Medical Writing

Regulatory Writing Basics

Contents

Regular Features

Themes of upcoming issues of *Medical Writing*

September 2014: The theme will be '**Non-clinical Health Writing**'. It will include articles on topics that medical writers might not be familiar with but can easily work on, such as veterinary medicine, cosmetics, and environmental toxicology. *The deadline for submitting articles to this issue was 9 May 2014.*

December 2014: The theme will be '**Post-approval Regulatory Writing**'. This issue will include articles on post-approval documents and pharmacovigilance, and the Guest Editor will be Sam Hamilton. *The deadline for feature articles is 8 August 2014.*

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

Regulatory writing basics

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Editorial

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The role of a regulatory writer is to produce regulatory documents (usually taken to refer to documents that are submitted in some form to the health authorities). These documents should adhere to the relevant guidance and be fit for purpose, meaning that they transmit the necessary information accurately, transparently, and clearly to the target audience (usually reviewers at the health agencies but readers might also be investigators or members of ethics committees).

In the Internet era, regulatory writers have instant and complete access to almost all the necessary guidelines governing these documents (and Raquel Billiones has gone to the trouble of compiling these guidelines; see p84). Yet there is actually rather little information in the public domain on how these guidelines should be applied and interpreted in practice. Some books are available on medical writing, but these have relatively little if anything to say about regulatory writing and focus on research articles and other aspects of medical communications. A quick search on the Amazon website revealed one book dedicated to regulatory writing.[1] The book was published in 2008, but guidance changes and clarifications are issued in the form of Questions and Answers documents to address contradictory or ambiguous aspects of the guidance.[2] So while the core skills needed for regulatory writing remain fairly constant, the details may change and the regulatory environment evolves.

This issue of *Medical Writing*, entitled *Regulatory writing basics*, is an attempt to fill, at least partially, the void of information on the subject and provide a useful reference guide for regulatory writers. (Here, I feel compelled to acknowledge that the original idea for this issue did not come from me but rather from Phil Leventhal, the regular *Medical Writing* editor). Regulatory writing is a wide field and so the scope of the articles has been limited to the types of document that an entry level regulatory writer is likely to encounter. It is also limited to pre-approval documents associated with drug development. The December 2014 issue of *Medical Writing* will be dedicated to the topic of post-approval.

At some point early in their careers, most entry-level regulatory writers work will work on a Clinical Study Report (CSR), which is covered in depth by Sam Hamilton (p86). For the most part, the guidelines covering the CSR are detailed and well developed, although they have occasionally been interpreted too literally. For example, the table of contents of the guidelines was interpreted by many companies as a template for their CSRs, resulting in the somewhat absurd situation of having the title page of the CSR listed as Section 1. This is a good example of the pitfalls of unthinking and rather slavish application of guidelines and also, I think, the desire of many companies to be as compliant as possible with the perceived letter of the guidelines while perhaps losing sight of their intent. A necessary skill of a regulatory writer is knowing when to treat guidance as set in stone and when it is appropriate to deviate from the letter of the guidance to ensure clarity and readability.

The Protocol is another document that writers may be involved in at some point in their careers. As Walther Seiler explains though (see p93), despite its obvious importance, the far-from-comprehensive guidelines and varied audience provide unique challenges and also interesting opportunities for regulatory writers. Like the protocol, the Investigator's Brochure (IB), comprehensively covered by Douglas Fiebig on p96, has a varied audience and can be used for a variety of purposes. The IB includes information from the entire drug development process, from preclinical studies through to the latest clinical studies and needs to be updated at least once a year. The coordination of input from such a wide variety of sources may be challenging, particularly as an IB update should be kept to a reasonable length. An update should not merely be a case of simply adding new data; decisions about which data to retain will need to be made and perhaps justified and discussed within a team, with the writer acting as a facilitator and arbiter.

The goal of drug development is to get approval for a drug. An issue about regulatory writing would therefore seem incomplete without reference to the centrepiece of an approval process, the Common Technical Document (CTD). This document binds together the existing documentation from drug development (quality, pre-clinical, and clinical) and also includes dedicated summary documents and a discussion of the data (overviews). Debbie Jordan takes us through the different components of the CTD, with special reference to the clinical modules, such as the clinical summaries and clinical overview, where the services of a medical writer are most likely to be employed (see p101). Regulatory writers will often have to make judgement calls about what is appropriate content for the clinical overview and what should be included in the summaries, although convincing the teams not to put too much detailed data in the overview, for example, is not always easy.

This issue also includes three articles intended to give some useful background for regulatory writers. First, Anga Abed, a medical writer at the European Medicines agency gives an overview and history of drug approval in the European Union (see p117). She explains how the fragmented approval processes in place 20 years ago has given way to a centralised, more efficient system. In addition to changes in the approval process, the conduct of clinical research has also been thoroughly overhauled, as discussed by Gabi Berghammer in her article on Good Clinical Practice (GCP), which also touches on the International Conference for Harmonisation (ICH) (see p106). The concept of GCP now permeates all levels of clinical research, and an awareness of GCP principles will be of great help to regulatory writers. The document types discussed in this issue are subject to ICH guidelines, so an understanding of the ICH and its unifying intent (as well as knowledge of the individual guidelines) is important. ICH has been with us for almost 20 years now, and its profound impact can be appreciated if, for whatever reason, you have cause to read pre-ICH documents. These can appear chaotic and incomplete, and extracting information from them can be time consuming. Safety is a fundamental aspect of the risk–benefit assessment of a new drug (and hence whether it will be approved). Safety reporting is much more homogeneous than efficacy reporting and is largely based on analysis of adverse events. Like the drug approval processes and clinical research conduct, safety reporting has also undergone marked changes over the last 20 years. In the ICH era, use of the Medical Dictionary for Regulatory Activities (MedDRA) is now mandated for reporting of adverse events and an article on the subject has also been included in this issue (see p113).

While it is hoped that this collection of articles can serve as a useful guide for regulatory writers, especially those in the early stages of their career, merely reading about regulatory writing will not be enough. Regulatory writing is more than just adhering to the regulations (which may be contradictory anyway). A common theme of the articles included here is that regulatory writers often have to act as negotiators and facilitators, finding a solution that is acceptable to different team members with very different agendas. The soft skills needed to deal with these situations are ones that a regulatory writer would be wise to develop. Attending conferences such as EMWA and exchanging experience with established writers will undoubtedly help, but there really is no substitute for direct experience, preferably with a mentor available to advise and guide you in tricky situations.

References

1. Wood LF, Foote MA, editor. Targeted regulatory writing techniques: clinical documents for drugs and biologics. Basel, Switzerland: Birkhäuser; 2009.
2. See for example: ICH E3 guideline: structure and content of clinical study reports questions & answers (R1); 2012 Jul 6. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf.

Message from the President

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These two years in the Executive Committee flew by. They will remain in my heart for ever. It is difficult to summarise the emotions and the things we accomplished these last two years. When this adventure started in Cyprus, Susan Bhatti, the previous EMWA President, and me met to discuss EMWA's situation and its objectives. We realised that EMWA is an excellent organisation with a great reputation and a clear strategy for its development, thanks to our previous presidents and Executive Committees.

Because we met most of our objectives we have a bright future. Thanks to excellent work by the Executive Committee and Head Office, we have improved the branding of EMWA, renewed the website, installed a new voting system, carried out several surveys, revised bank and insurance agreements, improved the productivity of Executive Committee meetings by adding winter and summer face-to-face meetings, increased the distribution of the journal, and added member benefits by building agreements with software vendors and other professional associations. By adding new sponsors, more members, and greater attendance at conferences, we have been able to maintain the annual fee and to offer discounts for those referring new EMWA members. This healthy situation, together with the great work of the Head Office, have also allowed us to begin planning conferences all the way until 2017, to create e-learning modules, and to put into place a new 3-year plan. Our collaborations with the European Medicines Agency and other professional associations show that EMWA is clearly a reference organisation for medical writing in Europe.

I will conclude by saying that governing the wonderful Executive Committee and Head Office has been a great pleasure. They have worked hard, but always with a smile, to make all of this happen.

I am more than confident that the new Executive Committee will continue the initiatives to better serve our members and the organisation and that Julia will be a great president!

I look forward to meeting you all in Florence.

Ciao,
Andrea

Thank you, Andrea, for guiding me through the past year on the Executive Committee and for preparing me for the role of President.

First, a little about my background and what I bring to the position of EMWA President. I am a PhD pharmacist who has worked in the pharmaceutical industry and medical communications for 25 years (how scary is that?). For the last 10 of these years, I have been free-lance and have enjoyed a good work-life balance as a medical writer, stand-in editorial director, and out-contracted publication manager.

I have been a member of EMWA for 15 years and gave my first workshop in 1999. Although I spent several years on the EMWA Professional Development Committee, my last year on the Executive Committee has been a true education on the complexity of the organisation and the dedication and commitment of our Head Office and my fellow committee members.

EMWA is already a successful organisation as evidenced by our recent spring conference in Budapest, which included an excellent symposium on transparency, comprehensive educational programme, and smooth logistics. We also have the impressive new website, a highly regarded journal and, of course, our growing public relations offerings. As the new President, I want to build on this success by supporting membership growth, expanding our association into e-learning and new media, and promoting links with other professional organisations. I am keen to ensure that EMWA can meet the needs of the membership now and in the future. I have already presented the vision for EMWA over the next three years and am currently working on the key areas and action points.

Our autumn conference this year will be in Florence (Andrea's home town!) – a fantastic opportunity to combine a beautiful and cultural setting with education, networking, and fun. I look forward to meeting even more of you there, but if you do want to get in touch before November, I would be delighted to hear from you.

Julia Donnelly

A guide to pre-approval regulatory documents

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The following table provides a list of the most common pre-approval regulatory documents for drugs with their associated guidelines and regulations. The clinical study report (p86), clinical study protocol (p93), investigator's brochure (p96), and common technical document (and components; p101) are dealt with in detail elsewhere in this issue.

Document	Commonly used abbreviation	Associated guidelines and regulations and other sources of information
Case report form	CRF	Good clinical data management practices, version 3 (September 2003), Society for Clinical Data Management
Clinical development plan	CDP	–
Clinical overview	CO	ICH M4E
Clinical study protocol	CSP	ICH E6; ICH E8; ICH E9
Clinical study protocol amendment	CSP amendment	ICH E6; ICH E8
Clinical study report, full or abbreviated	CSR	ICH E3; ICH E9; FDA GfI submission of abbreviated reports and synopses in support of marketing applications
Clinical trial application (EU)	CTA	EudraLex – Volume 10 Clinical trials guidelines; Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments, and declaration of the end of the trial (August 2003)
Common technical document	CTD	ICH M2, ICH M4, ICH M8
Data management plan	DMP	Good clinical data management practices, version 3 (September 2003), Society for Clinical Data Management
Developmental periodic safety update report	DSUR	ICH E2F; see also PBRER
Electronic case report form	eCRF	See CRF; 21 CFR Part 11
Electronic common technical document	eCTD	ICH M2, ICH M4, ICH M8
Informed consent form	ICF	ICH E6, HIPAA
Integrated summary of effectiveness (US)	ISE	FDA GfI Integrated summary of effectiveness; FDA GfI Integrated summaries of effectiveness and safety: location within the common technical document
Integrated summary of safety (US)	ISS	FDA GfI Integrated summaries of effectiveness and safety: location within the common technical document
Investigational medicinal product dossier, full or abbreviated (EU)	IMPD	Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments, and declaration of the end of the trial (March 2010); http://www.imp-dossier.eu/imdp_guidance/
Investigational new drug annual report (US)	INDR	FDA information on IND application reporting
Investigational new drug application (US)	INDA	FDA information on IND application
Investigator's brochure	IB	ICH E6
Investigator's brochure update	IB Update	ICH E6

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Document	Commonly used abbreviation	Associated guidelines and regulations and other sources of information
Marketing authorisation application (EU)	MAA	EMA guidance on applying for EU marketing authorisation medicinal products for human use; EudraLex – Volume 2 – Pharmaceutical Legislation Notice to applicants and regulatory guidelines for medicinal products for human use
New drug application, full or abbreviated (US)	NDA, ANDA	FDA information on NDA and ANDA
Orphan drug application	ODA	Common EMA/FDA application for orphan medicinal product designation; EMA regulatory and procedural guidance
Paediatric study plan (US)	PSP	ICH E11; FDA GfI PSP: Content of and process for submitting initial paediatric study plans and amended paediatric study plans
Paediatric investigation plan (EU)	PIP	ICH E11; EMA information on standard PIP, waivers, and modifications
Patient or subject narratives	–	ICH E2 series; ICH E3
Periodic benefit risk assessment report	PBRER	ICH E2C (R2)
Risk assessment plan	RAP	EMA information on RAP for marketing authorisation holders
Safety management plan	SMP	ICH E2 series
Statistical analysis plan	SAP	ICH E9; ICH E3
Summary of clinical pharmacology	SCP	ICH M4E
Summary of clinical efficacy	SCE	ICH M4E
Summary of clinical safety	SCS	ICH M4E

Abbreviations: CFR, Code of Federal Regulations; EMA, European Medicines Agency; EU, European Union; GfI, Guidance for Industry; FDA, Food and Drug Administration; HIPAA, Health Insurance Portability and Accountability Act; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; US, United States.

Effective authoring of clinical study reports: A companion guide

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Abstract

'Why write a clinical study report (CSR)? What are the guidance documents? Can I interpret them? Can I deliver my CSR on time?' This article addresses these questions – and others, provides a companion guide to CSR authoring for preregistration drug trials intended for regulatory submission in the EU, provides links to applicable regulatory guidance documents, and offers experience-based insights. Between 2008 and 2013, the authoring timeline for a medium complexity first draft (mean [SD]: 16.9 [8.2]; range: 5–45 working days) and final CSR from the first draft (mean [SD]: 25.7 [21.1]; range: 3–120 working days) varied widely across the industry. Understanding regulatory requirements and utilising project intelligence leads to informed CSR authoring and scheduling, thereby assuring a high-quality, on-time, final CSR.

Keywords: Clinical study report, Regulatory Guidance, ICH E3, ICH E6, Reporting

Reasons for writing a clinical study report

The regulatory and ethical basis for writing clinical study reports (CSRs) is grounded in Section 5.2.2 of the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6[1] (henceforth ICH E6):

> *Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).*

ICH E6 further directs us to the ICH Guideline for Structure and Content of Clinical Study Reports[2] (henceforth ICH E3):

> *The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports.*

A summary of the results must be produced[1] within a year of the end of the trial.[3] It is expected that in the later part of 2014, online posting of summary results on the European Medicines Agency (EMA) European Clinical Trials (EudraCT) database will become mandatory.[4]

Although the ICH region includes the EU, Japan and the USA, this article focuses primarily on the preparation of full CSRs for regulatory submission in the EU prior to approval (henceforth Marketing Authorisation Application [MAA]). Preparation of abbreviated and synopsis CSRs are additionally covered in brief.

The target audience for a CSR is most often the regulatory reviewer. However, CSRs are not always intended to contribute to an MAA. A CSR may report a 'proof of concept' study and may be used to secure development funding, or pass on information to an acquisitor of a drug. Such studies may subsequently be redesigned and repeated with greater regulatory rigour if repurposed for an MAA. In addition, some of the data in MAAs (including CSRs), submitted to EMA from March 2014, will be made publicly accessible.[5] This means that requests can be made for access to CSRs and datasets, and that successful requesters can reanalyse the data.

Whatever the reason for writing a CSR, and whatever the breadth of audience, a well-structured and well-written document will support the development programme, submission process, and ultimately labelling, because this key regulatory document is the basic building block of the MAA. Immediate reporting on completion of the study is recommended, not only because of summary

results public posting requirements,[1,3] but because the team's availability and recollection of study detail will most likely be optimal.

A 'fit for purpose' clinical study report

A 'fit for purpose' document fulfils reporting requirements and supports the work of the regulatory reviewer – a time-poor professional, often reviewing and comparing data across different MAAs. The regulatory reviewer will appreciate clarity, consistency, and brevity. They must be able to find information with ease. The CSR author is key in facilitating this process. Report version (draft or final) and date must be clearly displayed on the title page and on each page. A data cut date, included for long-running studies with interim reporting of data, supports pharmacovigilance (PV). Other examples include inclusion of selected tabular information in narratives and in-text inclusion of appropriate data rather than cross-referring to appended data. Relatively recent process developments in some larger companies (both sponsors and contract research organisations [CROs]), have resulted in a shift away from purpose-built in-text summary tables, to hyperlinking to end-of-text summary tables only, or direct import of (unedited) statistical outputs to the report body. Whilst no doubt intended to streamline statistical and reporting outputs, such developments may negatively affect the comprehensibility of the intended message, and on a practical level, navigation within the integrated document. As changes in company procedures result in template evolution, the CSRs in an MAA may be structured differently. This could reasonably be expected to impact the work of reviewers both within and between dossiers.

The integrated clinical study report: A multi-component document

Most pharmaceutical companies have their own CSR templates and guidance documents within which ICH E3 is contextualised and interpreted. Although ICH E3 is not a rigid template, the ICH E3 headings are henceforth used for reference purposes. The integrated CSR has two main parts: a 'text part' and an 'appendices' part:

- The text part, written by the medical writer, comprises Sections 1–13 and Section 15. Section 14 contains the end-of-text tables, figures, and graphs – essentially the summary statistical output – as well as clinical narratives,

if inclusion in the body of the report would disrupt the CSR flow. The medical writer or drug safety group usually write the narratives.
- The Section 16 appendices comprise study information, data listings, and relevant case report forms. The appendices may be collated and assembled into electronic folders by the medical writer or a document support group. A dedicated publishing group usually electronically integrates the text, Section 14 outputs and narratives, and Section 16 appendices.

The medical writer has a driving role in the preparation of all these components, and must engage with many other functions to produce a high-quality document, delivered on time.

Clinical study report structure and guidance: Text (Sections 1–13 and Section 15) and the statistical outputs (Section 14 and Appendix 16.2)

The definitive guidance for writing CSRs is ICH E3,[2] published in 1995, with supplementary questions and answers (Q&A) published in 2012.[6] For a complete understanding of the current CSR text requirements, the reader is referred to both.

After years of debate about the use of ICH E3 as a definitive template, the Q&A document finally clarifies what experienced CSR authors have long held – that '*ICH E3 is a guideline, not a set of rigid requirements or a template, and flexibility is inherent in its use*'. Restructuring the integrated CSR and appropriate placement of material not specifically covered in the guidelines is welcomed if this improves clarity. At its simplest, this may mean restructuring of text sections in, for example, a phase I safety and pharmacokinetic CSR, and inclusion of the full pharmacokinetic report in an appropriately placed 'ad hoc' appendix. Restructuring for its own sake can lead to differing CSR structures within an MAA which may be unhelpful for the regulatory reviewer.

The CSR text portion comprises a 'front end' section, predominantly methodological, followed by the meat of the document – the 'back end' results (including end-of-text statistical output data), discussion, and conclusion sections. The 'front end' broadly includes a 'stand-alone' synopsis, including key results but devoid of external references (to support its separate publication). Conflicts between ICH E3's maximum suggested synopsis length of three pages and subsequent Common Technical Document M4E guidance[7] of a 10-page maximum are now clarified in the 2012

Q&A document. The basic premise is to apply logic; a synopsis in the region of 10 pages is perfectly acceptable for a more complex study. In addition to the synopsis, the 'front end' should also contain ethical information; trial administrative structure; introduction; objectives; investigational plan (trial methodology); statistical methodology; and changes to the study or planned analyses. Much of the 'front end' material is summarised from precursor documents such as the Investigator's Brochure, protocol, and statistical analysis plan (SAP).

Multiple authors, inevitably with different perspectives and standards, may have contributed to these precursor documents. Note the use of the word 'summarised'. Text should not simply be lifted from the precursor documents, but adapted and repurposed, and written in the past tense, where appropriate. Existing textual information may be better presented in tabular form if this adds clarity and aids comprehension. Cross-referencing certain sections of precursor documents will avoid unnecessary repetition in the MAA. However, care must be taken to cross-reference only accurate original material. If accuracy is in question or text is open to interpretation, better practice is to include abstracted unambiguous information directly in the CSR text.

ICH E6 and ICH E3 were simultaneously developed. However, lack of confluence between requirements in ICH E6 Protocol Section 6.4 'Trial design' and ICH E3 CSR Section 9.2 'Discussion of study design and choice of control groups' can complicate reporting if the rationale behind the study design was not adequately described in the protocol. Such deficits are best addressed by improved protocol template instructional text.[8] CSR Section 9.2 authoring (where Protocol Section 6.4 is deficient) is easier with input from the original protocol development team.

Industry debate about summarising precursor document material in CSRs versus the merits (or otherwise) of only hyperlinking to the original document makes interesting reading (EMWA Group LinkedIn discussion started 08 November 2011, http://www.linkedin.com/groupItem?view=&gid=2717752&type=member&item=79357240&qid=06269034-6116-4370-9846-479f1297d239&trk=groups_items_see_more-0-b-ttl). Current guidance requires population of the relevant CSR 'front end' text sections.

The planned statistical analyses, finalised before locking of the database and described in the SAP, should follow the ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9[9] (henceforth ICH E9). ICH E9 refers the reader to ICH E3. Statistical outputs comprise the summary tables, figures and graphs, and data listings described in the industry as tables, figures, and listings (TFLs). These are most often generated by the statistical team using the 'gold standard' statistical software package, SAS® (http://www.sas.com). TFLs should follow ICH E3's Section 14 and Appendix 16.2 structural guidance to simplify the work of the medical writer and regulatory reviewer. Medical writing review of the SAP before finalisation is highly recommended to ensure confluence of statistical output structure with the guidance documents and to ensure that all summarisations and analyses that the writer might require are planned and programmed in advance.

Writing the 'back end' of the CSR – the results (including end-of-text statistical output data), discussion, and conclusion sections – is driven by availability of final TFLs. It is common to populate in-text summary tables with selected relevant data from the TFLs. The aim is to distil the voluminous output data into easily comprehensible packages of 'results messages', whilst maintaining absolute transparency. This process, if executed analytically and with elegance, should help identify 'signals in the noise'. Presentation of results must be factual; interpretation is not required, except in the discussion. Where sponsors undertake *post hoc* analysis, the appropriate place to report such data are in an *ad hoc* CSR appendix, considering that the only data reportable in a CSR are those for which the analyses were preplanned. If *post hoc* analyses are appended to the CSR, the associated rationale must be included in CSR Section 9.8 'Changes in the conduct of the study or planned analyses'. *Post hoc* analyses can be further reported in a journal article. Supportive analyses (planned, or post-hoc with explanation in CSR Section 9.8) to aid results interpretation, for example, may also be appended. The CSR discussion and overall conclusions section should not restate the results or introduce new results. In short, this section should be a more factually based version of its journal counterpart, with less hypothesising. Superlatives and overstating benefits must be avoided. This section should include discussion of any problems or perceived benefits; place the results into the context of currently available treatment modalities; and refer to ongoing and future development. An understanding of the development plan combined with regulatory insight will assist with preparation of this section. Communication between the CSR author and team members with wider strategic understanding of the product is usually necessary.

