.

Local SEO

Create a Google Business listing and greatly improve your visibility in searches. To set up, visit http://www.google.com/business/ and connect with customers when they're looking for you on Google Maps, search, or Google+.

Local SEO is becoming increasingly important because more and more people are using their phones to search locally, for example, for places to eat, drink, and shop. Ensure your business is set up locally on Google my Business and don't forget to include your phone number so that users can click to call you. Three out of four mobile searches trigger follow-up actions, whether that be further research, a store visit, a phone call, a purchase, or word-of-mouth sharing (source: Econsultancy) so it's vital that your business is featured.

Install Google Analytics

Google Analytics is a free tool and provides valuable insight into the search queries that generate traffic to your website, top referral websites, and what your visitors do once they arrive. By monitoring and understanding website traffic on a regular basis, you can identify the ways in which you can optimise your content for search.

Keep it clean

Keep the HTML code of your website clean by making sure it is formatted correctly, is readable, and as simplified as possible. Avoid anything that requires a lot of code as this will make it harder for search engine spiders to find your valuable content and ensure you get your keyword-rich copy as high up the page as possible.

To get started on your SEO strategy, Google has published a useful 'Search Engine Optimisation Guide' which will take you through everything from SEO basics, improving site structure and optimising content. Alternatively, if you would like to save yourself the headache and let a team of SEO experts help, get in touch or refer to the Recommended Agencies Register (RAR) for a list of reputable agencies.

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Freelance foraging

Horses at this event cannot only read, but know their left and right!

The Light Stuff

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Anecdotes and quotes related (more or less) to scientific writing

Pigeons are like editors, they both do the icky to your most cherished work, but at least pigeons don't say, Now it really sings.

Cecil Adams, *The Straight Dope*

Ignorant people think it's the noise which fighting cats make that is so aggravating, but it ain't so, it's the sickening grammar they use.

Mark Twain, *A Tramp Abroad*

Those who have knowledge don't predict. Those who predict have no knowledge.

Lao Tzu (6th century BCE)

If only he had had to prepare timelines and cost estimates! (editor)

Work on good prose has three steps: a musical stage when it is composed, an architectonic one when it is built, and a textile one when it is woven.

Walter Benjamin, critic and philosopher (1892–1940)

A man should never be ashamed to own he has been in the wrong, which is but saying, in other words, that he is wiser today than he was yesterday.

Alexander Pope, poet (1688–1744)

The men who try to do something and fail are infinitely better than those who try to do nothing and succeed.

Lloyd Jones, New Zealand author (1954)

I notice that you use plain, simple language, short words, and brief sentences. That is the way to write English – it is the modern way and the best way. Stick to it; don't let fluff and flowers and verbosity creep in. When you catch an adjective, kill it. No, I don't mean utterly, but kill most of them – then the rest will be valuable. They weaken when they are close together. They give strength when they are wide apart. An adjective habit, or a wordy, diffuse, flowery habit, once fastened upon a person, is as hard to get rid of as any other vice.

Mark Twain, Letter to D.W. Bowser, 20 March 1880

… and finally a Light Stuff challenge:

In the earlier part of the Twentieth Century, in the County of Caithness in the north of Scotland, great excitement arose when a pot (or part thereof) was discovered, apparently stemming from the Roman occupation of Britain. It was exciting because there was no archaeological evidence up to that point of the Romans having been that far north. The local newspaper, The Caithness Courier, gave prominence to the find, and quoted in full the inscription on the artifact. It was ITI SAPIS SPOTANDA BIGO NE (read slowly without the word breaks). The Courier never lived down its naivete.

I have seen the preceding text in several magazines over the years, including Nature or the BMJ once, if I remember correctly. When I was considering it for inclusion here, I googled it and was rather dismayed to find the exact text, word for word, on several internet sites – always without source. Does anyone know if this rather charming story is true or is also an attempt to fool the reader?

Oh, my brain!

A colleague alerted me to this brilliant bit of text from a document that she was editing:

Some different types of leukemia have been found to respond differently to different treatments.

This is like when Spock, attempting to disable an evil android, said to it, 'Listen carefully. Everything I say is a lie. I am lying'. The android then proceeded to melt down.

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