Clinical study report structure and guidance: Narratives (Section 14)

Clinical trial data are captured in two separate databases: the PV and clinical databases. The PV database captures safety data that the PV or drug safety group use to produce PV safety narratives on an ongoing basis throughout the study. The clinical database captures all trial-related data including safety data. Once all the data are clean, these two databases should ideally be reconciled. The categories of required CSR narratives are described in ICH E3.[2] CSR narratives are event- and clinical data-based and are distinct from the PV safety narratives which are subject- and PV data-based. PV safety narratives are written using Council for International Organizations of Medical Sciences (CIOMS) forms and are useful in part for preparing the CSR narratives. At reporting, data from the clinical database take precedence over data from the PV database, and this is the reason that data inconsistencies between PV and clinical narratives must be reconciled. Some companies routinely reconcile their PV and clinical study databases, and generate final CIOMS forms from the reconciled database. They place the final CIOMS forms in the CSR *in lieu* of preparing separate CSR narratives. This ensures that the narratives align with clinical data, but remain subject- and not event-based. Identification of the actual event(s) requiring narration may be confounded by this approach. Some categories of narratives may be waived by prior agreement with the regulatory body, for example, deaths, where 'death' is a study endpoint.

When writing large numbers of clinical narratives, analysis programming of subject profiles is a cost- and time-efficient approach worthy of consideration. Subject profiles gather narrative-relevant line listing data for one subject into a single file (similar to US archival listings). Narratives comprehension is aided with selected tabulations (e.g. laboratory data) to break up the prose. Partly tabular narratives also improve project efficiency.

Clinical study report structure and guidance: Appendices (Section 16)

Guidance on the content of CSR appendices is given in ICH E3;[2] instruction on how to adapt the original appendices for CSRs to be included in MAAs was clarified 9 years later in 2004.[10] Further clarification on CSR appendices content appeared in the Q&A document published in 2012.[6] To ensure CSR appendices are fit for inclusion in MAAs, all three guidance documents must be considered.

The resulting requirements now take into account study trial master file (TMF) and clinical supply database content. Although neither is submitted as part of the MAA, the drive to limit CSR appendix content to material necessary for CSR review, results in the 2012 clarification:

> *Supportive documents, such as investigator CVs, ethics committee approvals, informed consent forms, and batch numbers per subject are in the TMF or clinical supply database and should generally not be included in the CSR appendices.*

The medical writer should remind the responsible team member that the required information must be included in the TMF or clinical supply database by the time of filing of the MAA.

The 'take home' point is that CSR appendices should not be bulked out with redundant documents. In a region where documents used by non English-speaking investigators or subjects must be translated into different languages, local language version documents must not be included in CSR appendices.

The impending public disclosure of full CSRs in 2014 has prompted a shift towards appending details of named individuals formerly included in CSR text Section 6 'Investigators and study administrative structure', as well as the details of the sponsor signatory, to Section 16.

Abbreviated and synopsis clinical study reports

ICH E6 also reminds CSR writers that ICH E3:

> *… specifies that abbreviated study reports may be acceptable in certain cases.*

In the absence of EU-specific guidance, the consensus, supported by Alfaro *et al.* in 2007[11] is to follow the US guidance issued in 1999 by the FDA.[12] Abbreviated CSRs should report selected front-end material; subject disposition information; and crucially, safety data in full. Selected appendices are required with adaptation of the US list by omission of US archival listings.

The 1999 FDA guidance[12] also describes studies for which synopsis reports are acceptable. These are generally studies conducted only in sufficient depth to assess if they cast safety doubt on a product and are often studies for which marketing approval is not being sought. A synopsis report may follow the ICH E3 synopsis format, with supplemental safety discussion (or may substitute synopsis and discussion with published literature), and appended protocol and protocol amendment(s).

Table 1: Guidance documents and resources for content of clinical study reports in the EU: Chronological presentation

Reference number	Document name	Version and date	Web link	Source of and description of document content
Ref. 2	ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3	Step 4 30 November 1995	http://www.ich.org/ fileadmin/Public_Web_ Site/ICH_Products/ Guidelines/Efficacy/E3/ E3_Guideline.pdf	http://www.ICH.org 'This document describes the format and content of a study report that will be acceptable in all three ICH regions. It consists of a core report suitable for all submissions and appendices that need to be available but will not be submitted in all cases'
Ref. 1	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1)	Step 4 10 June 1996 (including the post Step 4 corrections)	http://www.ich.org/ fileadmin/Public_Web_ Site/ICH_Products/ Guidelines/Efficacy/ E6_R1/Step4/E6_R1__ Guideline.pdf	http://www.ICH.org 'This Good Clinical Practices document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors. and IRBs. GCPs cover aspects of monitoring, reporting, and archiving of clinical trials and incorporating addenda on the Essential Documents and on the Investigator's Brochure which had been agreed earlier through the ICH process'
Ref. 9	ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9	Step 4 5 February 1998	http://www.ich.org/ fileadmin/Public_Web_ Site/ICH_Products/ Guidelines/Efficacy/E9/ Step4/E9_Guideline.pdf	http://www.ICH.org 'The harmonised tripartite Guideline was finalised under Step 4 in February 1998. This biostatistical Guideline describes essential considerations on the design and analysis of clinical trials, especially the "confirmatory" (hypothesis-testing) trials that are the basis for demonstrating effectiveness'
Ref. 12	FDA CDER and CBER: Guidance for Industry: Submission of abbreviated reports and synopses in support of marketing applications	August 1999	http://www.fda.gov/ downloads/Drugs/ Guidances/ucm 072053.pdf	Introduction: 'This guidance focuses on the circumstances when full study reports, abbreviated reports, and synopses can be used to submit data concerning the effectiveness of new drugs and biological products'
Ref. 10	CHMP Note for Guidance on the Inclusion of Appendices to Clinical Study reports in Marketing Authorisation Applications	CHMP/EWP/ 2998/03/Final 23 June 2004	http://www.ema. europa.eu/docs/en_ GB/document_library/ Scientific_guideline/ 2009/09/WC500 003638.pdf	Introduction: '…The list of appendices includes a lot of information that may not be necessary for evaluation on a routine basis. Certain of the appendices should be submitted systematically with each report and others should be available on request … the following list has been established as the minimum required'
Ref. 11	Alfaro V, Cullell-Young M, Tanovic A. Abbreviated Clinical Study Reports with Investigational Medicinal Products for Human Use: Current Guidelines and Recommendations. Croat Med J. 2007; 48(6):871–77	December 2007	http://www.ncbi.nlm. nih.gov/pmc/articles/ PMC2213811/	Abstract: 'Some of the studies conducted during product development may ultimately not contribute to the evaluation of the effectiveness of a product for a specific indication. In these cases, abbreviated Clinical Study Reports are required to be submitted to the regulatory authorities. However, the ICH E3 guideline only provides information on the structure and content of full Clinical Study Reports. A guideline issued by the Food and Drug Administration of the United States in 1999 is the only document available from a regulatory authority that recommends which sections can be included in an abbreviated Clinical Study Report. This article describes which sections have to be included in abbreviated Clinical Study Reports written during clinical development of new medicinal products for human use'
Ref. 6	ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers	R1 6 July 2012	http://www.ich.org/ fileadmin/Public_Web_ Site/ICH_Products/ Guidelines/Efficacy/E3/ E3_QAs_R1_Step4.pdf	www.ICH.org 'Since reaching Step 4 and publication within the ICH regions, experiences by all parties with the implementation of the E3 Guideline have resulted in the need for some clarification. This supplementary Questions and Answers document intends to clarify key issues. In July 2012, minor typographical errors were corrected in the Answer to Question 6 and the document was renamed R1'

Abbreviations: ICH, International Conference on Harmonisation; IRB, Institutional Review Board; GCP, Good Clinical Practice(s); CDER, Center for Drug Evaluation and Research; CBER, Center for Biologics Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use.

For a complete understanding of abbreviated and synopsis CSR format, the reader is referred to both documents.[11,12]

See Table 1 for current guidelines on full, abbreviated, and synopsis CSR authoring.

Scheduling

A companion guide to CSR authoring is incomplete without considering how to meet the final CSR deadline.

The sponsor will predetermine the date of the final CSR which should take into account the summary results public disclosure requirement of one year after the end of the trial.[1,3] The CSR authors must meet the date by scheduling effectively the preparation of the various components of the integrated CSR. Planning must take into account study complexity and resulting CSR complexity, and an understanding of precursors and drivers (e.g. locking of the database, or availability of final TFLs) for medical writing tasks. CSR complexity is estimated by considering study and reporting variables, such as number of subjects; study phase; indication; number of secondary efficacy variables; number of unique TFLs; and analysis complexity.[13] It takes more time to author a 'high' compared to a 'medium' or 'simple' complexity CSR. Breaking the integrated CSR into smaller deliverables prepared on a timescale to fit with the final CSR deadline is recommended. The 'front end', including unpopulated in-text summary results tables, and appendices should be completed in advance of receipt of the final TFLs, which drive draft reporting. The commonly used strategy of reporting from draft TFLs is not efficient and is not recommended. Draft data changes in the final TFLs will mandate changes in the CSR. Early consideration of the reporting scenario is necessary as reporting postdates clinical, regulatory, and statistical tasks that may be delayed during the project. While it seems reasonable to expect a subsequent delay on the final CSR date, this cannot be assumed, and rarely happens.

There are no industry standard durations for analysis and reporting tasks, as shown by data collected at eight EMWA conferences over 5 years (2008–2013) (see Table 2).

Industry professionals, predominantly regulatory medical writers working for sponsoring pharmaceutical companies, contract research organisations, or independently (freelancers), provided data. Participants were asked to determine typical average durations (in working days, not ranges) in their organisation (or for freelancers, in their

Table 2: Clinical study report scheduling: Cumulative participant data[a] from eight EMWA conferences 2008 to 2013[b]

Analysis or reporting task for a 'moderate complexity' phase III study in 200 to 400 subjects	Duration in working days or number of cycles		
	N^c	Mean (SD)	Range
Last subject data in-house to DBL	77	6.6 (5.6) days	1–30 days
DBL to draft TFLs	77	13.9 (9.6) days	1–56 days
Draft TFLs to final TFLs	75	10.6 (6.1) days	1–30 days
Draft CSR authoring from final TFLs to first draft CSR	78	16.9 (8.2) days	5–45 days
First draft CSR to final CSR	78	25.7 (21.1) days	3–120 days
Number of client review cycles	77	2.6 (0.8) cycles	1–5 cycles
QA on final integrated CSR	77	6.6 (5.6) days	1–30 days

Abbreviations: SD, standard deviation; DBL, database lock; TFLs, tables, figures, and listings; CSR, clinical study report; QA, quality assurance.
[a]Data sourced from completed pre-workshop assignments for the advanced EMWA workshop 'Scheduling and proposal writing: the clinical study protocol and report'.
[b]EMWA conferences: Barcelona May 2008; London November 2008; Ljubljana May 2009; Frankfurt November 2009; Lisbon May 2010; Nice November 2010; Paphos May 2012; Manchester May 2013.
[c]Workshop participants providing data.

experience of working with a range of organisations) for analysis and reporting tasks for a 'moderate complexity',[13] phase III study in 200–400 subjects. Mean (SD) duration for preparation of the first draft CSR from receipt of final TFLs was 16.9 (8.2) working days ($N = 78$) – just over 3 working weeks. The range was 5–45 working days showing how greatly this varies throughout the industry. The draft to final CSR (mean [SD]: 25.7 [21.1]; range: 3–120 working days) timeline was wide ranging, possibly due to the variability in the number of client review cycles between report versions (Table 2).

Algorithm-generated reporting timelines offer a useful guide at the outset of a project; subsequent project-specific refinements add value. When faced with an immovable final CSR date, wider skills of the CSR author must be brought to bear. Persuading colleagues in related but independent functions to adhere to timelines, and managing client expectations, are integral to on-time production of the final CSR.

By understanding the regulatory requirements and utilising project intelligence, medical writers can schedule and author a high-quality, on-time, final CSR for preregistration drug trials in the EU.

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The clinical study protocol and medical writing: A good fit?

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Abstract

The characteristics of the clinical study protocol (CSP) are discussed with regard to (i) its structure and (ii) its development process. The benefits of medical-writing involvement into both aspects are highlighted. In particular, medical writers are encouraged to participate in the development of the CSP template of their organisation.

While the clinical study report (CSR) has been a part of the classical medical-writing repertoire since the inception of medical writing as a professional discipline several decades ago, the clinical study protocol (CSP) made it onto medical writing's radar only considerably later – and in many cases has still not done so. This is surprising given the eminent importance of this document; it is also rather unfortunate because – as I will try to demonstrate in this article – the CSP is a document type that can particularly benefit from medical-writing expertise. This holds true for two separate aspects: (i) the CSP document and its structure and (ii) the process of CSP development.

The CSP document: Structure and content

We must start with an observation that is remarkable in our highly regulated environment: there is no 'official' guidance available that addresses the content and structure of CSPs in as detailed a manner as, for example, ICH E3 does for CSRs. ICH E6 on Good Clinical Practice lists content items to be included in a CSP. However, this list is far from exhaustive; in particular, it is considerably less detailed than the guidance for the corresponding CSR section (ICH E3: Section 9 'Investigational plan'). Moreover, ICH E6 provides no advice on how the various pieces of information in a CSP are best organised and arranged. Recently, the SPIRIT

(Standard protocol items: Recommendations for interventional trials) initiative has published a far more extensive list of content items – however, again without any guidance on how to best structure a CSP document.[1,2]

As a consequence of this lack of guidance, there is a huge variability across the pharmaceutical industry in how CSPs are organised and structured – which contrasts sharply with the industry-wide relative homogeneity of CSR appearance as shaped by ICH E3. In turn, the quality of CSP documents with regard to how they are organised and how they present their information can vary greatly. Hence, the proportion of poorly written documents is considerably higher for CSPs than for CSRs. The originators of ICH E3 must have had the same impression when they included in their guidance the explicit advice that 'in each [CSR] section describing the design and conduct of the study, it is particularly important to clarify features of the study that are not well-described in the protocol'. This is truly one of my favourite sentences in the whole of ICH E3. It spells out clearly and correctly that the job on methods description in the CSR is not done by blindly pasting the CSP text and adapting its tense.

Obviously, it is easier to prepare a well-organised, well-written, user-friendly CSR than it is to produce an equally high-standard CSP. Why is that? There is more behind this than just the availability or absence of formal guidance. An important reason for this difference is the necessity for built-in redundancies in the CSP. The CSP has to describe many separate, but interlinked aspects which address, for example, the way examinations are conducted, which variables are collected at these examinations, how the collected variables lead to derived variables, how these are statistically analysed, which conclusions may be drawn from the results, and how all this relates to the objectives of the trial. Presenting all these inter-related aspects clearly, separately, and logically, without confusing and tiring the reviewer

with a mass of repetitive information, is a true challenge. Carefully managing redundancies in the CSP text is a key success factor for the preparation of a user-friendly CSP.

A further aspect which makes CSPs trickier than CSRs is the increased diversity of the CSP's target audience. While the CSR almost exclusively targets the reviewers in the regulatory agencies, the CSP targets a diverse set of readers which includes not only the investigators and their staff (obviously the most important audience), but also other external bodies such as ethics committees, independent data review committees, and regulatory agencies. Each sub-audience is primarily interested in selected CSP topics only; and none of them is likely to read a CSP from cover to cover. Consequently, user-friendliness of the CSP requires thoughtful structuring with meaningful headings to allow each sub-audience to quickly locate the pieces of information relevant to them.

Here, at the latest, is where a medical writer should enter the stage. The presentation of complex information in a well-structured manner, thereby addressing both of the above aspects, i.e. carefully managed redundancies and user-group-targeted organisation, is certainly a core competency of medical writing. Any CSP team is well advised to make use of this expertise. The most efficient utilisation of this competency goes even a step further: obviously, the principles of effective CSP organisation indicated above should already have been taken into account by the underlying CSP template and its associated guidance text. The absence of formal guidelines for CSP structure constitutes an enormous opportunity to develop a general CSP template that lays the foundations for future quality CSP documents. Wherever medical writers see a chance to contribute to a CSP template, they should not hesitate to do so as this can make a large difference to subsequent projects.

When it comes to populating the CSP template for a specific CSP, the CSP author should always be aware of the importance of the CSP's document quality: the way the CSP presents its information can have a huge impact on the smoothness of the trial conduct and thus on the quality of the data collected. Moreover, the CSP sets the stage for several other documents further down the road such as the statistical analysis plan, CSR, and clinical summaries. Therefore, the CSP should reflect very conscious and thoughtful decisions with regard to the choice of terminology, definition of terms, and the way information is worded.

Going into details of how exactly a CSP template could be structured and populated is beyond the scope of this article. Anyone interested in going further into the depth of this complex matter may consider the corresponding EMWA workshops.

The process of CSP development

Medical-writing participation in CSP development is not common practice; and if medical writers are involved, their experiences are mixed. For too many medical writers, active membership in a CSP team can be tantamount to weeks or even months in a torture chamber. Many medical writers will find themselves producing an endless series of consecutive draft versions of the full CSP document to accommodate continual input from the team members – only to be surprised by a team decision after the tenth draft to add to the study design a further treatment arm, a preceding wash-out period and three more visits during the treatment period, and also to change the statistical approach from superiority to non-inferiority – based on a redefined primary variable.

In view of the aforementioned complexities and redundancies of the CSP document, implementing such modifications clearly represents a high burden. Obviously, something very wrong happened in this scenario. But how can such an inefficient mode of working be avoided?

First, although seemingly trivial, we have to acknowledge the importance of almost every trial for the sponsor. Typically, a clinical study is a substantial investment of resources, sometimes to the limit of the sponsor's capabilities or even beyond. Occasionally, even the sponsor's economic survival may depend on the positive outcome of one single study. Hence, the burden on the responsible people to make the right decisions in designing the study may be enormous. Moreover, even within the sponsor's organisation, multiple stakeholders, potentially representing conflicting positions, may want to have a say in the objective, design, and setup of the study. Getting everyone to agree on and commit to one final CSP can be a challenge under such circumstances. As a result, the necessary process of the sponsor's internal thought maturation is rarely a straightforward path; instead, the team may frequently change its mind and may even turn repeatedly in circles during this expedition.

In principle, there is nothing wrong with this, and we should not even think of picking the battle of changing it. What we can and should do, however, is to ensure that this process takes place on the basis of the right document type.

Here, a document referred to as study concept, protocol outline, or the like comes into play.

Regardless what we call it, this document is characterised by the following features. First, it is restricted to the main medical-scientific content items only (in particular, objectives; key in-/exclusion criteria; treatment arms; complete schedule of activities; definition of the main variables and their statistical analysis). Second, and more importantly, it is almost completely devoid of the built-in redundancies typical of a full CSP document. Hence, while it can be a real nightmare to incorporate multiple substantial content modifications into an existing complete CSP document, capturing these modifications in a study concept is easy and straightforward. All maturation steps of the main study features should take place using this study concept as the basis for discussion. Maintaining such a study concept document during the process of thought maturation within the CSP team is certainly a valuable service that medical writing can offer. Collecting and consolidating sometimes conflicting contributions in an efficient manner is an expertise we routinely provide.

Importantly, work on the complete CSP document should only start after agreement on the study concept, which should include input from external sources such as key opinion leaders as well as approval from the sponsor's internal governance bodies. Ideally, at the final review of the full CSP, no comments will be raised that could already have been raised upon review of the study outline.

Even if a new study is planned that will be very similar to a previously completed study, I strongly recommend following the study-concept approach for CSP development, rather than already starting on the full CSP by editing the approved CSP from the earlier study.

Experience tells us that many CSP teams want to see a complete draft CSP document sooner rather than later in the process. Obviously, an education process is needed to raise the comfort level of CSP teams with the study-concept approach. The main arguments to support our case are that: (i) the amount of information contained in the study concept actually suffices to support practically all discussions and decisions on the main study features,

and (ii) expanding an approved study concept to a complete CSP document is very straightforward and can be done by a medical writer very quickly; thus, following the study-concept approach will not extend the overall CSP development timelines.

Conclusions

The CSP qualifies for inclusion into the standard medical-writing repertoire. It is a document type that can greatly benefit from medical-writing expertise with regard to both the organisation of the complete CSP document and the streamlining of the process of its development.

Take-home messages for medical writers

1. Get involved in the setup and maintenance of the CSP template used in your organisation.
2. Support the CSP team's ongoing discussions on the study design by maintaining a brief, concise study concept reflecting all decisions.
3. Make sure that work on the complete CSP document starts only once the study concept is finally approved.
4. Ensure that the final CSP is sound and consistent with regard to the choice of terminology, definition of terms, and the way information is worded.

Acknowledgements

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The Investigator's Brochure: A multidisciplinary document

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Abstract

The Investigator's Brochure (IB) is a multidisciplinary document that summarises the main elements of an entire development programme to date. Although the IB also serves other purposes, it is primarily written to enable investigators conducting clinical studies to assess the risks and benefits associated with an investigational product. The ICH E6 guideline specifies that an IB should include information on the investigational product itself as well as on its use in non-clinical and clinical studies, together with a section providing guidance for the investigator on the use of the drug. Beyond a need for good project management skills, the main challenge and responsibility for medical writers is to ensure that the information presented in an IB is as concise and focused as possible while remaining balanced and sufficiently complete to communicate what an investigator needs to know about using the investigational product.

Keywords: Investigator, Brochure, Non-clinical, Clinical, ICH E6, Medical writer

A summary for investigators, but also for other stakeholders

In drug development, the Investigator's Brochure (IB) summarises the main elements of the entire development programme to date, primarily for the benefit of investigators conducting clinical studies. In addition to information on the investigational product itself, the IB provides an overview of non-clinical and clinical findings together with guidance for investigators on the use of the product based on medical interpretation of these findings.

The availability of a current IB is a regulatory prerequisite that sponsors (drug companies) must fulfil when intending to conduct clinical studies, as specified in the ICH E6 Guideline for Good Clinical Practice.[1] Although the IB is primarily targeted at investigators to inform them of the benefits and risks associated with the use of an investigational product, it is also used by independent ethics committees when deciding on ethical approval for conducting a clinical study. An IB also has a number of other regulatory uses, for example, it is a requirement for Investigational New Drug applications in the USA as well as for Investigational Medicinal Product Dossier and Paediatric Investigation Plan submissions in Europe. In addition, an IB can form the basis of some other documents needed for regulatory interactions, such as briefing packages and some of the summaries required when applying for marketing authorisation.

Regulatory guidance on structure and content

Section 7 of ICH E6 provides what is essentially a table of contents that is almost always used unchanged. The highest level sections are:

- Summary
- Introduction
- Physical, chemical, and pharmaceutical properties and formulation
- Non-clinical studies
- Effects in humans
- Summary of data and guidance for the investigator.

An IB is first required when conducting the first clinical study in humans. However, it is a living document and will then need to be updated as the development programme progresses and further information becomes available. ICH E6 specifies that an IB should be 'reviewed at least annually and revised as necessary', and that 'more frequent revision may be appropriate depending on the stage of development and the generation of relevant new information'. By 'relevant new information' the guideline means information that substantially influences what is known about the characteristics of the investigational

product, especially safety, to the extent that this needs to be communicated to enable reassessment of the benefits and risks. Alternatively, some sponsors issue an addendum to the IB when needing to rapidly communicate 'relevant new information'.

When the investigational product is intended for use in multiple indications, the sponsor will need to decide whether to prepare separate IBs for the different indications, or whether all indications should be covered in a single IB. ICH E6 does not give any specific guidance on this, so the approach taken is often quite subjective. Factors that can influence this decision may include how closely related the different indications are, differences in the product formulation or route of administration, timings of different development programmes, and whether development programmes for different indications are being conducted by different sponsors. With multiple IBs, the extent to which safety information should be included from other indications will need to be appraised on the basis of clinical relevance for the indication in question.

Regarding authoring style, the guideline indicates that the IB should be presented in a 'concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment'. The guideline does not provide any recommendation for the overall length of an IB. As for most documents, a concise and focused presentation style will have the best chances of communicating the necessary messages to the intended audience. In practice, an IB should not need to exceed ~100 pages, and a shorter document can also be sufficient.

The challenges for medical writers

The overarching challenge when preparing an IB is to achieve the concise and focused presentation style, finding an appropriate balance between completeness and readability. Ultimately, of course, the IB should be both complete and readable, but this takes time and effort. Thus, all too often, with time in short supply, an IB can tend to become inflated with information to make it supposedly complete but then the result can often be quite unreadable. This type of situation calls to mind the French philosopher Blaise Pascal, who wrote: 'I have only made this letter longer because I have not had the time to make it shorter'. What all too often happens is that with each subsequent update of the IB new information is simply added. Instead, an IB should ideally be reworked at the time of each update so that the overall length still remains a maximum of ~100 pages.

So, when preparing an IB, it is essential from the outset to bear in mind the need for conciseness. Often, pushback can be encountered from team members when confronted with a need to reduce the length of their contributions, and here it is important for the writer to remember (and argue) that it is almost always possible to retain key messages while reducing length. It can help to quote Rabbi Hillel, whose recommendation for how the bible could be summarised in one sentence was: '*What you yourself hate, don't do to your neighbour*. The rest is commentary'. This is a nice way to persuade teams that no matter how much starting material you have, it can inevitably be condensed further.

A consequence of the pursuit for conciseness is that, at each update, the contents of the entire IB should be revisited not only in terms of what should be added, but also in terms of how much of the existing content can be reduced or omitted. Logically, the first edition will contain an emphasis on non-clinical information, with no clinical information at all. At each subsequent update, the proportion of clinical information in the IB will increase (bearing in mind that ideally the overall length of the IB should not increase), starting with pharmacokinetics and pharmacodynamics and then progressing to safety and efficacy information from the target population. At the same time, as more clinical information becomes available, the amount of detail may be decreased for the non-clinical information as the clinical performance of the investigational product becomes better understood.

The six main sections of an IB

Summary

The first main section of an IB is the 'Summary', which should provide a high-level overview of all the subsequent sections, providing a profile of 'physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information'. ICH E6 recommends that the Summary should 'preferably' not exceed two pages. In reality, this is rarely achieved, especially with later versions of an IB that may, for reasons explained above, already contain a large amount of information. It is often easiest for a writer to ensure that the Summary is brief if he or she is already involved in preparing the first edition of an IB. When a writer inherits a later version with an already lengthy summary, it can often be a challenge to convince the team that what has 'worked' in previous editions now needs to be substantially revised. But it is certainly worth a try!

Introduction

The Introduction should aim to provide a high-level overview of the investigational product and the setting in which it is being investigated. Information to be covered includes the generic and trade names of the drug product, its active ingredient(s), and the pharmacological class and position of the product being investigated within this class, especially potential advantages over other products within the class. This section should also summarise the rationale for investigating the investigational product, identifying anticipated prophylactic, therapeutic, or diagnostic indications, and provide an overview of the investigational approach as already conducted or intended.

While some or all of the subsequent sections of an IB may be provided in some form by various team members (more on this later), the Introduction is one section of an IB that the writer inevitably will be required to draft *de novo*. Typical sources of information may include the clinical development plan and presentations and briefing packages that may have been prepared previously.

Physical, chemical, and pharmaceutical properties and formulation

This is a brief section describing the chemical, physical, and pharmacological properties of the investigational product, in terms of the drug product and, where relevant, also the drug substance. The section should aim to provide the investigator with sufficient information on the investigational product so that potential risks associated with either the drug itself or any excipients can be assessed. This section should also provide information on storage and handling, including preparation steps needed prior to administration, such as reconstitution or dilution.

Typically, the information for this section will be provided by the Sponsor's Chemistry, Manufacturing, and Controls (CMC) department, but the writer may need to adapt the material provided to the required format for the IB.

Non-clinical studies

Non-clinical studies have a key function in the first edition of an IB as they provide the sole evidence upon which benefits and risks can be assessed before first administering the investigational product in humans. A complete summary of the non-clinical profile is required, although sometimes details of exploratory studies may be omitted if they have been superseded by more complete studies providing the same type of information.

The basic structure of this section is provided by ICH E6, and includes major subsections on non-clinical pharmacology, pharmacokinetics and metabolism, and toxicology. In turn, the Toxicology section should be subdivided according to the topics of single and multiple dose toxicology studies, carcinogenicity studies, 'special studies' (studies specific to the type of product being investigated, e.g. irritancy studies on a product applied topically), reproductive toxicity studies, and mutagenicity studies. The amount of non-clinical information to be summarised will vary between programmes, and may, for example, be less extensive for a human plasma protein (for which only limited testing in animals is possible) than for a new chemical entity intended for an oncology indication (with a high potential for toxicity).

Until the writer has some experience with summarising non-clinical studies, this section can often be daunting. Depending on the sponsor's process, the writer may be provided with more-or-less complete sections, including tables and figures, and in this case the writer's main task may be limited to addressing language and formatting issues to ensure consistency with the rest of the IB as well as any style conventions. At the opposite end of the scale, the writer may be asked to generate text and tables *de novo* on the basis of anything from final reports (best-case scenario) through to sometimes non-validated information of varying quality contained in PowerPoint slides or *ad hoc* documents produced previously for any number of reasons (worst-case scenario, rare but known to happen).

ICH E6 lists the type of information to be summarised for non-clinical studies. Beyond the aspects of study design and the animal species or tests systems used, the summaries should include, as applicable, information on the nature, frequency, and intensity of pharmacological or toxic effects, time to onset and duration of these effects, and reversibility of the effects. When a large number of non-clinical studies are available, it can be beneficial to provide the details of each study in a tabulated format, often in an Appendix, and then provide focused summaries of results and interpretations, supported by tables and figures, within the non-clinical section.

Effects in humans

This section should summarise the results obtained in all clinical studies conducted with the investigational product to date. ICH E6 specifies that information should be summarised on the 'pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities', and this list in effect

provides subheadings that may be suitable for this section.

The earlier clinical studies (Phase 1) are focused on pharmacokinetics, pharmacodynamics, and product metabolism, usually in healthy subjects, whereas the later studies (Phases 2 and 3) provide efficacy data from the target population of patients for which the investigational product is intended. All clinical studies report safety, with the most comprehensive safety information being derived from longer-term use in Phases 2 and 3 studies.

ICH E6 specifies that 'where possible, a summary of each completed clinical trial should be provided'. However, while it is often easiest just to include self-contained summaries of each clinical study, adding new summaries with each update of the IB, this should not be the only approach. Instead, keeping them as concise as possible, the summaries should ideally be supplemented by a synthesis of the overall picture that has emerged from the sum of the information provided by individual studies.

In the case of pharmacokinetics, such a synthesis should be structured from information obtained in single and multiple dose studies that provide information on absorption, plasma protein binding, metabolism, distribution, and elimination. As appropriate, pharmacokinetic information may be analysed for specific subgroups as well as for the population as a whole, at a minimum typically by sex, age, and hepatic and/or renal impairment. Further aspects of the pharmacokinetic profile to be presented are potential effects of other drugs and food on the pharmacokinetics of the investigational product (and potential effects of the investigational product on other drugs), and population pharmacokinetic analyses.

In the case of efficacy and safety, wherever study designs permit, a pooled analysis of data can provide a suitable synthesis based on information from a larger number of subjects than available in individual studies. For efficacy, this may not always be possible due to differences in study design, in which case the synthesis should then be an integrating discussion of the efficacy findings drawn from across the range of studies conducted. For safety, a pooled analysis is almost always meaningful for eliciting potential safety signals. However, such a pooled analysis is often logistically not possible for an IB, due to resourcing and prioritisation issues, in which case a side-by-side analysis (as a tabular summary) of safety data from different studies can also provide insight. Because pooled analyses are rarely conducted specifically for IBs, this is the situation that is generally encountered by writers unless such an analysis happens to be available close to the time of preparing the IB, for example, for a regulatory submission. Irrespective of the approach taken, the aim is to summarise safety information in such a way that the investigator can readily understand the types of safety issues that may be encountered by patients treated with the investigational product.

As for the non-clinical section of the IB, the writer may be provided with text, tables, and figures that then only need to be revised for language and consistency. Alternatively, the writer may be provided with clinical study reports and be asked to write the clinical section *de novo*. In this case, it is important to work closely with the sponsor to ensure that the desired messages are synthesised from the various clinical studies contributing information to the IB, including the interpretation of efficacy and safety analyses across population subgroups.

Finally, if the investigational product has already been marketed anywhere at the time of preparing the IB, then the post-marketing safety information obtained by the sponsor will also need to be summarised. Although such safety data are generally not collected as rigorously as in clinical studies, the post-marketing safety database will often include data from a larger number of subjects than can be obtained from clinical studies conducted prior to marketing. Typically, this section will be provided by the sponsor's Pharmacovigilance department.

Summary of data and guidance for the investigator
The guidance for the investigator can be viewed as a kind of discussion section in which the totality of the non-clinical and clinical experience is summarised and interpreted so that inferences for the use of the investigational product in future studies can be drawn. Thus, any non-clinical findings of potential concern will need to be discussed in terms of either what has been observed in clinical studies conducted to date or what may be anticipated in future clinical studies.

This section should also provide practical information for the management of subjects being treated with the investigational product. If applicable, information should also be drawn from published knowledge on other drugs in the same class. This section of the IB will generally contain subheadings that are also used in prescribing information, such as 'Therapeutic indications', 'Contraindications', and 'Warnings and precautions for use'. Thus, this section may be viewed as a precursor of the prescribing information that is prepared when marketing approval is applied for.

Unless writers are medically qualified, they are unlikely to be asked to prepare the guidance for

the investigator *de novo*. Instead, this section is likely to be provided by the sponsor, with the writer then conducting a linguistic and consistency check versus the rest of the IB.

The project management aspect

In addition to writing the IB, or parts of an IB, the writer also needs to be a good project manager to ensure preparation to the required specification and availability on time. While this principle also holds true when writing almost any type of document, the IB can be among the more challenging in this respect because it covers the entire development programme and therefore the writer often has to interact with team members from a range of functions to obtain the information needed. Sometimes members from non-clinical and CMC departments are less familiar with the document standards required for writing an IB and are less sensitive to the often tight timelines involved. The writer is therefore often the person who needs to address these issues by interacting directly with team members to ensure that they understand which material is required, and by when.

Depending on the sponsor's approach to preparing IBs, the process may start with the writer having to identify the people to interact with for each section. If they are going to provide text and table or figure contributions, then it can help to be proactive by ensuring that the correct IB template is available to the team, either by distributing the file or by supplying a link to where the document is located. In the case of IB updates, the final version of the previous edition of the IB will usually serve as the template for the next edition. While it is unrealistic to expect perfect formatting and consistency when team members submit their contributions (it is the writer's job to ensure this!), providing a template or document in the correct format nevertheless increases the chances of receiving material in a useable format.

Another project management challenge is the need to track the reviewing and revision of individual sections. If no one else is responsible, then the writer is well advised to draw up timelines for writing, reviewing, revision, and finalising the IB and distribute these to the team so that everyone is aware by when the approved document is required.

Ideally the writing, reviewing, and revision steps should be planned for the IB as a whole so that team members from different functions can consider the totality of the information being presented. In practice, some contributions may be provided later than others, forming rate-limiting steps for the IB as a whole, and this needs to be planned for accordingly, for example, with truncated review cycles that are separate from those for the main document. There can be a number of permutations for this type of situation, and the writer should develop strategies for minimising the chances of the overall timelines being threatened.

Conclusions

The IB is a living document, needing regular updating, that presents writers with an interesting opportunity to interact with a diverse team drawn from a range of functions contributing to the development of the investigational product. This diversity can increase the logistical challenges involved in obtaining the material needed for preparing the IB. Depending on the process foreseen for preparing the IB, the writer may be involved in coordinating and revising text contributions received from various team members, or the writer may be required to write some or all of the IB based on reports and other material received as source information. Whichever process is involved, the main challenge and responsibility is to ensure that the information presented in the IB is as concise, complete, and focused as possible, and that the IB is appropriately structured to enable it to effectively communicate what an investigator needs to know for evaluating the benefits and risks of using the investigational product.

Acknowledgements

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An overview of the Common Technical Document (CTD) regulatory dossier

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Abstract

The Common Technical Document (CTD) was designed to provide a common format between Europe, USA, and Japan for the technical documentation included in an application for the registration of a human pharmaceutical product. The CTD dossier is divided into five main modules: Module 1 – Administrative information and prescribing information; Module 2 – Overviews and summaries of Modules 3–5; Module 3 – Quality (pharmaceutical documentation); Module 4: Non-clinical reports (pharmacology/toxicology); Module 5: Clinical study reports (clinical trials). Detailed guidelines are provided describing the content of each module and the majority of submissions must now follow the CTD format for submission dossiers.

Keywords: Common Technical Document, Harmonisation, ICH M4, Regulatory submissions

Background

Prior to the implementation of the Common Technical Document (CTD) in 2002, each of the three major regulatory regions (European Union (EU), USA, and Japan) had its own set of guidelines and format for the submission of a regulatory dossier to obtain marketing approval for a new drug or a variation to the licensing of an existing drug. In Japan, the GAIYO was required, which organised and presented a summary of the technical information; in Europe, Expert Reports and Tabulated Summaries were required and Written Summaries were recommended; and in the USA, the Food and Drug Administration (FDA) had guidance documents regarding the format and content of the New Drug Application (NDA). To complicate things further, countries within the EU also had their own guidelines and formats, making submission to multiple countries and multiple regions a time-consuming and repetitive process.

In 2000, representatives from the European Medicines Agency (EMA), the USA FDA, and the Ministry of Health, Labour, and Welfare in Japan developed a set of guidelines defining the structure and content of the dossier for an application for the registration of a new medicine that could be used across all three regions. These guidelines were developed under the umbrella of The International Conference on Harmonisation (ICH) and have become part of the family of ICH guidelines. The aim of the CTD was simple – it would provide a common format for the technical documentation that would significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and would ease the preparation of electronic submissions. In addition, regulatory reviews and communication with the applicant would be facilitated by a standard document of common elements and the exchange of regulatory information between Regulatory Authorities would be simplified.[1]

The first set of ICH CTD guidelines were published in 2002, and currently there are four ICH guidelines on the CTD (M4, M4Q, M4S, and M4E), along with four question and answer documents. In July 2003, the CTD became the mandatory format for NDAs in the EU and Japan, and the strongly recommended format for NDAs submitted to the FDA. Since the implementation of the CTD format in the EU, USA, and Japan, the CTD has also been adopted by several other countries including Canada and Switzerland. The paper CTD is now destined to be replaced by its electronic counterpart, the eCTD,[2] with the eCTD being mandatory for the centralised procedure in the EU since 2010.

General principles

As for all documents, the display of information in the CTD should be unambiguous and transparent. The ICH M4 guidance document on the

organisation of the CTD[1] recommends that text and tables are prepared using margins that allow the document to be printed on both A4 paper (EU and Japan) and 8.5×11" paper (USA). Times New Roman, 12-point font, is recommended for narrative text. Acronyms and abbreviations should be defined the first time they are used in each module and literature references should be cited at the end of each module in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[3]

Every document included in the CTD should be numbered starting at page 1, except for individual literature references where the existing journal page numbering is considered sufficient. It is of note that the ICH M4 guidelines state that it is not necessary to display the page numbers as '1 of n', where n is the total number of pages in the document. All pages of a document should include a unique header or footer that briefly identifies its subject matter (e.g. an abbreviation of the full section number and title, i.e. 2.7 Clinical Summary). To avoid fifth, sixth etc. level subheadings (e.g. 2.6.6.3.2.1) within a document, the M4 guidelines[1] allow a shortened numbering string. In this case, the document number and the name (e.g. 2.6.6 Toxicology Written Summary) should appear in the page header or footer and then an abbreviated section numbering used within the document, e.g. 1, 1.1, 2, 3, 3.1, 3.2 etc.

Overall organisation of the CTD

The overall structure of the CTD is detailed in the ICH M4 guidelines[1] and includes a granularity section that provides guidance on document location and pagination within the CTD dossier. This granularity information is particularly useful if the dossier contains multiple indications or multiple components of the investigational medicinal product (IMP). In addition to the M4 guidelines, a set of questions and answers is also provided to address the most common issues raised.[4]

The CTD dossier is divided into five main modules (see Figure 1):

Module 1: Administrative information and prescribing information
Module 2: Overviews and Summaries of Modules 3–5
Module 3: Quality (pharmaceutical documentation)
Module 4: Non-clinical reports (pharmacology/toxicology)
Module 5: Clinical study reports (clinical trials).

Module 1 is not strictly included in the CTD since it contains documents that are specific to each region, e.g. application forms or the proposed label. This module will not be discussed in any further detail in this article since the content and format of this module is specific to individual Regulatory Authorities.

Modules 2–5 though are common to all regions and these comprise the main body of the CTD. Module 2 contains the CTD overviews and summaries. It starts with a general introduction to the drug, including its pharmacological class, mode of action, and proposed clinical use. Module 2 then provides an overall summary of the 'quality'
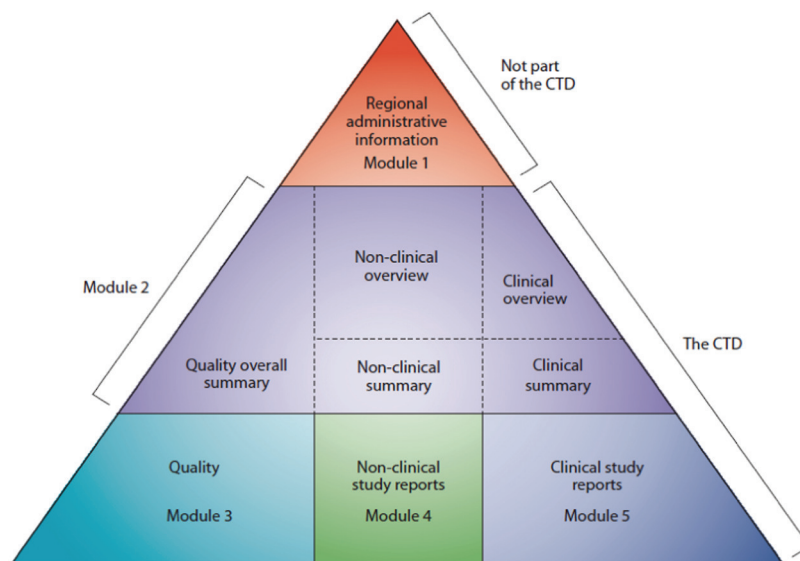

Figure 1: The CTD triangle.

information (i.e. the pharmaceutical documentation), as well as the Non-Clinical Overview and the Clinical Overview, the Non-Clinical Written Summaries and the tabulated summaries, and the Clinical Summary. The information provided in Module 2 is based on the foundation material that is provided in Module 3 for the quality information, Module 4 for the non-clinical information, and Module 5 for the clinical information.

Module 2: CTD overviews and summaries

Module 2 contains seven sections that should be maintained in the following order:

2.1 Table of contents
2.2 Introduction
2.3 Quality Overall Summary
2.4 Non-clinical Overview
2.5 Clinical Overview
2.6 Non-clinical Written and Tabulated Summaries
2.7 Clinical Summary.

Module 2.2: Introduction
The introduction in Module 2.2 should be a general introduction to the IMP, including its pharmacological class, mode of action, and proposed clinical use. In general, the introduction should not exceed one page.

Module 2.3: Quality overall summary
The quality overall summary (QOS) is a summary of the chemical and pharmaceutical data in the dossier (including data for biological/biotechnological products). Guidance on the structure of the QOS is provided in ICH M4Q guidelines,[5] with answers to the most common issues raised provided as a separate document.[6] The structure of the QOS broadly follows the structure of the data included in Module 3. The QOS should not include information that has not already been included in Module 3 or in other parts of the CTD.

The aim of the QOS is to discuss the critical parameters of the product, but it should also address issues that arose during development and provide justification for instances where guidelines were not followed etc. The QOS should normally not exceed 40 pages of text, excluding tables and figures (in cases of biotech products and products manufactured using more complex processes it can be longer but should not exceed 80 pages, excluding tables and figures).

Module 2.4: Non-clinical Overview and Module 2.6: Non-clinical Written and Tabulated Summaries
The structure and content of Modules 2.4 and 2.6 are specified in the ICH M4S guidelines,[7] with answers to the most common issues raised provided as a separate document.[8] The main purpose of the Non-Clinical Written and Tabulated Summaries in Module 2.6 is to provide a comprehensive factual summary of the non-clinical information on pharmacology, pharmacokinetics, and toxicology. The Non-Clinical Written Summaries are generally in the region of 100–150 pages long. A total of 34 templates are provided for the preparation of the Tabulated Summaries in the ICH M4S guidelines.

The interpretation of the data, the clinical relevance of the findings, any association between non-clinical findings and quality aspects of the IMP, and any implications of non-clinical findings for the safety of the IMP in humans should be addressed in the Non-Clinical Overview (Module 2.4). If relevant guidelines on the conduct of the studies exist, then these should be noted as being adhered to, or justification provided if there were any deviations. The non-clinical testing strategy should be discussed and justified and a comment on the Good Laboratory Practice (GLP) status of the studies should also be included. Reference to the scientific literature and characteristics of related products should also be taken into account (i.e. if a particular finding has been seen with a drug in the same class as the IMP this should be discussed). Thus, the Non-Clinical Overview is an integrated and critical assessment of the pharmacological, pharmacokinetic, and toxicological aspects of the IMP in animals. The Non-Clinical Overview should generally not exceed 30 pages.

Module 2.5: Clinical Overview and Module 2.7: Clinical Summary
These modules are usually the documents a medical writer is most likely to be asked to write. The structure and content of Modules 2.5 and 2.7 are specified in the ICH M4E guidelines,[9] with answers to common issues raised provided as a separate document.[10] The Clinical Overview is a short document that provides a Critical Assessment of the clinical data, whereas the Clinical Summary is a longer document that focuses on data summarisation and integration. The Clinical Summary and Clinical Overview provide the supporting information for the Summary of Product Characteristics (SmPC) or the product label (included in Module 1 of the CTD), so it is important these documents are consistent.

The primary purpose of the clinical summary is to provide a comprehensive factual summary of the

clinical data. This includes information provided in the clinical study reports located in Module 5, information from any meta-analyses or other cross-study analyses that have been conducted, and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations and should not provide any interpretation of the data – this is covered within the Clinical Overview. The Clinical Summary is divided into sections covering biopharmaceutics and associated analytical methods, clinical pharmacology, efficacy, and safety. The synopsis from each study report is also included in this module (or appropriately hyperlinked in an eCTD). The clinical summary is between 50 and 400 pages long, although it may be longer if more than one indication is included.

The Clinical Overview is a key document in the CTD dossier. The Clinical Overview is divided into six sections: product development rationale, biopharmaceutics, clinical pharmacology, efficacy, safety, and risk/benefit conclusions. In contrast to the factual presentation in the Clinical Summary, the Clinical Overview provides a critical analysis of the drug development programme and its results, including discussion and interpretation of clinical findings, and the relevance of other information (e.g. pertinent animal data or product quality issues that may have clinical implications). It is important to remember that the Clinical Overview presents the conclusions and implications of the data and it should not repeat the information presented in the Clinical Summary or elsewhere in the CTD. The Clinical Overview should present the strengths and limitations of the development programme and study results, analyse the benefits and risks of the IMP in its intended use, and describe how the study results support critical parts of the prescribing information. The quality of the clinical programme and performance of the studies, including a statement regarding Good Clinical Practice (GCP) compliance, should also be included. The clinical overview should also discuss the place of the IMP in the clinical armamentarium if approval is given for a licence. Appropriate reference should be made to the literature to put the results into context. Finally, the Clinical Overview should provide an evaluation of the benefits and risks of the IMP based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimise benefits and manage

risks. The Clinical Overview should be a relatively short document of approximately 30 pages.

Module 3: Quality

Module 3 presents the chemistry, manufacturing, and controls reports for the product included in the registration dossier. Full details of what should be included in Module 3 are provided in the ICH M4Q guideline.[5] Sections on both drug substance and drug product are included in this module. The main headings in this section (that must not be altered) are as follows:

3.1 Table of contents of Module 3
3.2 Body of data
    3.2.S Drug Substance
    3.2.P+ Drug Product
3.3 Literature references used in Module 3

Module 4: Non-clinical study reports

Module 4 presents the non-clinical reports included in the dossier. The structure and content of Module 4 is specified in the ICH M4S guidelines.[7] The main headings in this section (that must not be altered) are as follows:

4.1 Table of contents of Module 4
4.2 Study reports
    4.2.1 Pharmacology
    4.2.2 Pharmacokinetics
    4.2.3 Toxicology
4.3 Literature references used in Module 4.

Module 5: Clinical study reports

Module 5 presents the clinical reports included in the dossier. The structure and content of Module 5 is specified in the ICH M4E guidelines,[9] which provided a specific placement of clinical study reports and related information to simplify preparation and review and to ensure completeness. The placement of a report is determined by the primary objective of the study, with each report appearing in only one section. If there are multiple objectives, the study should be cross-referenced in the various sections. The main headings in this section (that must not be altered) are as follows:

5.1 Table of contents of Module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
    5.3.1 Reports of biopharmaceutic studies
    5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials

5.3.3 Reports of human pharmacokinetic (PK) studies

5.3.4 Reports of human pharmacodynamic (PD) studies

5.3.5 Reports of efficacy and safety studies

5.3.6 Reports of post-marketing experience

5.3.7 Case report forms and individual patient listings

5.4 Literature references.

Issues

Although the development of the CTD has been largely successful and all dossiers now use the CTD format (with newer dossiers moving to the eCTD format), some regions still persist in retaining some of their original pre-CTD dossier requirements. The most common example of this is the FDA requirement to submit an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in the USA submission, even though the intent was that the Clinical Summary would replace them (Module 2.7.3 Summary of Clinical Efficacy was the replacement for the ISE and Module 2.7.4 Summary of Clinical Safety was the replacement for the ISS). The guidance provided is therefore to include the full ISE and ISS in Module 5 and then condense this into a summary format for the Module 2.7 documents.[10]

The CTD has been largely successful in meeting its objectives of providing a common format for the information included in a submission dossier. However, it is of debate whether this has resulted in the suggested reductions in time and resources needed to compile applications.

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Good clinical practice (GCP): A universal call for ethics in biomedical research

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Abstract

Today, the principles of good clinical practice (GCP) form such an integral part of the development of new medicines that they could easily be taken for granted. Yet, the road to a universal code of ethics in human experimentation is paved with tragedies which have only gradually led to tightened rules on human experimentation. Awareness of the historical roots of GCP helps explain that GCP, rather than representing a seemingly endless series of regulations, finally provides an international ethical and scientific quality standard designed to protect the rights and safety of individuals consenting to participate in clinical trials and to ensure the integrity and credibility of clinical research data. For medical writers, familiarity with the principles of GCP, which in the European Union are now a legal obligation, is an essential prerequisite for providing documentation in compliance with the ethical and scientific principles of GCP: not only are medical writers expected to frame clinical research into a language that enables independent assessors to evaluate the methodological validity of a study and the safety and efficacy of a given drug, they also compose documents that may be instrumental in assuring the rights and safety of clinical trial participants.

Keywords: Good clinical practice (GCP), Medical writing, Ethics in human research

The decision to allow a new medicinal product to enter the market can have far-reaching consequences for millions of patients around the world. Today, the development of a new medicine is so inextricably linked with the concept of good clinical practice (GCP) that it is hard to believe that GCP has only been around for about 20 years.

Historical perspective

The realisation that it is important both to thoroughly assess medicinal products before allowing them to be marketed and to safeguard the interests of those healthy individuals or patients in whom new products are first assessed was nurtured by a series of tragedies – caused either by a lack of ethical judgement, a lack of awareness, or a combination of both.

First directive on informed consent, Prussia 1891

The advances in science in the late nineteenth century were accompanied by an increased demand for experimentation in human subjects. Human experiments were mainly carried out in hospitalised patients or prisoners and without their consent. In 1891, the public controversy about the ethics of such practices caused the government of the Kingdom of Prussia to pass a directive decreeing that tuberculin for the treatment of tuberculosis 'must in no case be used against the patient's will'.[1] Nine years later, the first regulations regarding non-therapeutic research in Western medicine were passed.[1]

The Neisser case and the first detailed directive on informed consent of 1900

In 1898, the German Albert Neisser, professor of dermatology and venereology, published the results of studies designed to find a cure for syphilis. He inoculated serum from patients with syphilis into patients who had been hospitalised for other reasons. When some of the 'vaccinees', most of whom had been prostitutes, actually contracted syphilis, Neisser claimed that their infection was a result of their professional activity. In response to the public outcry triggered by the case, the Prussian parliament, assisted by a scientific commission composed of leading German experts such as Rudolf Virchow, in 1900 issued the first directive in history to require unambiguous consent of the subject after proper information given by a physician, the *Richtlinien für Wissenschaftliche Experimente* (Guidelines for Scientific

Experiments).[1] These guidelines may be the first reported regulatory document applicable to the field of human experimentation and recognising the need for the protection of vulnerable populations.[2]

Guidelines for new therapy and human experimentation of 1931

Continued criticism of unethical human experimentation caused the government of the Weimar Republic to issue detailed *Richtlinien für Neuartige Heilbehandlung und für die Vornahme Wissenschaftlicher Versuche am Menschen* (Guidelines for New Therapy and Human Experimentation) in 1931. These guidelines clearly differentiated between therapeutic and non-therapeutic research and, on some counts, included regulations that were even stricter than those contained in the Nuremberg Code of 1947 or the Declaration of Helsinki of 1964. For example, human experiments in dying patients were absolutely prohibited.[1] Thus, contrary to common belief, the concept of informed consent had developed long before World War II and was introduced not at the instigation of the research community but by government authorities.

Human experiments during World War II and the Nuremberg Code of 1947

However strict these pre-war regulations, they were unable to prevent some of the worst atrocities ever to be performed under the cloak of medical research. The Doctors' Trial, one of the subsequent Nuremberg Trials held in the US occupation zone from 1946 onwards, brought to light the gruesome experiments performed during World War II in huge numbers of Jewish prisoners, members of the Roma population, mentally or physically disabled Germans, and prisoners of war. One category of experiments was performed with a view to advancing the survival of German military personnel and included freezing, transplant, infection, and mustard gas experiments in prisoners. Another sought to advance the racial goals of the Nazi ideology using medical experiments in twins as well as artificial insemination and sterilisation studies, all performed with a view to creating a master race. These experiments left thousands of victims physically and mentally mutilated, dead, or killed for the purpose of post-mortem measurements.[3]

The final judgement of the Doctors' Trial passed in 1947 enumerated a set of 10 principles of what the trial's medical expert witnesses, Drs Leo Alexander and Andrew Ivy, and the trial's judges and prosecutors considered legitimate medical research, derived from the natural law of all people.[2] These 10 points were to make up the Nuremberg Code.[4] As Grodin put it, 'Medical ethics would forever be changed after the Holocaust'.[2]

Declaration of Geneva of 1948

Spurred by the revelations of the Doctors' Trial and details about the terrifying human experiments performed by the Japanese Army at the biological and chemical warfare research Unit 731 in China during World War II, the idea of establishing an international medical organisation setting ethical guidelines for physicians across the world was born in the House of the British Medical Association in 1945, a popular meeting place for doctors from all the allied nations during the war. In 1947, the World Medical Association (WMA) was founded. Among its first activities was the drafting of a modernised version of the ancient Oath of Hippocrates, which was adopted by the General Assembly of the WMA in 1948 as the Declaration of Geneva.[5] Also inspired by the horrors of World War II, the idea for a position paper on recommendations guiding physicians in biomedical research involving human subjects was born in 1953. Before the adoption of this guidance document – which would come to be referred to as the *Declaration of Helsinki* – another disaster was to shake the world of medical research.

Thalidomide disaster

Thalidomide had been developed in the 1950s as an anticonvulsant drug. Early trials showed it to be unsuitable for this purpose but indicated that it had sedative properties. It was first marketed in Germany in 1957 as an over-the-counter drug considered safe even for use during pregnancy, and it was also found to be a highly effective anti-emetic alleviating morning sickness.[6] By 1960, thalidomide was sold throughout Europe and South America, in Canada, and in many other parts of the world.[7]

By about the same time it had become clear that long-term use of the drug was associated with peripheral neuritis. The British Medical Journal in 1960 published a letter by Leslie Florence[8] about peripheral neuritis in four of his patients, further nurturing FDA medical officer Frances Oldham Kelsey's long-held suspicion about thalidomide's safety. Although Germany was already witnessing an increase in teratogenic deformities in children born to mothers who had used the drug during pregnancy, no link with thalidomide was established until 1961,[9] when, in response to reports by

the German paediatrician Hans-Rudolf Wiedemann and the geneticist and paediatrician Widukind Lenz, the drug was finally taken off the market by the German health authorities.[8] By that time, thalidomide had caused the deaths of more than 2000 children and serious birth defects in about 10 000 children,[9] most of them in West Germany. At the time, drugs were tested in rodents only, and because they were thought to be incapable of passing the placenta, were not tested for teratogenic effects.[10] In the wake of the thalidomide disaster, many countries introduced stricter assessment, approval, and monitoring procedures for new medicinal products.

Declaration of Helsinki of 1964

The Declaration of Helsinki – the first significant effort by the medical community to regulate research in human subjects that had been on the agenda of the WMA since after World War II – was finally adopted in 1964. It expanded on the principles of the 1947 Nuremberg Code and linked them to the 1948 Declaration of Geneva – but may also have had much to do with the devastating effects of thalidomide on thousands of babies. Among its general principles are that 'medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights', and that the goal of generating new knowledge 'can never take precedence over the rights and interests of individual research subjects'. Consistent with the mandate of the WMA, the Declaration of Helsinki addresses the medical profession only.[11]

Guidelines for GCP by the World Health Organization of 1995

Four years after the adoption of the Declaration of Helsinki, the World Health Organization (WHO) convened the Scientific Group on Principles for Clinical Evaluation of Drugs in 1968 and charged it with formulating principles for the clinical evaluation of drug products.[12] In 1975, WHO formed another Scientific Group responsible for drawing up relevant guidelines. The reports that resulted from this work formed the basis for the WHO guidelines for GCP for Trials on Pharmaceutical Products published in 1995,[13] which in turn found their way into the 1996 guideline for Good Clinical Practice E6 by the International Conference on Harmonisation (ICH)[14] or the international standard EN ISO 14155:2011, Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice published in 2011.[15]

Based on the 'ethical principles which have their origin in the Declaration of Helsinki', the WHO guidelines for GCP extended these principles to apply not only to physicians, but to all parties involved in clinical trials – from sponsors, investigators, site staff, and contract research organisations to ethics committees, regulatory authorities, and clinical trial participants.[14,15]

Guideline for Good Clinical Practice E6 by the ICH of 1996

In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) passed its guideline for Good Clinical Practice E6, based in part on the guidelines drawn up by the WHO.[16] Although both guidelines share the same content, an important difference is that the ICH guideline for Good Clinical Practice E6 was drawn up as a regulatory standard with the express purpose of harmonising the technical requirements for the registration of medicinal products across the three main ICH regions, i.e. the USA, Japan, and Europe, whereas the WHO guidelines for GCP are intended as an educational tool for regulatory agencies in countries where no other guidance exists.

In Europe, efforts at harmonising regulatory requirements had dated back to the 1980s, as the then European Community started to move towards the development of a single market. In 1990, in response to increased globalisation, the ICH was established to bring together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the USA to achieve 'greater harmonisation to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner'.[16] ICH harmonisation efforts are summarised in guidelines developed in a step-wise approach, from consensus building in Step 1 to adoption of the guideline in Step 4 and implementation in each of the three ICH regions in Step 5.[17] Guidelines are divided into four categories, with quality, safety, and efficacy guidelines reflecting the three criteria for approving and authorising new medicinal products and multidisciplinary guidelines covering cross-cutting topics (Figure 1).

The benefits of ICH range from reducing duplication of testing and reporting, providing guidance on the preparation of regulatory documents, such as clinical study reports, use of a harmonised submission dossier format, i.e. the common technical document, or the creation of a joint medical terminology, i.e. Medical Dictionary for Drug

Figure 1: Four categories of ICH guidelines. Source: http://www.ich.org/products/guidelines.html.

Regulatory Affairs (MedDRA) – all designed to streamline the dossier compilation and review process across regions and getting high-quality, safe, and effective medicinal products to patients in a more timely fashion. The ICH guideline for Good Clinical Practice E6 is part of the efficacy category of ICH guidelines.[16]

Principles of GCP

In brief, the principles of GCP are designed 'to ensure that clinical research participants are not exposed to undue risk and that the data generated from the research are valid and accurate'.[14] They are intended to be applied during all stages of drug development and specify standards for designing, conducting, recording, and reporting clinical trials.

- In terms of *study design*, GCP requires a written study protocol describing the trial's objectives, design, methodology, and statistical considerations, an investigator's brochure summarising the available clinical and non-clinical data on the investigational product, scientific soundness and feasibility, and bias-reducing measures such as randomisation and blinding.
- In terms of *study conduct*, GCP requires approval of the study by both independent ethics committees and regulatory authorities, compliance with the protocol, freely given informed consent, data confidentiality, adequate medical care for subjects experiencing adverse events or adverse drug reactions, product accountability, adequate qualification and training of all study personnel, and appropriate resources.

- In terms of *recording standards*, GCP requires that case report forms be completed accurately and in agreement with the patient records, reliable data handling, security systems preventing unauthorised access to the data, internal audits overseeing the conduct of the trial, and adequate management and archiving strategies for study files.
- In terms of *reporting*, GCP requires adverse events, interim and final reports, and monitoring, audit, and inspection reports to be compiled and archived.

Importantly, the principles of GCP 'may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects'.[16] The 13 core principles as enumerated in the ICH guideline for Good Clinical Practice E6 are given in Box 1.

Box 1: Thirteen core principles of GCP as spelled out in the ICH guideline for Good Clinical Practice E6

1. *Ethical principles.* Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s).
2. *Favourable benefit–risk profile.* Before a clinical trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A clinical trial should be initiated and continued only if the anticipated benefits justify the risks.

3. *Subject rights.* The rights, safety, and well-being of the trial subjects override the interests of science and society.
4. *Adequate supporting data.* The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. *Scientifically sound protocol.* Clinical trials should be scientifically sound and described in a clear, detailed protocol.
6. *Ethics committee oversight.* A trial should be conducted in compliance with the protocol that has received prior institutional review board/independent ethics committee approval or favourable opinion.
7. *Medical care by qualified physician.* The medical care given to subjects, and the medical decisions made on their behalf, should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist.
8. *Qualified personnel.* Each individual involved in conducting a clinical trial should be qualified by education, training, and experience to do their respective task(s).
9. *Informed consent.* Freely given informed consent should be obtained from every subject prior to participation in the clinical trial.
10. *Record-keeping.* All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
11. *Subject confidentiality.* The confidentiality of records that could identify subjects should be protected – respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. *GMP manufacturing.* Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. *Quality assurance and monitoring.* Systems with procedures that assure the quality of every aspect of the clinical trial should be implemented.

GCP in the European Union

In 2001, the principles of the ICH guideline for Good Clinical Practice E6 found their way into European legislation with the implementation of the Clinical Trials Directive (i.e. Directive 2001/20/EC) and the accompanying guidance documents. In 2005, the GCP Directive (i.e. Directive 2005/28/EC) clarified the principles of GCP in the European context as required by Directive 2001/20/EC. Directives 2001/20/EC and 2005/28/EC had to be transposed into national law by May 2004 and January 2006, respectively.

Importantly, both directives apply to interventional 'clinical trials on medicinal products for human use' only. They do not apply to non-interventional studies, i.e. 'studies where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation', nor do they apply to clinical investigations that do not involve medicinal products, such as studies assessing medical devices[17] or other non-pharmacological interventions, such as surgical techniques[18,19] or diagnostic procedures.[20] For clinical investigations involving medical devices, the aforementioned harmonised EU standard EN ISO 14155:2011 provides practical guidance on the conduct and reporting of clinical investigations. Unlike GCP in clinical studies with medicinal products as implemented in Directive 2001/20/EC, therefore, the use of GCP in other areas of clinical research is not mandatory in the European Union (EU).

Ethics is a perpetually evolving subject in the face of a constantly changing social and political environment and rapid development in the fields of science and technology. For example, the year 2013 saw the seventh revision of the Declaration of Helsinki. In July 2012, the European Commission, adopted a proposal for a clinical trials regulation designed to repeal Directive 2001/20/EC,[21] which is widely considered to have curbed the attractiveness of the EU for conducting clinical trials by introducing unnecessarily tight administrative and regulatory requirements. Between 2007 and 2011, the costs for conducting clinical trials in the EU more than doubled, insurance fees for industry sponsors increased by 800%, and the number of applications for clinical trials dropped by 25%.[22] Also, considering that about 24% of clinical trials (with about 67% of enroled subjects) in Europe are performed in at least two EU member states, an EU regulation, which immediately and simultaneously takes effect in all members states, is likely to more effectively harmonise clinical trial procedures throughout Europe than EU directives, which still have to be transposed into national law and leave considerable leeway as to how the provisions set out in the directive are actually implemented in each member state.

GCP for medical writers?

The ICH guideline for Good Clinical Practice E6 calls for 'each individual involved in conducting a clinical trial' to be qualified to do their respective task. According to Directive 2001/20/EC, compliance with GCP not only 'provides assurance that the rights, safety and well-being of trial subjects are protected and that the results of the clinical trials are credible' but is also a legal requirement throughout the EU. Therefore, being thoroughly familiar with the principles of GCP is as important for medical writers as for other members of a clinical development team.

For one thing, medical writers are expected to frame clinical research rationales, processes, and data into a language that enables independent assessors and reviewers to determine whether the study results presented are indeed 'credible' and evaluate the safety and efficacy of a given medicine. To be able to do so, medical writers need to understand what was done and why. For another, although medical writers are not directly involved in patient care, the documents they write and compile may play an essential role in assuring the rights and safety of healthy individuals or patients participating in clinical research – many of whom may be faced with serious illness and some of the most daunting questions of their lives. In this vein, the principles of GCP – and the historical developments that lead up to their adoption – are a constant reminder that the primary and ultimate purpose of clinical research is to promote health and well-being and to ensure respect for the dignity of all human life.

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Adverse event reporting: A brief overview of MedDRA

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Abstract

Since its inception 20 years ago, the Medical Dictionary for Regulatory Activities (MedDRA) has become the lingua franca of safety reporting in a regulatory context. The standardised reporting across different regulatory regions and languages is a major strength of MedDRA. The detail offered by the large number of terms may, in principle, be considered an advantage too, but increased granularity is not without its problems. Awareness of the potential issues with MedDRA should help medical writers provide clear, transparent safety reporting.

Keywords: MedDRA, Safety reporting, SMQs

While efficacy endpoints used in clinical trials can vary greatly according to therapeutic field, stage of development, and study design, safety endpoints are usually much more uniform. Safety reporting is generally based on analysis of adverse events and safety laboratory variables. Nowadays, adverse events in most trials and indeed adverse events analysed as part of post-marketing pharmacovigilance activities are reported using the Medical Dictionary for Regulatory Activities (MedDRA). This ubiquitous dictionary is essentially a terminology database that is used for converting the event reported by the investigator (known as the 'verbatim term' or 'literal term') into a standard term in a process known as coding. Once adverse events have been properly coded, frequencies and incidences of adverse events can be analysed in the search for safety signals.

History of MedDRA

In the days before the International Conference on Harmonisation (ICH), many different coding dictionaries were used. The Food and Drug Administration, for example, preferred the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) coding system. Other commonly used systems included the International Classification of Diseases and the World Health Organisation's Adverse Reaction Terminology. Some companies even developed their own in-house terminologies. Such a variety of coding systems hindered the comparison and pooling of safety data and represented a large burden on companies who might be forced to re-code data for submissions to different regulatory regions.

The incipient form of MedDRA (known as MEDDRA) was drawn up by a working group consisting of regulatory authorities from the UK, Spain, and France, along with industry representatives.[1] A meeting of the Council for the International Organisation of Medical Sciences (CIOMS) in 1994 suggested that this dictionary could be adopted as the global standard for adverse event coding.[2] The decision was enshrined by the ICH in their M1 multidisciplinary initiative (see http://www.ich.org/products/meddra.html). MedDRA rapidly gained ground as the preferred coding system, and today, the adverse events in most regulatory submissions are coded using MedDRA.

Operational overview

MedDRA files are only available to subscribers. The annual subscriptions are free to regulatory authorities, patient care providers, and non-profit organisations such as academic institutions and medical libraries.[2] Pharmaceutical companies pay a subscription on a sliding scale according to revenue. In line with its aims to be a global standard, MedDRA is available in a variety of languages (including the major European languages and Japanese) with an exact mapping between languages of terms down to the preferred term level (though lowest level terms (LLTs) may be language specific).

MedDRA is subject to revisions; new versions are issued every 6 months. The company responsible for maintenance is the MedDRA Maintenance and Support Services Organization (MSSO), contracted to the International Federation of Pharmaceutical Manufacturers and Associations. The MSSO reports to the steering committee of the ICH

through its management board. As might be expected, the changes made in early versions, when MedDRA was still finding its feet, were larger than those in later versions. MedDRA is, however, still evolving and it is therefore important to document which version of MedDRA was used for an analysis (given that, for example, preferred terms may be in different primary system organ classes (SOCs) in different versions). Certain complications may arise with long studies that have different interim analyses performed at different times with different versions of MedDRA. The recommendation is that each analysis should be performed using the most recent version of MedDRA available.

Organisation of MedDRA

MedDRA is a hierarchical system comprising five levels (see Figure 1). At the top of the hierarchy are the 26 SOCs (note these correspond to 'body systems' in COSTART, and some still use this term erroneously in relation to MedDRA). Most of the statistical outputs used by a regulatory writer for safety reporting will be based on preferred terms (considered to be a single medical concept), grouped into SOCs in many cases. Below the preferred terms come LLTs, which often provide synonyms for preferred terms. The availability of several LLTs for a preferred term assists in coding because there is likely to be a close match with the verbatim terms recorded by the investigator. As an aside, MedDRA uses British spelling for preferred terms and all terms above preferred terms in the hierarchy. American spelling is included for LLTs (primarily to assist in coding). When reporting MedDRA terms in free text, most would consider it acceptable to change the term to American spelling if the rest of the document uses American spelling. Likewise, it
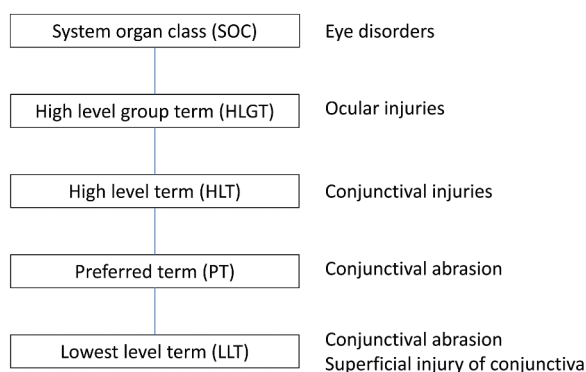
would also be considered acceptable to change a MedDRA term from, for example, 'acid base balance abnormal' to 'abnormal acid base balance' to enhance readability.

MedDRA is denominated a multiaxial system. This means that a given preferred term can belong to different high-level terms, high-level group terms, and therefore SOCs. There is always however, a primary SOC with which a given preferred term is associated. For example, urinary tract infection is usually placed in the 'gastrointestinal disorders' SOC. But this event is clearly also an infection and so can also belong to the 'infections and infestations' SOC, which would be considered the secondary SOC. According to MedDRA, this flexibility is an advantage of MedDRA. In practice, I have never seen an analysis of secondary SOCs (in pre-submission documents, though the approach may conceivably be used more often for pharmacovigilance purposes). So if you are interested in infections because the investigational medicinal product suppresses the immune system, it is not particularly helpful if isolated infections are spread over a range of SOCs diluting the safety signal. An alternative to analysis of secondary SOCs is to use a standardised MedDRA query (SMQ).

Standardised MedDRA queries

As mentioned above, similar types of event (such as infections) can be assigned to different SOCs. In addition, there are some preferred terms that map to a single SOC. For example, the preferred term 'platelet count decreased' maps to the SOC 'Investigations' while the closely related preferred term 'thrombocytopenia' maps to the SOC 'Blood and lymphatic system disorders'. Even an analysis of secondary SOCs would be unable to combine these terms in the search for a safety signal. To overcome this problem, MedDRA allows what are known as SMQs, which replaced the now obsolete special search categories.[3]

An SMQ is essentially a list of preferred terms that relate to a specific medical condition,[4] such as anaphylactic reaction (which could be manifest in a number of different events, each belonging to different SOCs). SMQs are in constant development through collaboration between the CIOMS and ICH. Updates are issued along with the 6-monthly updates to MedDRA itself. New SMQs may be developed, sometimes on the request of MedDRA users, for example, if there is concern about a particularly novel adverse effect for a new drug. It should be stressed that the SMQs cannot be tailored

System organ class (SOC)	Eye disorders
High level group term (HLGT)	Ocular injuries
High level term (HLT)	Conjunctival injuries
Preferred term (PT)	Conjunctival abrasion
Lowest level term (LLT)	Conjunctival abrasion Superficial injury of conjunctiva

Figure 1: The MedDRA hierarchy with terms corresponding to the preferred term 'Conjunctival abrasion'. Note that the LLT and the preferred term can be identical (examples taken from Mozzicato[2]).

by the users and are not designed according to the specifications of the drug companies; the CIOMS and ICH committees have the ultimate say. When a database is analysed using an SMQ, all events that match terms in the SMQ list will be retrieved. Clinical judgement must then be applied to determine whether the results represent a significant safety signal.

Is MedDRA a panacea?

The developers of MedDRA would have us believe that MedDRA coding is objective given the high granularity of the LLTs and that it is clinically validated because it is developed and maintained by medical experts.[2] This may very well be true but, according to a systematic review of coding of adverse events in clinical trials, there is little evidence to support this affirmation (and the authors also noted how surprising it was that the system that forms the basis for all regulatory safety reporting has been subject to so little publicly available research on the topic).[5] The only study which assessed the correlation between coding of verbatim terms by two blinded coders found that 12% were coded differently.[6] The authors did, however, note that training for investigators in recording verbatim terms could improve the quality of coding. If coding is subjective, there is in theory potential for influence to be exerted (either intentionally or inadvertently) to enable a favourable outcome. However, adverse events are generally coded independently prior to analysis of the data (only on very rare occasions might the coding of an adverse event be queried and such a query would be documented). The potential for such influence would therefore seem limited.

MedDRA has also been criticised for being too granular. With the COSTART system, there were ~1200 terms. MedDRA however, has ~18 000 preferred terms and 66 000 LLTs.[2] The problems associated with granularity have been alluded to above, and more advanced search strategies such as analysis of secondary SOCs and SMQs, if performed, can go some way to alleviating the problem. But typically, the summary of product characteristics or package insert will summarise adverse events by frequency. In a summary table that presents adverse events reported with an incidence of 5% or more, a more general concept that is broken down into several more granular concepts may disappear from the table.

In some cases though, the criticism runs deeper and MedDRA (which do not forget is essentially an industry initiative in collusion with ICH and regulatory authorities) has been accused of providing drug companies with enough wriggle room to hide safety signals. Perhaps, the most notorious case was the trial of the antidepressant paroxetine in adolescents, in which suicidal tendencies were coded as aggression or exacerbation of depression.[7] This is an example often used by critics of the pharmaceutical industry as an example of a broken system (see, e.g. Ben Goldacre's book, *Bad Pharma*[8]). Although this example was tragic and shocking, we should remember that drugs are regularly pulled from development because of safety issues though this is rarely a newsworthy event (an obvious selection and reporting bias is in operation here).

With the increased transparency and more rigorous requirements for disclosure of trial data, in time it will presumably become possible to track drugs whose development is discontinued for safety reasons and compare these drugs with those that are withdrawn from the market after approval. In addition, detailed pre-approval data will be available for analysis in cases when drugs are withdrawn after approval. This should give a more accurate and objective picture of how well MedDRA fairs in detecting safety signals and could give some indications as to how and why some drugs slip through the safety net. In the meantime though, medical writers should be aware of the need to document how adverse events are coded, including providing a glossary for mapping the verbatim terms reported by the investigators and the preferred terms to which these events have been coded.

Conclusions

MedDRA has both strengths and weaknesses. The standardisation across regulatory regions and languages is certainly welcome. The large number of preferred terms and LLTs may be considered a strength in some senses in that it may allow more objective coding but a weakness in that it may mask certain safety signals. Unfortunately, little information is available on the sensitivity (how many 'bad' drugs are detected before approval) and specificity (how many 'good drugs' are discontinued from further development). Likewise, the constant evolution MedDRA could be considered a strength in that it can adapt to new situations but a weakness in that it may create problems when comparing similar sets of data coded with different versions of MedDRA. Awareness of these issues can help regulatory writers ensure that safety reporting is as clear and transparent as possible.

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The approval process of medicines in Europe

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Abstract

The European system of approval of new medicines comprises an European Union (EU)-wide authorisation procedure (the so called centralised procedure) alongside national procedures based on different EU Member States working together and recognising each other's evaluations (the so called decentralised and mutual recognition procedures). It is a system that has evolved over the past half century from one with wholly separate national systems to one where EU countries now harness their regulatory and scientific expertise to harmonise and improve the evaluation of medicines across Europe. Today, the purely national procedure is rarely used by applicants and only when they seek marketing authorisation in a single Member State. Although the different procedures may give an impression of complexity, they have simplified the authorisation process across Member States, reducing the times for new medicines to obtain marketing authorisation and improving patient access to new medicines.

Keywords: European Medicines Agency, Centralised procedure, Decentralised procedure, Mutual recognition procedure, Medicines approval

The current European system of medicines approval consists of a centralised authorisation procedure as well as national authorisation procedures based on simultaneous authorisation in more than one European Union (EU) Member State and the mutual recognition of marketing authorisations. In addition, there are medicines authorised in single Member States under purely national procedures. The centralised procedure and the European Medicines Agency, which manages the procedure, have both been in operation since 1995. This paper describes the history of the approval system and the harmonisation that has occurred over the past half century and gives an overview of the way medicines are approved in the EU today.

The history of the pharmaceutical regulation system in Europe

Although many European countries have long had laws regulating the use of various medicines, modern pharmaceutical regulation in Europe can be considered to have started in the 1960s and has not stood still since. In the aftermath of the thalidomide tragedy, there was increased legislative control of pharmaceuticals, with regulatory agencies being created all over Europe to approve medicines and Member States working on European harmonisation, leading to the first pharmaceutical Directive in 1965 (Council Directive 65/65/EEC).[1] The Directive required all medicines to have a marketing authorisation and also aimed at harmonising standards for the approval of medicines within Europe. In addition, this law encouraged the creation of a single market for pharmaceuticals in the EU at a time when every country had its own separate approval procedures which meant that companies had to submit separate applications for approval of a medicine in each country.

In 1975, two Council Directives were introduced, the first (Council Directive 75/318/EEC, 1975[2]) relating to the testing of medicines required to be carried out by companies seeking a marketing authorisation, and the second (Council Directive 75/319/EEC, 1975[3]) establishing a procedure for marketing authorisation with the aim of promoting the free movement of medicines. The procedure was based on the mutual recognition of national assessments whereby a company could seek marketing authorisation for a medicine in one Member State on the basis of an existing marketing authorisation in another. The Directive also established an advisory committee to the European Commission called the Committee on Proprietary Medicinal Products (CPMP) to help EU Member States to adopt a common position with regard to decisions on issuing a marketing authorisation. However, the opinions of the CPMP were not binding and the system had come under criticism for being slow, bureaucratic, and ineffective, with Member States

failing to recognise each other's assessments and seeking arbitration from the CPMP on nearly every occasion.[4] The procedure was called the 'CPMP procedure' and was later simplified and became the 'multi-state licensing procedure'. However, the procedure, though improved, was still considered by many to be ineffective and was little used by industry.[5]

In 1985, the single market project was launched, which included plans for the creation of the European Medicines Agency.[6] In 1986, a new procedure for the authorisation of medicines called the 'concertation procedure' was introduced. This procedure was mandatory for biotechnology medicines, requiring a community-wide licensing opinion by the CPMP for these medicines before marketing authorisations could be granted in any Member State. However, this opinion was again not binding on Member States and Member States could still approve or reject applications without reference to the opinion.

A major step in harmonisation was taken in 1993 with the Council Regulation (EEC) 2309/93,[7] which established the European Agency for the Evaluation of Medicinal Products, now known as the European Medicines Agency. In addition, the concertation procedure was modified and became the centralised procedure. The Regulation, which came into force in 1995, also re-established the CPMP as a 'new' CPMP to issue the Agency's opinions on the granting of marketing authorisations in accordance with the centralised procedure, which now led to legally binding Commission decisions. The CPMP was later renamed the Committee for Medicinal Products for Human Use (CHMP).

As the mandatory scope of the new centralised procedure was limited to biotechnology medicines, it replaced existing national procedures for these medicines. The concept of mutual recognition for other medicines remained and was introduced into European pharmaceutical law in 1993 (Council Directive 93/39/EEC, 1993[8]).

By 1995, a harmonised European system of medicines approval had therefore emerged consisting of a procedure based on mutual recognition of marketing authorisations by Member States on the one hand and a procedure providing a community-wide licensing opinion on the other hand. The mutual recognition procedure had two precursors: first, the CPMP procedure which operated from 1976 to 1985; then the multi-state licensing procedure in operation from 1985 until 1995, which in 1995, became known as the mutual recognition procedure. The procedure providing a community-wide licensing opinion, the centralised procedure, developed from the concertation procedure which operated from 1986 until 1995. Whereas the early

procedures were hampered by a lack of binding opinion by the CPMP, by 1995 this was no longer the case and pharmaceutical regulation in Europe had become better harmonised and more effective. After 1995, additional changes were made to this European approval system to further strengthen it. They included the introduction, in 2005, of a new procedure called the decentralised procedure which sought to avoid the potential for disputes which was identified over time as a problem with the mutual recognition procedure as Member States in which approval is sought were not involved early enough in the evaluation.[9]

The current EU system

The centralised procedure

The advantage of the centralised procedure is that it requires a single application which, if successful, results in a single marketing authorisation with the same product information available in all EU languages and valid in all EU countries, as well as Iceland, Liechtenstein, and Norway. The scientific assessment of the marketing authorisation application is carried out by the CHMP. The scientific review process consists of alternating periods of active evaluation and periods during which the clock is stopped in order to give the applicant time to resolve any issues identified during the evaluation. In total, the duration of the process is up to 210 'active' days before an opinion is issued by the CHMP.

Once an opinion has been given, it is forwarded to the European Commission which then has 67 days to issue a legally binding decision on the marketing authorisation. The mean approval time for medicines in 2012 approved by the EMA was 14.8 months.[10] Once a marketing authorisation has been granted, the applicant can start to market the medicine in any EU Member State of its choice. However, in practice before a medicine is marketed, it will be subject to pricing negotiations and a review of its cost-effectiveness. This is carried out at national level by Member States to determine reimbursement criteria.

Initially, the centralised procedure was mandatory only for biotechnology medicines, as was the case with the previous concertation procedure. Over time, however, the mandatory scope of the centralised procedure has been gradually expanded and by 2005, it included orphan medicines (medicines for rare diseases) as well as human medicines that contain a new active substance (not previously authorised in the Union before 20 November 2005) and that are intended for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions, and viral diseases. In

2009, the centralised procedure also became mandatory for advanced therapy medicines. The centralised procedure is also optional for other medicines that contain a new active substance not authorised in the Union before 20 November 2005, and for products which are considered to be a significant therapeutic, scientific, or technical innovation, or for which an EU-wide authorisation is considered to be in the interests of public health (Figure 1).[11]

The first medicine authorised under the centralised procedure was the fertility treatment Gonal-F in October 1995.[12] The EMA now receives around 100 applications per year (Figure 2) of which, around 10% do not result in an opinion but are withdrawn, and around 5% result in a negative opinion (Figure 3).[10] Since the establishment of the agency in 1995, over 700 human medicines have been approved using the centralised procedure. In the early years, only innovative products were approved via the centralised procedure but as data exclusivity for the first products approved began to expire, generics were also approved centrally.[13] The number of applications for generics using the centralised procedure has increased over the years, peaking in 2010 with around 50% of all applications being generics (Figure 4).[14] Today, most medicines containing a new active substance are approved using the centralised procedure.
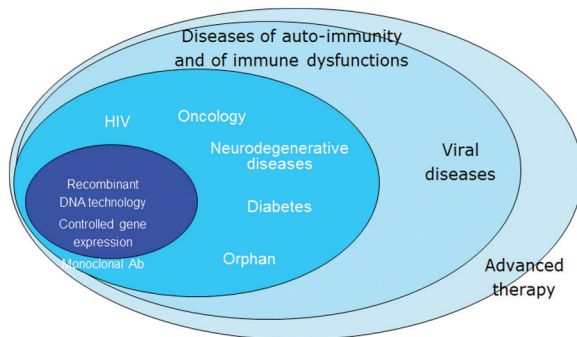
Figure 1: Mandatory scope of the centralised procedure.
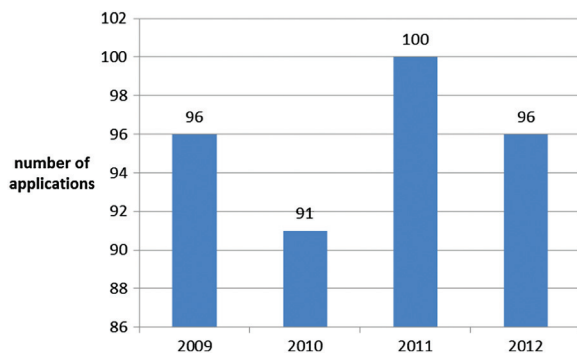
Figure 2: Number of applications received yearly by the EMA (2009–2012).
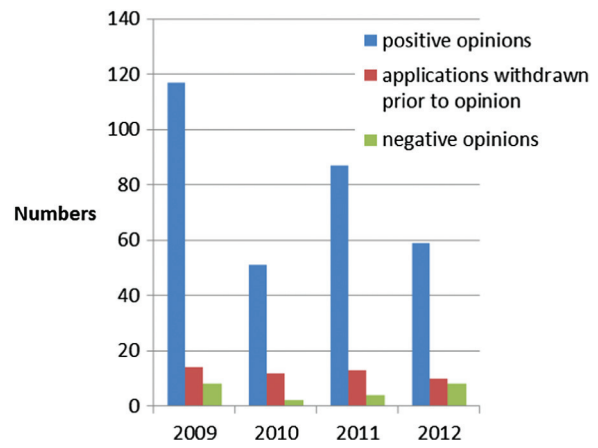
Figure 3: Outcome of evaluation (2009–2012).
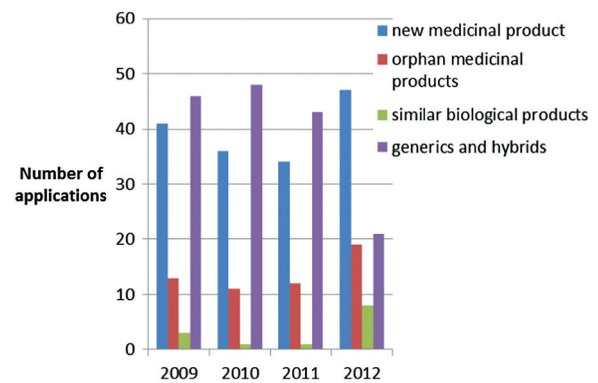
Figure 4: Type of application received by the EMA (2010–2012).

The mutual recognition procedure

The mutual recognition procedure has been in place since 1995 and evolved from the multi-state licensing procedure. The applicant must initially receive national approval in one EU Member State, referred to as the 'reference Member State' and then seek approval for the medicine in other, so-called 'concerned Member States' in a second step based on the assessment done in the reference Member State. This process has significant differences from the former multi-state licensing procedure, notably the requirement that disagreements between Member States must now be resolved at EU level. Disagreements are handled by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a body representing Member States, which is responsible for any questions in two or more Member States relating to the marketing authorisation of a medicinal product approved through the mutual recognition or the decentralised procedure.

If there is a disagreement between Member States on grounds of a potential serious risk to public health, the CMDh considers the matter in order to reach an agreement within 60 days. If this is not possible, the procedure is referred to the CHMP in

a procedure called a referral. The CHMP will then carry out a scientific assessment of the relevant medicine on behalf of the EU.[15]

In contrast to the previous procedure, the outcome of the CHMP is binding on the Member States involved once it has been adopted by the European Commission. The timelines for assessment by CHMP is 60 days.

Since the introduction of the decentralised procedure, the mutual recognition procedure is used for extending existing marketing authorisations to other countries.[9]

The decentralised procedure

In the decentralised procedure, the applicant chooses one country as the reference Member State when making its application for marketing authorisation. The chosen reference Member State then prepares a draft assessment report that is submitted to the other Member States where approval is sought for their simultaneous consideration and approval. In allowing the other Member States access to this assessment at an early stage, any issues and concerns can be dealt with quickly without delay, which sometimes is known to occur with the mutual recognition procedure. Compared with the mutual recognition procedure, the decentralised procedure has the advantage that the marketing authorisation in all chosen Member States is received simultaneously, enabling simultaneous marketing of the medicine and reducing the administrative and regulatory burden.[9] Today, the decentralised procedure is mainly used for applications for generic medicines.[16]

As for the mutual recognition procedure, disagreements are handled by CMDh or the CHMP in case no agreement can be reached at CMDh level.

Conclusion

In summary, the current procedures for approving medicines in Europe have resulted from a drive to harmonise and improve medicines regulation and have, for most medicines, replaced approvals based on purely national authorisations. Over the years, the scope of the centralised procedure has been widened and today most medicines containing new active substances are approved using the centralised procedure. The mutual recognition and decentralised procedure are mainly used to extend existing marketing authorisations or for generic medicines. Half a century of harmonisations has led to a system that is simplified, improving access to medicines by reducing the times for new medicines to obtain a marketing authorisation.

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Conflicts of interest and disclaimers

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its scientific committees or working parties.

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Highlights from our sister publications

European Science Editing

Under the heading 'Moral philosophy of scholarly publications' – ethical issues, to you and me – Vijay Prakash Mathur and associates provide a broad overview of some of the no–no's when publishing scientific papers.[1] Redundant publication, gift authorship, and plagiarism all get a mention, as do several other topics that will be familiar to anyone with even a passing interest in publication ethics. The authors attempt to cover a lot of ground in just a few pages, which inevitably means that some things only get briefly touched upon (a notable exception being authorship, which is discussed in some detail). Nonetheless, their article constitutes a useful introduction for anyone oblivious to the malpractices it highlights, and is complemented by a letter from (anti-)plagiarism guru Miguel Roig, who provides clarification of a number of important points.[2]

In the same issue of the journal, Laura Fascio Pecetto introduces BioMed Central author academy, a web resource offering useful general guidance on manuscript preparation to budding authors/writers.[3,4] Elsewhere, journal editor Denys Wheatley criticises what he perceives to be the overuse of dramatic words such as 'reveal', 'sacrifice', and 'perform' in the scientific literature, and ponders what should be done about it.[5]

AMWA Journal

Much of the Winter 2013 issue of the *AMWA Journal* is devoted to reports from the 73rd Annual American Medical Writers Association Conference, held in Columbus, Ohio in November 2013. Highlights include a short but handy summary of a lecture on how to convert a CSR (clinical study report) into a manuscript[6] – which incidentally is the subject of an EMWA workshop.[7]

Non-conference articles cover a range of interesting topics. In one well researched and thought out piece, medical editor Kelly Schrank discusses the benefits of creating and using a checklist when editing, acknowledging the initial outlay of time but arguing that it is easily outweighed by improvements in editing speed and objectivity.[8] She further points out that checklists can make it easier to return to a half-finished editing job following an interruption and provides practical advice on checklist creation and optimisation.

Career help comes in the form of a tip sheet on opportunities in the non-profit sector, with information based on but not solely applicable to the US job market.[9] Like in *Medical Writing*, freelancers have their own section, which offers additional career advice in a Q and A format.

Elsewhere, Kryder *et al.*[10] present the results of a survey on the challenges faced by medical writers, editors, and other medical information professionals. The challenges that were most frequently selected by respondents were 'Establishing a healthy work/life balance due to unreasonable workloads/timelines' and 'Inadequate recognition of the value delivered by the profession'. I am sure a few of us can relate to these sentiments!

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Recommended procedures for retracting articles: Inadequate and patchily applied? Analysis of a recent article in *PLoS One* examining the fates of retracted articles

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Abstract

Retraction of research articles ruins careers, dents confidence in the scientific literature, and can have a profound impact on meta-analyses. Retraction rates have seen a big recent rise, as journals act increasingly quickly to remove articles that are found to have broken ethics rules. In several notorious cases, many such articles have been linked to a single researcher. A 2014 study published in *PLoS One* sought to determine whether 88 articles by one of the worst known offenders were retracted as recommended and, if so, whether their retraction conformed to Committee on Publication Ethics guidelines and other recommended practices.

Keywords: Retraction, Retraction notice, Ethics, Watermark, Fraud

Box 1: Committee on Publication Ethics (COPE) guidelines relating to retraction[4]

'Notices of retraction should:

1. Be linked to the retracted article wherever possible (i.e. in all electronic versions)
2. Clearly identify the retracted article (e.g. by including the title and authors in the retraction heading)
3. Be clearly identified as a retraction (i.e. distinct from other types of correction or comment)
4. Be published promptly to minimise harmful effects from misleading publications
5. Be freely available to all readers (i.e. not behind access barriers or available only to subscribers)
6. State who is retracting the article
7. State the reason(s) for retraction (to distinguish misconduct from honest error)
8. Avoid statements that are potentially defamatory or libellous'.[1]

In one of a number of famous recent cases of mass retraction,[1] 88 research articles by German anaesthetist Joachim Boldt were recommended for retraction in 2011 due to ethics violations.[2] Writing in *PLoS One*,[3] Elia *et al.* describe the fates of Boldt's articles, focussing on points 1–3 and 5–7 in the Committee on Publication Ethics (COPE) guidelines (Box 1),[4] and a couple of others: free availability of the retracted article and preservation of the original content. This Anglo-Swiss alliance of researchers present what, on the face of it, is a surprising and disappointing result: only five retractions (all from the same journal) fulfilled all of their predefined criteria.

Look a little more closely, however, and things are not so clear-cut. No fewer than 25 articles were deemed to have been inadequately retracted for the reason 'PDF not adequately marked'.[3] In 14 cases, inadequate marking was defined as the retracted article having an opaque 'RETRACTED ARTICLE' watermark, rather than a transparent one. Conversely, 10 articles whose retraction watermarks were almost invisible were deemed to be adequately marked. COPE's advice that articles'

Physostigmine for the prevention of postanaesthetic shivering following general **anaesthesia** - a placebo-controlled comparison with nefopam.
Röhm KD, Riechmann J, **Boldt J**, Schuler S, Suttner SW, Piper SN.
Anaesthesia. 2005 May;60(5):433-8. Retraction in: Anaesthesia. 2011 Jul;66(7):646.
PMID: 15819761 [PubMed - indexed for MEDLINE]
Related citations

A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study.
Piper SN, Röhm KD, Suttner SW, Maleck WH, Kranke P, **Boldt J**.
Anaesthesia. 2004 Jun;59(6):559-64. Retraction in: Anaesthesia. 2011 Jul;66(7):646.
PMID: 15144295 [PubMed - indexed for MEDLINE]
Related citations

Prevention of propofol-induced injection pain by remifentanil: a placebo-controlled comparison with lidocaine.
Roehm KD, Piper SN, Maleck WH, **Boldt J**.
Anaesthesia. 2003 Feb;58(2):165-70. Retraction in: Anaesthesia. 2011 Jul;66(7):646.
PMID: 12625310 [PubMed - indexed for MEDLINE]
Related citations

Figure 1: Selected results from a PubMed search for 'Boldt J[Author] AND Anaesthesia[Journal]' (National Library of Medicine [NLM]).

retracted status 'should be indicated as clearly as possible'[4] would seem to be better fulfilled by an opaque watermark than by a faint one.

Making retraction obvious

PubMed uses no watermarks, bold, or pallid, to draw users' attention to the fact that an article has been retracted. A PubMed search for Boldt's publications in the journal *Anaesthesia* returns an unremarkable looking list of results, part of which is shown in Figure 1. It is quite possible to miss the links to the citations for the retraction notices if you are not looking for them.

What happens when you select one of these articles for further inspection? Click on the link to the middle paper in Figure 1 and you will be given a link to the citation for the retraction notice, just above the abstract (see Figure 2).[5]

Okay, you probably wouldn't miss it, but a brighter, more eye-catching alternative would

probably be better. Something as simple as high-lighting the retraction information in red might work.

The publisher of the article in Figure 2, Wiley, does a better job, prefacing the article's title on its website with 'THIS ARTICLE HAS BEEN RETRACTED'.[6] There is no missing that! Moreover, clicking on the 'Get PDF' link takes you to a copy of the article bearing a transparent watermark of the kind that Elia *et al.* like (Box 2).[7]

Box 2
Unfortunately, I cannot show a screenshot of the first page of the retracted article, as I intended, because Wiley denied permission, citing concerns that it might 'incorrectly imply that the retraction applies to a particular Wiley journal, or indeed to Wiley in particular'. I do not feel that a journal or publisher that retracts an article should fear being stigmatised, assuming they are not culpable in some way. In the present case, there is a prominent reference to 'approval of the local ethics committee and written informed consent' in the *Materials and methods* section. That there seemingly was no ethics approval (see below) reflects author fraud, not an oversight by the journal or publisher. I argued as much in an email to Wiley, but they merely confirmed their original position.

Non-retraction

Nine of Boldt's articles were not retracted at all within the two years following publication of the original retraction recommendation. But, then, look at the wording of that recommendation: the 88

Figure 2: One of Boldt's retracted articles in PubMed, with a link to the appropriate retraction notice citation (NLM).

articles are ones for which 'LÄK-RLP [Landesärztekammer Rheinland-Pfalz, the State Medical Association of Rheinland-Pfalz] was unable to verify IRB approval'.[2] What does 'unable to verify IRB approval' mean? And why the uncertainty? COPE recommends that journal editors should consider retraction if a publication 'reports unethical research'. Is it certain that Boldt's articles do so?

Elia *et al.* received a partial explanation for failures to retract when they contacted the publishers of Boldt's articles: six articles were not retracted because of 'legal threats from Boldt's co-authors'.[3] While the authors do not elaborate on the nature of these threats, it should be noted that smaller journals often lack the resources to engage in costly legal battles. Certainly, any situation where journal editors feel unable to retract condemned articles is a cause for concern.

Retracted articles: To delete or preserve?

Elia *et al.* further contacted the editors-in-chief who had not retracted Boldt's articles to their satisfaction. The editor of one journal that had deleted the content of the retracted articles disagreed that retracted articles should be preserved because he felt their data were 'false and therefore valueless'.[3] I'm not sure I agree. Are data obtained in an unethical way automatically false and valueless? The Boldt case is not one of data fabrication. One could argue that the data should perhaps be deleted because they are not false and valueless. Because people could choose to ignore the apparent ethics breach and use the data anyway.

Room for improvement?

In summing up, the authors highlight what they consider to be the problems with current retraction procedures:[3]

- Uncertainty as to which forms of misconduct warrant retraction
- Lack of clarity concerning who is responsible for retraction
- No oversight when it comes to checking that articles have been retracted, and in the correct way

They sign off by proposing solutions that clearly apportion responsibility for executing and monitoring retraction, and that protect editors from litigation. Sensible ideas, but they beg a vexing question, one that applies to so many worthy efforts to improve publication and post-publication processes: How should one implement them?

Suggestions, anyone?

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The needs assessment in continuing medical education

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Abstract

The needs assessment component of a continuing medical education grant proposal document describes why a specific programme should be developed. Medical writers frequently play a central role in producing the needs assessment as an important first step in the development of an educational activity. By focusing on very specific practice gaps, and highlighting how the programme would help close those gaps, the medical writer plays a critical role in helping accredited sponsors document educational needs, and subsequently obtain funding for the activity.

Keywords: Continuing medical education, Needs assessment, Practice gap, Best practice, Evidence-based, Learning objective

Introduction

Continuing medical education (CME) comprises educational activities that function to maintain, develop, and enhance the knowledge, skills, and professional performance that healthcare providers use to manage their patients,[1] and it is typically how providers earn educational credits to maintain their professional licenses.[2] Its ultimate goal is to enhance patient outcomes by improving providers' practice behaviours.[3] Although the educational activities may take various formats, including live events, online programmes, educational videos, self-study guides, and monographs, their common aim is to update providers on current and emerging information on treatment paradigms, evidence-based clinical practice guidelines, and other topics.[2] Programmes are regulated by regulatory bodies that set and enforce standards for determining the eligibility of organisations for CME accreditation, and require programmes to indicate objectives based on the identified needs of the target audience.[4] These include the Accreditation Council for Continuing Medical Education in the United States,[5] and the European Accreditation Council for Continuing Medical Education in Europe.[6]

The needs assessment and its components

What is a needs assessment?

The needs assessment (NA) is one of the most important parts of an educational grant proposal, and serves to help produce an effective CME activity.[7] It is the component of a grant document that CME companies submit to funding bodies such as industry sponsors to obtain funding for CME programmes for healthcare providers. Data have shown that CME programmes based on well-conducted NAs are effective in changing providers' practice behaviours.[3]

Glossary of key CME terms

- *Continuing medical education (CME)* – Educational activities that function to maintain, develop, and enhance the knowledge, skills, and professional performance that healthcare providers use to manage their patients, and it is typically how providers earn educational credits to maintain their professional licenses.
- *Needs assessment (NA)* – The component of a grant document that CME companies submit to funding bodies such as industry sponsors to obtain funding for CME programmes for healthcare providers.
- *Professional practice gap* – The difference between what providers already know and what they should know to be competent or an expert in their field.
- *Clinical practice gap* – The gap between current and optimal medical practices. It might refer to a gap in patient care, for example, or a lack of knowledge, skills, or attitudes. It justifies the need for education.

- *Learning objectives (LOs)* – What participants can expect to get out of the activity. In contrast to the overall goals, the LOs are precise and measurable aims that define how the programme will improve participants' knowledge and skills, and subsequently enhance patient outcomes. In essence, an LO represents an action statement that contributes to the goal being achieved.

CME programmes are developed based on an identified professional practice gap – the difference between what providers already know and what they should know to be competent or an expert in their field (Figure 1). The NA is performed to determine what the intended audience needs to learn from the planned activity,[2] and represents the basis for the whole programme. It specifically identifies the gap between current practice and best practice and essentially represents a systematic means of collecting information that helps to determine the instructional solutions to close it. This information is subsequently used to identify programme goals and LOs.[7]

Where do data for the NA come from?
Data for the NA are derived from three areas[8]:

Inferred needs

- New diagnostic or treatment methods/technologies/agents

- New indications for current agents
- Opinions of key experts about advancements on medical knowledge
- Regulatory and legislative changes that affects patient care

Verbalised needs

- Survey results of potential learners
- Learner evaluations of previous CME activities
- Consensus opinion of members of a medical specialty group

Proven needs (based on objective data sources)

- Guidelines and recommendations published by professional societies
- Quality assurance data
- Review of journal articles
- Morbidity and mortality data

What are the main components of the NA?
The NA highlights four key features:

- *Current clinical practice:* What learners currently know and do.
- *Best clinical practice:* What learners should know and do.
- *Clinical practice gap:* The gap between current and optimal medical practices. It might refer to a gap in patient care, for example, or a lack

Identify educational needs
Consider the target audience of healthcare professionals that can benefit from additional education about a particular topic.

↓

Identify clinical practice gaps
The educational topic may have one or more clinical practice gaps. These represent the gaps between current and optimal medical practices.

↓

Produce NA from the identified needs
Each gap may have one or more needs. These needs represent what is required to close the clinical practice gap, and they can comprise data on the knowledge, competencies, and performance of the target audience.

↓

Develop educational programme
The educational programme represents the CME activity to address the needs of the target audience and close the clinical practice gaps. Tthe programme must provide education on the specific topic that helps the target audience achieve specific outlined learning objectives.

↓

Identify outcomes
These represent what the target audience will do differently as a result of the educational programme.

↓

Evaluate the programme
Evaluation is an important aspect of any CME programme and helps evaluate its effectiveness. Participants may, for example, be asked to complete questionnaires comparing their pre- and post-activity knowledge. They may also be asked about what practice changes they will implement as a direct result of the activity.
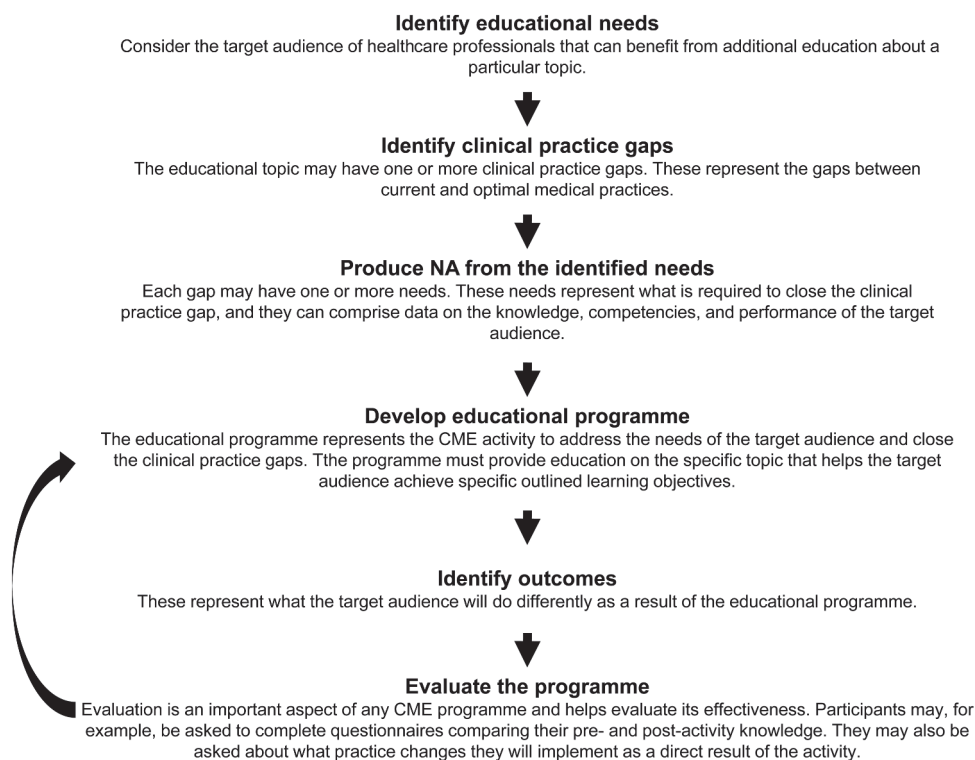
Figure 1: The hierarchy of CME and the NA. Medical writers are generally involved at the third and fourth steps, after data on educational needs and clinical practice gaps have been collected.

of knowledge, skills, or attitudes. It justifies the need for education.[7]

- *LOs:* What participants can expect to get out of the activity.

How to make the NA compelling

Since it is becoming increasingly difficult to obtain funding for CME programmes, the NA must stand out to gain approval. To achieve this, the NA must:

Be specific

Data must demonstrate a mechanism for measuring and publishing outcomes of educational activities, and therefore the NA should target specific aspects of a condition, rather than provide a general overview about it. Although a literature review may be informative, it may do little to document the very focused needs of the target audience with respect to managing the condition, and may therefore not be effective in gaining funding approval. In contrast, if the NA discusses data about certain practice gaps and describes how the proposed programme would target those needs, and highlights how the specific issues would be overcome by education, then it is more likely to be approved for funding.

Incorporate evidence-based data

Gaps in provider knowledge are typically identified via two methods:

- *Published or collected data:* For example, evidence-based articles published in the medical journals; healthcare statistics on government

websites, quality assurance reports, and pre-test and post-test results.

- *Physician self-assessment:* This may include physician self-testing results and quality assurance reports.

Data should be linked with the appropriate target audience specialty where possible, and also with particular geographic regions where relevant (see Figure 1).

Present fair balance

Studies have demonstrated that when CME programmes favour the supporting company's products, healthcare professionals in attendance prescribe these products more frequently than those from other companies.[9] Consequently, although one particular pharmaceutical company may be the sponsor, it is in the best interest of the target audience and their patients that the CME programme presents a fair balance among competing therapeutic and diagnostic choices.[10]

Include measureable LOs

LOs, a key component of the NA, are identified by investigating the issues that led to the gap (learner needs),[7,9] and must be measureable through observation or documentation.[4] When composing LOs, it is important to differentiate between the terms 'goal' and 'LO'. A goal represents the broad aim of a CME activity, while LOs represent more precise and measurable aims that define how the programme will improve participants' knowledge and skills, and subsequently enhance patient

Table 1: Examples of LOs related to CRC and mCRC

Current clinical practice behaviour	Best clinical practice behaviour	Educational need – the professional practice gap	LOs
Physicians who treat patients with CRC are unaware of current screening guidelines based on patient risk stratification and the guidelines for alternative screening tests for CRC	Physicians must follow the updated guidelines for patient risk stratification and utilise an appropriate CRC screening regimen	Physicians lack the most up-to-date information on current clinical practice guidelines relating to patient risk stratification and alternative screening tests for CRC	Determine the appropriate risk stratification for an individual patient and select the appropriate CRC screening strategy
Physicians lack knowledge of available therapeutic agents to treat mCRC and how to select the most appropriate options for individual patients	Physicians must stay abreast of current and emerging data to make individualised, evidence-based decisions about therapeutic agents that take into account patient risk factors, as well as drug-associated adverse effects and toxicities	Physicians lack the most up-to-date clinical trial data on available and emerging agents for the management of mCRC, that take into account patient risk factors, as well as drug-associated adverse events and toxicities	Select appropriate therapy for individuals with mCRC after considering patient characteristics, clinical factors, and the safety and efficacy of available therapeutic agents
Physicians are challenged to manage nonadherence with treatment regimens in patients with mCRC	Physicians must understand factors associated with treatment non-adherence and use a combination of strategies, including amending the treatment regimen, to improve adherence to medication	Physicians do not engage with patients sufficiently to identify non-adherence to treatment regimens	Identify the therapy-related, patient-related, and provider-related factors leading to medication non-adherence

outcomes.[11] In essence, an LO represents an action statement that contributes to the goal being achieved. For example, while the goal of a CME programme on colorectal cancer (CRC) might be 'to provide education that will enhance participants' competence in their ability to apply knowledge learned to patient care strategies', its LOs will be more specific and focused (Table 1).

The ideal LO has three components[11]:

- The learner
- A measureable action verb
- The desired result of learning.

The action verb is a key component.[11,12] Not all verbs are created equal, however. Verbs such as 'discuss', 'identify', and 'perform', are more measurable as a direct outcome of a CME programme and are considered more effective as components of LOs. Verbs such as 'understand', 'appreciate', and 'learn', on the other hand, are considered weak for this purpose since they are less measureable, and should therefore be avoided.[11]

Match the practice behaviours, gaps, and LOs

Be sure to match up the current and best practice behaviours with the practice gaps. And, in turn, make sure the LOs reflect the specific gaps. In the CME programme on CRC, current clinical practice behaviour might be that 'clinicians lack knowledge of available therapeutic agents for mCRC, and of how to select the most appropriate options for individual patients', while best clinical practice behaviour would require that 'clinicians must stay abreast of available and emerging data to make individualized, evidence-based decisions about therapeutic agents for mCRC'. The corresponding practice gap would be that 'clinicians lack the most up-to-date clinical trial data on available and emerging agents for the management of mCRC, that take into account patient risk factors, as well as drug-associated adverse events and toxicities' (Table 1).

Conclusion

The NA is an important part of the CME grant, and justifies the agenda for the programme. It should be crafted with provider performance improvement in mind, and must focus on important issues relevant to participants' practice, and provide evidence-based information on common practice problems. To improve the chances of funding for the activity, medical writers must ensure that the NA is specific, gap-based, free of commercial bias, and includes measureable LOs.

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Origin and development of English for Medical Purposes. Part II: Research on spoken medical English

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Abstract

In the second part of the review on 'English for Medical Purposes', I present the main results of the research conducted on spoken interaction in medical settings. I start with those EMP studies that have a clear pedagogical goal, followed by EMP research that consists in the linguistic analysis of medical conference presentations. The third category of EMP studies discussed is of a sociolinguistic nature and consists in the literature on healthcare (doctor/patient) communication.

Keywords: Medical English, Spoken, Medical conference, Doctor–patient communication

Introduction

In the first part of this short review paper on English for Medical Purposes (EMP), I dealt with written medical discourse.[1] This second part focuses on research on *spoken* medical discourse.

Research on spoken medical discourse

We should distinguish three partially overlapping categories within EMP research conducted on spoken interaction in medical settings. The first group of EMP studies has a pedagogical goal and focuses on improving the English language skills of non-Anglophone medical students and health professionals in order to equip them with the communicative skills they need to participate in their academic cultures. The second body of research consists in linguistic analysis of medical conference presentations. The third category of EMP studies is of a sociolinguistic nature and refers to the literature on healthcare (doctor–patient) communication, the aim of which is to analyse, *inter alia*, the way doctors and patients (and/or their family) interact in medical consultations. These three categories are briefly discussed below.

Pedagogical aim: Developing oral skills of non-native English-speaking medical students and health professionals

Quite a few research-based EMP courses encompass doctor–patient communication skills. Maclean *et al.*,[2] for example, report the case of Cuba, where it is the Ministry of Public Health, not the Ministry of Education that takes full responsibility for all medical education, including the English language training of medical undergraduates and postgraduates. A major step in the development of EMP teaching in Cuba was the establishment in 1989 of a link with the Institute for Applied Language Studies of the University of Edinburgh, Scotland, which has specific experience in the field of medical English as well as a broad teacher education expertise.[3] A similar project is now running with the University of Westminster (UK).

In the literature on healthcare professional settings, we could also cite the research conducted by Shi *et al.*,[4] who analysed and identified the communicative skills and needs of Hong Kong medical students expected to work in hospitals as doctors. The authors video- and audio-taped sessions of ward teaching, and identified which linguistic skills the students needed in order to achieve various cognitive learning objectives, such as using appropriate everyday and technical terms to translate information from doctor–patient (in Cantonese) to doctor–doctor discourse (in English). In the course that was later developed, video sequences were used along with teaching tasks in order to improve student's performance through practice. The study illustrates how authentic data can be exploited to

construct a tightly focused curriculum addressing students' needs.

Another example of an EMP course with a focus on spoken (doctor–patient) communication is that described by Basturkmen.[5] The course was designed for overseas-trained doctors who seek work in New Zealand. Prior observations of medical consultations, with their typical sequence and associated language of doctor–patient consultations, were used as materials for the course design. Role-play or simulation exercises to rehearse language and skills useful in the clinical context are used all through that textbook. Needless to say, developing oral skills is also very important for those medical professionals from developing countries who often seek to migrate to, or practice in, Anglophone countries.

Other EMP specialists have focused their attention on more occluded genres, such as nursing care plans. Hussin,[6] for example, analysed the linguistic needs for immigrant nurses-in-training in English dominant settings where there is a shortage of domestic healthcare workers, such as in Thailand. In such countries, there is indeed an urgent need to train clinic and hospital staff to interact with English-speaking patients.

It is also noteworthy that the EMP site of Tokyo Medical University offers an EMP interactive course covering 18 modules of clinical therapeutics (https://www.emp-tmu.net/login/?PHPSESSID= b3 46b5abe51dcea1b2e1769d618cfc8e).

The language of medical conference presentations

Medical conference presentations have also attracted the attention of EMP researchers, but less widely than the previously reported research. The most frequently cited research in this specific area is that of Betty Lou Dubois,[7] whose interest in the juxtaposition of the visual with the verbal led her to examine the use of slides in biomedical speeches. She later studied the design and presentation of posters at biomedical meetings[8] and the use of imprecise numerical expressions in biomedical slide talks.[9]

More recent research on medical conferences was done by Webber[10,11] who examined the question–answer phase following medical presentations and analysed the interactive features of medical conference monologues, for example the use of personal pronouns, specific discourse markers, and imprecise quantifiers. If-conditionals, as a multifunctional resource in medical conference presentations, have been analysed by Carter-Thomas and Rowley-Jolivet.[12]

Sociolinguistic research: Healthcare provider–patient communication

The third category of research conducted in Anglophone medical settings encompasses the interactional, sociolinguistic, and micro-ethnographic literature on healthcare communication, especially doctor–patient and, but to a lesser extent, doctor–nurse–patient communication. The great majority of this type of research points to the conflictive nature of these encounters.

Not surprisingly, then, the role, form and frequency of questions have been the most frequently analysed features of such interactions. The findings of that research confirm the asymmetrical power relations of medical consultations. West[13] found, for instance, that almost 90% of questions were asked by doctors, and Ainsworth-Vaughn,[14] although reporting a lower percentage (62%), remarks that question frequency in medical consultations seems to depend on the patient's gender, culture and ailment, and whether it is the first or a control consultation.

A description of consultations conducted in English between doctors and patients of various nationalities in the hospitals of Abu Dhabi (United Arab Emirates) also puts forth the asymmetrical relations of medical consultations.[15] The principal finding of that study is that doctors employ a doctor-centred consultation style in the sense that they tend to ask closed questions, seldom enquire about their patients' social and/or psychological history and/or check their patients' understanding. Patients want to express the subjective experience of their illness and how it impacts their daily lives, whereas doctors strive to direct the course of the interview so as to reach a diagnosis. This is what Mishler[16] very aptly calls 'the struggle between the voice of the life world' and 'the voice of medicine'.

There has also been a great interest in the study of patients' narratives as an important constitutive element of medical discourse and as a source of information for clinical problem solving.[17,18] As far as I know, Carol Berkenkotter's book[19] is the first and only book that exclusively focuses on psychiatric interviews. There the author examines the evolving role of case history narratives in the growth of psychiatry as a medical profession and illustrates how discursive changes occurring over time in this genre mirror evolving assumptions and epistemological commitments among those who cared for the mentally ill.

Euphemisms and the use of metaphors in doctor–patient communication, especially distressing and taboo subjects, such as death and dying, have also been the subject of several studies. For example, Allan and Burridge[20] analysed the motivation of euphemisms in medicine, while Tsai[21] made a cross-cultural analysis of birth and death metaphors.

These and other topics that reveal the complexity of doctor–patient interaction can be found in

specialised journals, such as *Communication and Medicine*, and in books.[14–17] The second part of Gotti and Salager-Meyer's book specifically presents the results of discourse analysis research on doctor–patient end-of-life discussions and post-traumatic stress disorder, on issues related to gender-relevant differences in the description of chest pain, doctor–patient communication in multi-lingual settings, and psychiatric interviews.[22]

For lack of space, this overview (Parts I and II) is necessarily limited and partial, but I believe it illustrates the liveliness of EMP research. For over 30 years this field of research has accumulated a significant body of knowledge on the linguistic, sociolinguistic, and rhetorical features of both written and oral English-medium medical discourse.

Acknowledgements

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Did minor flaws in a new drug reveal major flaws in company publication practices?

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Abstract

Pradaxa, a new drug for the treatment of blood clots, has been revealed to produce some negative side effects on a minor population of patients, according to a new study. However, the road leading to the publication of this study revealed that companies may be more concerned with protecting profits than publishing facts.

Keywords: Pradaxa, Blood clot, Warfarin

A multi-billion pharmaceutical shows a dark side, revealed by recent set of documents providing evidence of shady practices aimed at silencing an inconvenient research report in favour of maximising profits.

A recent article by the *New York Times* points to some disturbing practices followed by the makers of Pradaxa, also known as dabigatran, a drug currently prescribed against blood clots and stroke.[1,2] Since its approval in 2010, Pradaxa has earned its maker more than $2 billion in sales in the USA alone, being prescribed to more than 850 000 patients and gaining substantial terrain to warfarin, the most widespread generic drug for the treatment of these conditions.

In the article, the *New York Times* points to actions painting Boehringer Ingelheim (BI) as a pharma giant with a more keen interest in protecting benefits than learning the truth about an approved drug.[2] The controversy follows recently released court documents[3] that are part of several ongoing lawsuits made by the family of deceased patients, who claim BI failed to properly inform them about the risk of taking Pradaxa.

Since its release, the drug has been linked with multiple cases of fatal bleeding, with more than 1000 deaths reported so far. The drug has also been linked to several adverse effects, including gastrointestinal problems, increase of heart attack risk, and most significantly, an increased risk of haemorrhage.[4] The European Medicines Agency identifies bleeding as the most serious side effect, occurring in 1 of 10 patients, as well as several incompatible conditions that may lead to adverse reactions in people who take the medicine.[5]

Despite the apparent risks, BI stands by the drug, pointing out that it is backed by the Food and Drug Administration, and by multiple clinical trials.[1] But, as the *New York Times* reports, the newly court-released documents, which include emails, memos, and internal presentations, reveal the concerns and efforts made by some company employees to deal with a new research report undermining Pradaxa's charms.[2]

The report, led by Paul A. Reilly, clinical programme director at BI, found that not all people, and in particular older patients, metabolise the drug in the same way and that a small population of patients would benefit from monitoring their blood.[6] More specifically, the report finds that a small number of patients did not absorb the drug efficiently, whereas others absorbed it a bit too well, leading to an increased risk of bleeding.

The new research weakens one of Pradaxa's biggest selling points, namely, that unlike warfarin, blood tests are not a prerequisite for using it. This means that a wide variety of patients are able to access the drug, and the drug is favoured because it does not require nasty and constant blood tests to monitor its function, as warfarin does.

The original report went on to describe the ideal blood level of Pradaxa, saying that keeping patients within this range would be optimal for preventing stroke and bleeding.

Time for a change?

The controversy focuses on one important question: Can pharma companies be trusted with handling

their own results? The recently released evidence suggests several questionable internal practices, from both legal and ethical standpoints. In the end, the controversial paper was published, albeit not with all of its original results. According to a BI representative, the scientist decided not to report the suggested optimal dosage of this drug. Taken together, this story had a positive ending, as the results were seen outside of the company, but the difficult path up to publication suggests a worrying underlying problem.

According to the *New York Times*, before the publication of the research report, employees from different levels questioned the plans to publish the report. Their main concern was how the results may 'negate a decade's worth of work proving that patients taking Pradaxa would not need regular tests'.[2] Also, concern was raised that the results would not help in the company's race against other new anticoagulants, like Xarelto and Eliquis.

Regarding all these issues and the court-released documents, BI claimed that the research results 'represent small fragments of the robust discussion and debate that is a vital component in all scientific inquiry, and in the research and development of any important medication such as Pradaxa'. In practice, BI will now have to re-think its original strategy which sold Pradaxa as a one-size-fit-all drug that requires no testing, which is a positive outcome.

Now the ball is in the court of regulators, who ought to question the legal and ethical integrity of big pharma companies and decide if they need a hand in deciding whether profits are more important than safety, even if the safety issues involve just a small number of patients.

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What every medical writer needs to know

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Abstract

A medical writer is never done with learning. In the fast-paced world of online communications, learning means getting involved in the digital environment and using tools like social media, websites, and blogs to enhance your online presence and develop your career. Health Writer Hub, a new global community for health and medical writers offering tips and advice focused on digital communications, getting started, freelancing, finding employment, and more, can be useful to achieve these goals.

Keywords: Career development, Digital communications, Online networking, Websites, Blogging, Social media

Health and medical writing is a prosperous career choice, with more and more people toying with the idea of either living the dream and becoming a freelance writer, or taking their valuable medical qualifications and becoming a medical writer with an employer. If there was one piece of advice I could give to anyone who wants to be or is already in the business of creating medical content, it would be this: your learning is never done. Whether you are a relatively new medical writer or have 20 years of experience under your belt, constant learning is the only way you can stay up-to-date with your profession.

Learning is also what drives you to be competitive. If you are dedicated to learning, developing, and growing your career, you can easily stand out in an increasingly popular market.

What does learning mean for medical writers?

Joining professional associations gives you the chance to network and to obtain formal training through courses/workshops they offer. This step is key for anyone who cares about his/her career. But what is just as important is knowing that the learning landscape is changing. This means understanding where the future of health and medical writing is headed and therefore we need to get familiar with the online world.

Writing as a profession is evolving because reader behaviour has been changing. Consider these: everyday, 294 billion email messages are sent, 4.7 billion minutes are spent on Facebook, and 864 000 hours of video are uploaded to YouTube.[1] People spend a lot of time online. Reports say that national newspaper circulation in the UK fell by 22.5% from 2007 to 2012 and that if this rate stayed constant, there will be a loss of 45% of newspaper sales in 10 years.[2] No wonder newspapers and magazines are closing down. In fact, some medical journals are only available in digital format. Over 92 000 pieces of digital content are published every day.[3]

It is not just the future of content that medical writers need to be mindful of. We also need to embrace digital communications wholeheartedly. Medical writers who are serious about their careers should have a strong online presence such as:

1. Websites with a portfolio of work. Speaking from experience as someone who has hired medical writers in the past, I can say that if a writer does not have a website with writing samples, I lose interest in pursuing them. The best writing websites appear simple, clean, and professional, with links to writing samples as well as a biography and contact details. These days, it is so easy to set up a website for free that there is almost no excuse for not doing so. If you are not sure where to start, try with Google: there are probably more than 1 million pieces of content alone on this very topic! If you are a freelancer, you may have a business website already and this is one of the best ways to generate new leads – providing you rank well in the search engines.

2. LinkedIn. A professional profile on LinkedIn with a brief overview of your work history can do wonders for your online reputation.

Keep your profile up-to-date by ensuring all your jobs are listed and encourage your colleagues and peers to recommend you. Add examples of published work to your profile and join relevant medical writing groups. There are some very active health and medical writing groups with thousands of members. You should also choose a professional profile image and change it regularly.

3. Twitter. This microblogging platform is essential for journalists and writers. You can follow your peers, find out about trending topics, discover new leads, and network with other writers online. Twitter requires effort and persistence – a little bit of 'Tweeting' each day will pay off in the long run.

4. Facebook. The importance of Facebook for business is increasing and if you have a freelance writing or communications business, Facebook can be an exceptionally valuable tool in terms of networking and sharing content. Find other business you work with (e.g. graphic designers or website designers) and connect with them when you are getting started. Like Twitter, Facebook requires effort and the more you can hone in on your target audience, the better engaged your followers will be. A business Facebook page is probably going to be more useful for you if you are a freelancer as opposed to an employee.

5. Google+. While Google+ has not been as popular as Facebook, it is still an important social media presence for writers to make use of. Ever wondered how you can get your image to appear in the SERPs (search engine results pages). This is achieved by Google Authorship – a crucial feature to utilise if you are setting up your blog or website and want to rank well in search engines.

How can medical writers learn about changing trends?

Following industry-leading writers and bloggers online is vital. But while generic advice usually translates well to the health and medical writing profession, we all prefer to read about specific information related to our medical writing niche. Health Writer Hub (http://www.healthwriterhub.com) is a newly created global community for health and medical writers that provides weekly tips for novice and experienced medical writers. Advice focuses on new technologies to help writers get better at what they do and ultimately develop their careers: for example, blogging and strategies for getting started, what Instagram is and how to use it for business, and tips on SEO (search engine optimsation) copywriting, online medical news and feature writing, and online marketing.

Medical writers should not be afraid to get involved in the online space – even if they are only writing for print publications, because eventually all printed materials will become digital. The earlier you start moving in this space, the better for you.

Joining Health Writer Hub

Health Writer Hub can help to keep you up-to-date with how you can benefit from the changing digital environment. You can also join Health Writer Hub's Writer Directory, register for job alerts, get regular health and medical writing advice, and stay connected to a growing, professionally relevant community.

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Author information

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Profile

An interview with Laura McMahon on the role of clinical research coordinators in Italy

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Clinical research coordinators (CRCs) – a CRC is not a clinical research associate but one is frequently mistaken for the other – have a fundamental role in clinical research. Their work involves a wide range of activities and responsibilities in conducting clinical trials according to good clinical practice under the immediate supervision of the principal investigator.

Laura McMahon has a long experience in this field in Italy. After obtaining a CRC certificate from the Association of Clinical Research Professionals in London, she immediately started working as a CRC in the oncology and haematology departments of different hospitals in Venice and Treviso. Since 2010, she is the president of a unique association in the Italian scene, the Italian Data Managers Group (Gruppo Italiano Data Manager; GIDM) which despite its name, is devoted to the CRC profession and dates back to 1998. GIDM lists among the many responsibilities of a CRC some activities which are very much linked to medical writing. We turned to Laura to find out how clinical research coordination and medical writing are interlinked in Italy.

Medical Writing (MEW): At the conference 'Evolution of clinical research in Italy' held in Chieti on the 26 January 2004, it was stated that the responsibilities of a CRC include writing the documentation for the Independent Ethics Committee (IEC), preparing mid-term study reports, collaborating in the writing of the study protocol – activities that are typical to medical writers. In your opinion are these two professions seen as two distinct roles in Italy or do they often overlap?

Laura McMahon (LM): Besides the clinical hypothesis to be investigated, the linguistic quality of study protocols is paramount in making sure that concepts are unequivocally clear and understandable. Not only a 'sloppy' protocol may dim the clinical significance of the research, but ambiguity may lead to personal interpretation, with potential adverse effect on patients' safety and data accuracy. The right balance between exhaustive clinical information and readable materials is at times difficult to achieve. It is the case, for instance, of informed consent forms for study participants which need to comply with normative requirements on completeness and, at the same time, be comprehensible to the lay reader.

CRCs in Italy are required to draw up all study documents before submission to the IECs and I do not think medical writers in Italy are usually involved in the drafting process. I do not think they are perceived as two different professions, as medical writing is not that widely known in Italy. I believe there is a need to promote the field of medical writing in the country.

MEW: Has this scenario changed in the last few years?

LM: I believe awareness is increasing, and despite professional medical writing's inconspicuous status in Italy, emphasis on robust background in the linguistic setting and specific training is arising. Globalisation of research and of readership requires papers to be clear, concise, and understandable and medical writers are highly knowledgeable on the quality standards required for publication. On the other hand, CRCs have the organisational and managerial skills to manage the practical aspects of protocols–such as case report form design, pharmacovigilance reporting, and adherence to normative and local regulations.

The reduction of resources in recent years has brought on an increased pressure on CRCs who are required to be skilled not only in theoretical and practical aspects of protocol development but also in English, information technology, and medical writing. Funds for research, especially for investigator initiated trials are limited and integration of professional expertise is required in order to optimise budgets.

MEW: Would CRCs benefit from specific medical writing training?

LM: Absolutely! I would be the first to avail of such an opportunity! Perfecting a harmonious overall view of the whole project would result in a better

written and understandable protocol. I think we would immensely benefit from writing tools and strategies, such as abstract writing, for instance. We are sometimes asked to revise the contents of manuscripts for editorial submission and although we perceive some sort of linguistic awkwardness, we feel unqualified to convey ideas that may have an impact on scientific content.

MEW: How can medical writers help CRCs?

LM: Collaboration is the key word in this world. The competence of medical writers can complement the proficiency of CRCs and the merging of both expertise would result in a successful cooperation. It would definitely be a great asset to have a medical writer go over the proofs or, even better, have a medical writer involved right from the very beginning of an editorial process or in the early phases of the study protocol development.

MEW: Do you think the role of medical writers will change in the next 10 years? If yes, how?

LM: I think there is a 'cultural' void with regards to the relevance of medical writing in clinical research which definitely needs to be promoted and encouraged. Physicians should be more aware of the role of medical writers and their contribution to overall quality of scientific documents. I hope this awareness will increase in the next 10 years.

I would like to see in the next 10 years an increase in courses and educational initiatives focused on written communication. Every year, there are a number of educational activities on the elaboration of clinical protocols that take place in Italy but they are mostly focused on methodology and statistical issues. I do not think there have been many training opportunities on medical writing to date. The Italian contribution to the scientific community has always been excellent, but summing up the contents of a whole publication in a 250-word abstract is a huge challenge, even for accomplished clinicians.

The EMWA autumn conference in Florence will definitely be a great opportunity for Italian medical writers and related professions to take part in an international event devoted to training and networking. As Laura McMahon says in this interview, we need to speak out loud and promote the role of medical writers.

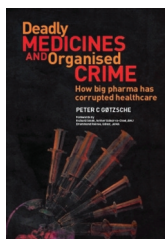*Laura McMahon can be contacted at ricercaclinicatreviso@yahoo.it.*

In the Bookstores

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Deadly Medicines and Organised Crime: How big pharma has corrupted healthcare
by Peter Gøtzsche;
Radcliffe Publishing, 2013.
ISBN: 978-184619-884-7 (paperback).
24.99 GBP. 310 pages.

Deadly Medicines and Organised Crime is written in a similar genre to the last book I reviewed for *Medical Writing*, namely Ben Goldacre's *Bad Pharma*.[1] I am not sure if that genre has a generally accepted name, but perhaps we could go with 'conspiracy theories about big pharma' for now.

There is a lot of nonsense in Goldacre's book, and while Goldacre has some quite sensible points hidden among all the hyperbole, Peter Gøtzsche manages to take the nonsense to a whole new level. If Gøtzsche does make sensible points in this book, then in my view they are too well hidden.

Before you even get as far as reading the actual text, the back cover of the book gives you a flavour of what you have let yourself in for. We are treated to the statistic 'prescription drugs are the third leading cause of death after heart disease and cancer'. That statistic is pure nonsense. The World Health Organization lists the top three causes of death worldwide as ischaemic heart disease, stroke, and lower respiratory infections.[2] Prescription drugs do not even make it into the top 10.

Gøtzsche attempts to justify this statistic in the book by means of some back-of-a-fag-packet cobbling together of various statistics from various different sources, but it is not convincing. It seems remarkably similar to an article on Mercola.com, a well-known source of alternative medicine nonsense, which among other things perpetuates anti-vaccination myths and peddles conspiracy theories about how the 'cancer industry' would not allow cancer to be cured.[3] If I were trying to make people believe I was a serious researcher, I would not want to keep that kind of company. One of the big problems with the 'drugs are third leading cause of death' statistic is that it only counts the harms of drugs, and takes no account of the number of lives saved by drugs, but if you want to read a more thorough debunking of the statistic, then I can recommend Harriet Hall's article on the Science-Based Medicine blog.[4]

Much of the other evidence in the book is similarly dubious. In one chapter, we are told that big pharma is just like 'organised crime'. The evidence for this is that many big pharma companies have been fined millions of dollars for breaking the law. Well, that is true, but as an experienced researcher, Gøtzsche really ought to understand the importance of a control group. Most large companies get fined for breaking the law from time to time. It is not something to be welcomed, but is a fact of modern society. I had a very quick look at whether big pharma were worse than other companies, and found no evidence that they were.[5]

The book claims to be 'evidence-based', and it is true that each chapter contains an impressive-looking list of references. However, if you look closely at the evidence sources cited, there are far fewer than you might have expected from the peer-reviewed literature. Many of the references are to books or newspaper articles, and even when they are references in peer-reviewed journals, they are often to non-peer-reviewed articles such as news items or editorials.

Cited evidence is also chosen selectively. One chapter is entitled 'Very few patients benefit from the drugs they take'. It is illustrated with just two examples: statins for primary prevention of cardiovascular disease and antidepressants. Antidepressants are well known for being of dubious efficacy, and to think that it is somehow scandalous that most patients do not benefit from primary cardiovascular disease prevention is to misunderstand its purpose. Because cardiovascular disease is so widespread in the population, even if most patients do not benefit from primary prevention, the population benefits can still be huge.

I wonder if that chapter might have turned out differently if Gøtzsche had chosen propofol for anaesthesia and omeprazole with antibiotics for ulcer healing as his examples?

Bizarrely, after having argued that statins do more harm than good, in another chapter he criticises the pharmaceutical industry for doing placebo-controlled

studies with statins, because 'many of the trials were unethical, as patients on the placebo were denied an effective drug'. This is the kind of thing that makes you realise just how badly written the book is and turns it into what feels like an exercise of riding the crest of the Goldacre *Bad Pharma* wave, rather than being evidence-based.

One little example of just how far Gøtzsche appears removed from reality is when he claims that zero progress has been made against cancer in the last 30 years. According to Cancer Research UK, long-term survival from many cancers has doubled since the 1970s, and much of that improvement is due to better treatments.[6] I wonder if Gøtzsche would respond to this by saying that Cancer Research UK are biased because they are just part of the 'medico-industrial complex'? (And yes, Gøtzsche really does use that phrase in the book.)

Medical writers will be dismayed to read how he describes our profession, referring to ghostwriting as if it is the norm for medical writers. He (rightly) talks about how unethical ghostwriting is, but he completely fails to mention the role of ethical medical writing assistance or the existence of widely accepted guidelines for ethical medical writing, such as those published by EMWA.[7]

How does Gøtzsche suggest the problems of the pharmaceutical industry can be fixed? He mentions various solutions, and one of them is actually quite sensible. He suggests that when pharmaceutical companies break the law, their executives should be held personally liable. This seems entirely reasonable to me, and in fact could be applicable to more than just the pharmaceutical industry, as corporate law-breaking is common across a wide variety of industries.

Unfortunately, Gøtzsche does not limit himself to sensible suggestions. He would like to see for-profit companies taken out of drug development altogether, and the task given to state-run organisations – a system of drug development that did not work well when tried in the old Soviet Union.

Gøtzsche also suggests that we should only take drugs if they are absolutely essential, and points out that most are not. It is true that not all drugs are absolutely essential as in immediately life-saving, but many drugs have a huge effect on quality of life. I suffer from allergic rhinitis. Well, I say 'suffer', but in fact as long as I remember to take my daily dose of loratadine, I do not suffer at all. If I did not take it, I'd be troubled by a blocked nose and frequent sneezing. Do I *absolutely need* to take loratadine every day? No. But does it hugely improve my quality of life? You betcha.

And what of Gøtzsche's apparent argument that no one should take drugs for primary prevention of cardiovascular diseases? It is true, of course, that many individuals do not benefit from primary prevention, but many others do. A paper published in the *New England Journal of Medicine* estimated that drugs for primary prevention of cardiovascular diseases reduced the annual number of deaths from coronary heart disease in the USA by about 160 000 from 1980 to 2000.[8]

I worry that a book like this has the potential to do real harm. There are many unscrupulous vendors of enormously dubious alternative medicine out there who love to tell us that the pharmaceutical industry is out to get us. That is a classic marketing tactic for those selling homoeopathy, magic crystal healing, or other forms of quackery. Charlatans are already gleefully pointing to Gøtzsche's book as evidence that they were right all along, the pharmaceutical industry is evil, and so we should all use their own particular kind of snake oil instead.

For example, this book now features on the above-mentioned Mercola.com.[9] It also features on the website of the Alliance for Natural Health,[10] which among other things promotes a rabid anti-vaccinationist point of view. And as if that was not bad enough, Gøtzsche has another fan in 'What Doctors Don't Tell You'.[11] For those who are unaware of this publication, it promotes homoeopathy as a cure for cancer, vitamin C as an alternative to antiretroviral medicine for HIV infection, and, needless to say, all the usual anti-vaccination nonsense.[12] I am pretty sure Gøtzsche would be just as disapproving of all this as he is of conventional medicine, but he is naive if he did not realise that his book would be used for marketing quackery.

I think you can tell from my review that I was not impressed with the book, and I really cannot think of any good reason to buy it. In my opinion, you would be far better off saving the money you would have spent on it and buying a couple of nice bottles of wine instead.

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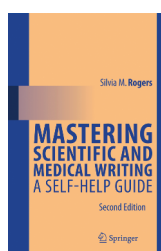
Mastering Scientific and Medical Writing: A Self-help Guide
by Silvia M Rogers;
Springer, 2014 (2nd edition).
ISBN: 978-3-642-39445-4.
26.99 GBP. 116 pages.

Concise guide for writers wishing to improve the clarity of their writing

With *Mastering Scientific and Medical Writing: A Self-help Guide*, EMWA member Silvia M Rogers delivers a useful little resource containing widely applicable advice. While it offers something for everyone who wishes to better their writing, novices and non-native users will likely benefit most, especially those with mother tongues whose writing conventions differ markedly from those of English. That the importance of good writing cannot be underestimated is both valid justification for the book's existence and the clear message of its short but well written introductory chapter.

In its nine other chapters, divided into numerous subsections, *Mastering Scientific and Medical Writing* provides valuable practical tips on all of the major aspects of writing. The main focus of Chapter 3 is spelling and punctuation. Rogers claims that poor spelling undermines the credibility of the science. I would hope that this is not so, although a writer who writes carelessly (as opposed to badly) justly risks being judged accordingly. Also covered are spellcheckers and US versus British English. Rogers claims that, 'Without any doubt, a mixture of British and American English is tiresome and annoying to the reader'. Not this reader. She also provides handy guidance on the use of optional hyphens and non-breaking spaces and hyphens, but some of her advice on hyphens and en dashes I disagree with. Rather than fault on the part of the author (or me), this perhaps reflects the very nature of discourse on writing and language: lack of consensus and outright disagreement. Illustrating the point, Rogers' rules for abbreviations ('a glossary never replaces the introduction of the abbreviated term in the text') do not fully concur with the views of Barry Drees, expressed in a recent issue of *Medical Writing*.[1]

The next chapter tackles grammar. After a slightly confusing introduction to tense, albeit compensated by good summary tables, Rogers gives excellent guidance on massive problems such as non-parallelism and dangling participles/dangling gerunds, as well as the 'which/that' problem, use of 'respectively', subject–verb agreement, and single and plural forms of collective nouns, all with helpful examples.

With the title 'Quoting Published Material', it is strange that Chapter 7 does not include any information on using quotes (a topic covered in a later chapter). Instead, it focuses on reference formats. Given the subject matter, it is perhaps unfortunate that Rogers does not provide a reference for the claim that '50% to 70% of all quoted literature references contain at least one erroneous item'.

Chapter 8 ('Avoiding Discrimination') gives advice on avoiding sexist, racist, and ageist descriptions. Racism is dealt with very superficially, with few details and no examples. A topic that is perhaps more pertinent, that of not defining patients by their disease (i.e. avoiding descriptions such as 'schizophrenics' and 'diabetics'), is completely overlooked.

Continuing the ethics theme, the next chapter is on plagiarism. Rogers describes its different forms, notably providing a nice explanation of self-plagiarism. She raises the subject of possible allowances for writers whose first language is not English, something I advocate, before concluding with brief but excellent advice on avoiding plagiarism.

While not without flaws, all of this book's chapters contain at least something that warrants a look. Chapter 2 essentially serves as a second, more substantial introduction that briefly (too briefly in my opinion) debunks some of the myths as to what constitutes good writing and introduces ways to make writing more elegant and concise. The highlight of Chapter 5, which covers style, is a concise and coherent examination of when to use the active and passive voices, a contentious issue if ever there was one. Chapter 6 ('Redundancy and Jargon'), meanwhile, boasts a good list of tautologies to avoid. The last chapter ('Structuring Scientific Texts') provides foundation-level guidance on targeting an audience, structuring an article, and writing an abstract.

The 10 regular chapters are complemented by both an excellent set of practical exercises that enables the reader to put their learning into practice and a multi-section appendix, the first section of which effectively summarises the book by listing the 'rules' of scientific writing. The appendix also provides a useful comparison of British and US spellings and explains how to use some of the commonest punctuation marks, although there is no mention of the distinctions in punctuation use between British and US English. A table of awkward phrases to avoid is rather subjective, and some of the preferred alternatives do not seem to work. Better is a long list of academic titles and honours, which can be very difficult to translate between languages.

Rogers repeatedly urges us to follow house style and be consistent, to choose meaning over rules. Quite right. She sometimes breaks her own rules, but I guess we all do.

Importantly, she covers recent trends, such as the use of data as a collective noun ('data is'), non-italicisation of Latin abbreviations, and the gradual abandonment of phantom rules of grammar (e.g. that one may not split an infinitive or end a sentence with a preposition). However, her non-acceptance of 'they' as a third-person gender-neutral pronoun is at odds with modern thinking.

While I cannot endorse all of its advice, there is no denying that *Mastering Scientific and Medical Writing* packs in plenty of useful tips for budding writers. And, in spite of repetition in places and a slight lack of cohesion across chapters, the excellent cross-referencing makes navigating it simple. My main criticism is that the book just isn't long enough, that the coverage of certain topics is miserly. Finally, a word of caution: We writers should be aware that for almost every 'rule' of writing there will be people, often many, who hold a contrary view.

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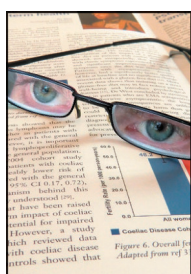
Journal Watch

Dedicated medical writing rotation for pharmacists, publication of drug industry funded research, and evidence-based medicine for clinical decision making

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Dedicated medical writing rotation for pharmacists

The ability to write up results and contribute to the medical literature is an important skill in a number of professions, including pharmacy practice. Some pharmacy residency programmes require that their participants produce a manuscript of publishable quality (although it may never actually be submitted); however, there is rarely any formal training in medical writing skills. In a recent original article, a group of pharmacists suggested that a structured residency rotation dedicated to medical writing should be considered to fill the knowledge gap that often accompanies medical writing skills in these students.[1] This may have implications for training other healthcare professionals and professional medical writers.

The purpose of the article was to describe the design and implementation of such a residency programme dedicated to developing medical writing skills. Faculty involved in the rotation should have medical writing experience, such as publication in peer-reviewed journals and acting as a peer reviewer for biomedical journals. The medical writing rotation is designed to introduce the resident to aspects of medical writing such as reasons to publish, different types of manuscript, authorship and acknowledgement considerations, composition of a manuscript, submission and publication process, and peer reviewing. At the end of the rotation, each resident is required to prepare, with appropriate assistance, a manuscript for intended publication.

At the time of publication, five postgraduate year 2 residents had completed the medical writing rotation at a tertiary care academic medical centre in the US. Since then, five manuscripts written by the residents have been accepted for publication in peer-reviewed journals. Therefore, a structured medical writing rotation during a pharmacy residency programme can help participants develop skills that are important for contributing to the medical literature in the future.

Publication of drug industry funded research

The *British Medical Journal* (*BMJ*) and associated journals have stopped publishing research funded by the tobacco industry. The reasons are that 'the research is corrupted and the companies publish their research to advance their commercial aims, oblivious of the harm they do'. In this 'Head to Head' article,[2] the authors debate whether these arguments also apply to research funded by the drug industry and if, therefore, journals should also stop publishing the results of drug company-funded trials.[2]

The 'Yes' argument claims that drug company-funded research is flawed and is published to encourage sales. They propose a new model where trial planning begins with a systematic review of previous work to determine if a new trial is necessary; if yes, the systematic review and new trial protocol should be posted publically on the internet for review and comment. The statistical analysis plan should be written before any data are available for analysis, and posted with the protocol. Upon trial completion, the entire anonymised data set should be made available for everyone to analyse. Journals should then publish the results from the systematic review and all independent analyses of the trial data.

The 'No' argument states that the tobacco and drug industries are fundamentally different – tobacco industry products harm health whereas pharmaceutical products aim to improve health – and that there are plans to increase integrity in the publication of drug company-funded research. Many steps are being taken to improve transparency in the evidence base for new drugs (e.g. mandatory prospective trial registration, reporting of all results, access to patient level data on the benefits and harms of interventions); these rules should also be applied retrospectively to previously unreported

trials. The *BMJ* are keen to publish papers from the Restoring Invisible and Abandoned Trials initiative, where academics can find and publish previously unreported trials if the original investigators declined to publish, and also trials where there was no evidence of benefit, providing the research questions are important and the methods are robust.

The article concludes by considering if editors would be afraid or unable to ban drug company-funded research, given the income journals receive from advertising, reprints, and sponsorship from the pharmaceutical industry. The current *BMJ*'s editor in chief has stated that 'If these efforts do not soon bring about a necessary sea change in the way industry funded trials are performed, the BMJ may well decide to stop publishing them. Whether an editor would survive such a decision is a question I may have to test'.[3]

Evidence-based medicine for clinical decision making

There is currently much debate about the merits of using evidence-based medicine for clinical decision making. An oral history of evidence-based medicine film was made last year for a joint *Journal of the American Medical Association* (*JAMA*) and *BMJ* celebration; this film has been published online (bmj.com/evidence and the *JAMA* network) and was summarised in a recent editorial.[4] While there is some support for the argument that evidence-based medicine leaves no room for discretion and has fuelled over diagnosis and treatment, others do not agree.[5]

In her recent editor's choice in the *BMJ*,[6] Fiona Godlee introduces a commentary about the Wingspan intracranial stenting device.[7] The article notes that this device is currently licensed for use in people with a previous stroke on the basis of a single, industry funded, uncontrolled study of 44 patients, whereas the only randomised trial showed clear evidence of increased deaths and strokes when the device was compared with medical treatment.[7] The special regulatory programme for high-risk devices in rare conditions under which Wingspan was licensed is the subject of an accompanying commentary[8] that highlights the generally poor quality of the evidence for such devices. The authors' of these commentaries conclude that there should be greater regulatory scrutiny of the safety and effectiveness of medical devices.

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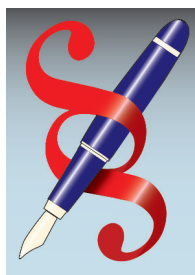
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Regulatory Writing

The essence of regulatory writing as defined by its jargon

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In this issue of *Medical Writing* dedicated to regulatory writing, many of the articles provide some glimpses of the day-to-day problems and dilemmas faced by regulatory writers. It is hard, however, to describe the essence of regulatory writing in a succinct and compre- hensive fashion. For my column in this issue, I have provided a glossary (by no means exhaustive) of some of the more common terms used by regulat- ory writers, with an description of what they mean in the context of day-to-day working life. My hope is that through describing the way jargon is used by regulatory writers, I can transmit a feel for the less intangible aspects of the job.

Alignment	A submission contains many different documents and components, authored by many different people. It is important (and not always easy) to ensure that these convey the same key messages, that is, that they are aligned.
Backburner	The first of the entries related in some way to time management. At a given time, a regulatory writer will usually have several projects at various stages of completion. It is important to *prioritise*. Projects that are not on a *critical path* can be relegated to the backburner.
Best practice	In an ideal world, we would always follow procedures that through collective experience have been shown to produce the best results (best practice). Most of the time, this is the case, but sometimes the singularity of a project, or extremely tight timelines might require a certain deviation from best practice and demand a *workaround*.
Critical path	A project where there is absolutely no slack in the timelines is said to be on a critical path. Usually, this means leaving other projects on the *backburner* to ensure that the project on a critical path is completed successfully.
Debrief	When a hectic project comes to an end, especially one that has not gone entirely according to plan, a debrief is often held to identify mistakes and discuss learnings from the experience in the hope that the next project may go more smoothly.
Downtime	Work will often come in fits and starts, and often there will be gaps in your work schedule. Ideally, this downtime should not be spent just reading the newspaper online but rather filling in knowledge gaps, or possibly *frontloading* projects on the *backburner*.
Drop-dead date	The absolute last date when a project (or project component) should be completed.
Escalate	A large part of a regulatory writer's job involves resolving conflicts within a *team*. When, despite your best and most creative efforts and *workarounds*, the conflict remains, you may hear mention of escalation, usually to senior management for arbitration. You can also threaten to escalate, for example, if a reviewer repeatedly fails to provide timely review comments.
Fit for purpose	It seems stating the obvious that documents should be fit for purpose, that is, the content, level of detail, and presentation are sufficient for the particular purpose of the document. Some might say that dotting all the i's and crossing all the t's might be too much effort for too little reward (providing of course the actual data are accurate). The threshold between what is fit and unfit for purpose is, however, subjective and poorly defined. If in doubt, it may be best to dot those i's and cross those t's if not doing so may detract from the authority of the document.
Frontloading	As mentioned in some other entries, *timelines* can often be tight and so frontloading is common practice to alleviate stress later on down the line. For example, as Sam Hamilton explains (see p86), in a clinical study report (CSR), the patients and methods section, or front-end of a CSR, is largely independent of the actual results and so can be written before the final statistical outputs are available. But too much frontloading can be a waste of precious time if the work has to be thrown away, and can also be dangerous if a lot of fiddly adjustments are needed later (with the risk that they are overlooked).
Heads-up	Reviewers of regulatory documents are often busy people involved in many projects at the same time. A heads-up e- mail is a courtesy to them to help them plan their schedule. Personally, I do not think these should be sent too early (except in holiday season) as people might forget and the *timelines* may well shift.
Heavy lifting	I have heard this term used to refer to work that is fairly straightforward, but quite repetitive and time-consuming (and boring). An example would be putting together tables. Once this work has been done, you can then move on to more creative tasks such as writing the wrap-around text and adding the interpretation.

In the loop	To keep someone informed of the situation. The number of people kept in the loop is a judgement call, though. There are only so many threads that someone can reasonably follow, and too many mails can create excessive background noise. Often, keeping someone in the loop is merely a question of covering your back. If something goes wrong, you can say 'well you were copied into the discussion'.
Mentor	Regulatory writing is not something that you can study at university (though there are some medical writing courses that include aspects of regulatory writing). And of course, the workshops on offer at EMWA conferences are a valuable source of knowledge and an opportunity to share experience. But the fact remains that most writers need to learn on the job and there really is no substitute for direct experience. In this respect, it is common practice for senior medical writers to mentor their more junior colleagues.
On-boarding	On-boarding refers to the process of integrating new writers into the team and helping them learn not only about medical writing itself but also the idiosyncrasies of the company. In many cases, this will involve the figure of the *mentor* as an efficient way to bring a new recruit up to speed.
Prioritise	An important aspect of time management is knowing what project should take priority. The equation can be a complex one and involve not just the *timelines* themselves, but also the consequences of missing a deadline.
Pushback	If someone (an internal reviewer within the company or perhaps an external reviewer in a health agency) demands actions perceived as being unreasonable, you (or the team depending on the context) may decide to pushback. This often requires tact and diplomacy (and occasionally *escalation*).
Rapport	A big part of regulatory writing is negotiating compromises between different *team* members. Your job will be easier if you have managed to build up a good rapport with the team.
Sanity check	Ideally, we would like all projects to go smoothly with no mad rushes at the end. Meanwhile, in the real world, substantial changes may be made late in the process. In such cases, another look at the document after a good night's sleep and a rest (sanity check) may be highly desirable to pick up any fatal flaws.
Team	A team is a group of people assigned to a particular project, each with a particular responsibility or competency (e.g. safety scientist, toxicologist, regulatory partner). In a big pharma company, the team may be at different sites and in different time zones. Most documents a regulatory writer will work on require contributions from different team members, and many will be developed in a team context with meetings or teleconferences to discuss the salient points and resolve issues. As a medical writer, it helps to have a good feel for team dynamics and a good *rapport* with team members.
Timelines	Timelines are an omnipresent aspect of medical writing. Many regulatory documents come with very specific deadlines, and the route to completion will involve many milestones. Developing timelines to reach those milestones, taking into account document complexity and availability of *team* members, is not an exact science and another aspect where experience is important.
Touch base	This jargon for contacting someone often has certain connotations. Thus, 'I just wanted to touch base about … ' can sometimes be translated as 'you haven't forgotten about me have you/you will provide those comments won't you … ?'.
Workaround	In an ideal (though ultimately rather boring) world, everything would go smoothly and according to plan, and we would follow *best practice*. The real world often throws up problems that need a certain creativity (thinking outside the box). The resulting workaround recognises that not everything follows the ideal pattern, while still striving to adhere as closely as possible to *best practice*.
Work–life balance	The concept of work–life balance is not unique to regulatory writers, of course, but I have heard it mentioned from time to time, usually during the *debrief* of a particularly tortuous submission with tight *timelines*. On average though, my impression is that regulatory writers enjoy a reasonable work–life balance.

Medical Communication

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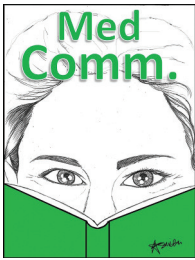
The first Geoff Hall Scholarship Award

Dear all,

My first duty is to thank all of the new and aspiring medical writers who sent an entry to Head Office for the Geoff Hall Scholarship Award. The committee has awarded one scholarship this year, but we urge anyone who was not successful to please try again, if you are eligible. The title for next year's essay is: 'Are Medical Writers Ghostwriters?'.

This year's essays certainly sparked some debate, and our decision was not easy. However, I am delighted and very privileged to be able to introduce you to the first winner of a Geoff Hall Scholarship: Menorca Chaturvedi. I had intended to write a little bit about her background and experience myself, but she sent me such a lovely letter that I thought it much more appropriate that she introduces herself. Her letter is below, followed by her winning entry.

Lisa Chamberlain James
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Dear Lisa,

As evident from my CV, I am a Master's student in Life Science Informatics at University of Bonn, Germany; currently working on my Thesis at Swiss Tropical and Public Health Institute, Basel, Switzerland. I have been actively involved in writing, editing, and blogging for over 5 years, and I love doing so. A few months ago, I started getting to know more about the field of Science Communication/Medical Writing, and realised that this would be something I would truly enjoy doing for the rest of my life.

I took up bioinformatics in college due to my love for science, but those 4 years gave me lot of opportunities to explore my potential as a writer, editor, and team manager. I became a part of the University newspaper, and learnt the art of writing effective reports under the guidance of Prof. Venkat Pulapaka, who then was the Head of the School of Journalism at SRM University. I was later promoted to be the joint student editor of the newspaper. Meanwhile, I also started writing for *Youth Ki Awaaz,* a platform for voicing opinions on social issues and went to become the sub-editor for a few months. Besides this, I wrote science articles for the newsletter of the School of Life Sciences at my University, and was incharge of managing the newsletter for the National Technical Festival of SRM University, right from the start to the end. I have also been involved in conducting various events and conferences at my University and also headed the domain of 'Literary' events at the National Cultural Festival in 2011.

During my 6-month internship in Heidelberg last summer, I attended the Career Day sessions organised at EMBL and DKFZ, respectively. I met a lot of professionals from the field of Medical Writing and Science Communication and used the opportunity to find out all that I could by having discussions with them. It was during the EMBL Career Day that I found out about the European Medical Writer's Association while talking to Dr Julia Forjanic Klapproth. I became a member of the organisation and decided to attend the workshops to get professionally trained. Unfortunately, I could not register for the November Conference due to financial constraints, but made up my mind to try for the Geoff Hall Memorial Scholarship.

Winning this Scholarship means a lot to me. I will definitely be attending all the conferences during the next 2 years, and beyond, while striving to improve my writing skills and become a successful Medical Writer. I am extremely grateful to EMWA for giving me this opportunity.

Thank you

Yours sincerely,
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Where does medical writing fit in research?

'The Editor's Foreword' in *The Frankenstein Diaries*,[1] 'translated from the original German and edited by The Reverend Hubert Venables', asked the readers to believe that the legend of Frankenstein was indeed true.[2] The book was filled with diagrams of the experiment carried out by Dr Victor Frankenstein, the scientific equipment used at that

time and excruciating details of the 'creature' or 'monster' that was created.

While we know that this was a mere work of fiction, the fact remains that no research can be communicated to people unless it is documented in a precise and clear fashion. The art of communicating scientific information by specialised writers is known as Medical Writing. With the advancing technology, an increasing number of scientific developments are being made continuously. Different kinds of information need to be communicated clearly to different target audiences.[3] While pharmaceutical companies might be most interested in clinical study procedures and drug regulatory dossiers, researchers would focus on compiling their studies clearly for publication in scientific journals. Similarly, people buying medical products would expect clear instructions to come along with the packaging, and medical writers are sought to prepare the promotional literature, brochures, and handouts for healthcare products.

Some of the oldest documents on medical studies found include *De medicina*,[4,5] written by Celcus, said to be a physician himself who lived between 25 BC and 50 AD, the Kahoun[6] papyrus dating back to 1950 BC, which talks about human medicine, veterinary medicine, and mathematics and the Ramesseum IV and V papyri, dating back to around 1900 BC. Thus, it is evident that writing has been an integral part of medical research from centuries ago. Producing documents that are not well written will not help transfer knowledge to others, and neither will it be useful to those interested in making advancements in that field.

As technology has made it easier for scientists to generate more data, effective analysis and interpretation of the data is the need of the hour. Although medical writers are not required to carry out the research themselves, they have a strong understanding of the subject in order to interpret the results and present them in a simplified manner. Unless the objectives and results of a study are presented in a simplified and appealing way, one cannot expect people to understand the significance of the study. Hence, it is vital to be a skilled medical writer who can decide on the most effective ways to present data from research.

Another aspect of carrying out research is getting grants in order to carry out the proposed studies. This is where Grant Writing comes into play, and medical writers help facilitate research by writing effective grant proposals for scientific studies. It is important to write a persuasive research proposal such that the application stands out, and results in obtaining funds. Certain funding agencies might need the proposals to comply with certain guidelines or formats. Hence, one has to be very methodical and cautious while working on any such proposal.

Medical Writing also includes Medical Journalism, an area that helps bridge the gap between the scientific community and the general public. Medical Journalism strives to give the public an insight into the research carried out by scientists. It could be quite difficult for a layman to understand the latest scientific developments by reading scientific journals. Hence, it is important to simplify the data while presenting it to the readers and yet, make them understand the research as closely as possible. Besides, a medical journalist has to be very careful while writing reports and cannot go ahead with it without understanding the research very well. Since scientists explain their studies on a very technical level in journals, it is possible that they might find it difficult to explain it in an over-simplified way to the general public. This is where a medical writer or medical journalist comes into the picture, and formulates an articulate report such that the essence of the research is intact and the communication barrier between scientists and the public is bridged.

Summing up, I feel that communicating one's research to the scientific community as well as to the general public is equally important, and requires skilled writers having a scientific background. Medical Writing is an essential part of research and aids scientists in communicating their findings to the world. As Crandall *et al.*[7] put it, even though technology is changing the way scientists engage in research or teach, 'the written word remains one of the most important means for communicating that information to others'.

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News from the EMA

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The articles included in this section are a selection from the EMA's news and press release archive for December 2013 – February 2014.

More information on the work of the EMA can be found on its website: http://www.ema.europa.eu

European Medicines Agency to push ahead in 2014 towards publication and access to clinical trial data

The European Medicines Agency (EMA) has now reviewed all comments received on its draft policy on publication and access to clinical trial data. While the comments received showed that there is large support for the Agency's plans to allow access to clinical trial data submitted as part of marketing authorisation applications, they also highlighted that there is a need for further analysis and clarification of certain aspects.

The Agency will continue to work with stakeholders, including industry, academia and civil society organisations, to further clarify and fine tune the proposed rules to achieve the broadest possible consensus. This work will be guided by a set of key principles that were agreed with the Agency's Management Board on 12 December 2013. The policy on publication of and access to clinical-trial data and an implementation plan will be discussed at the March 2014 Management Board meeting.

The key principles include a stepwise approach for implementation with, as a first step, preparation for the publication of clinical study reports redacted as appropriate, the development of a methodology for de-identification of patients, and the definition of a standard format for the submission of data. The principles also foresee the introduction of preliminary steps prior to data access designed to address the risk of possible unfair commercial use of data while ensuring proactive and non-selective access ('use control' not 'access control').

The Agency reiterates its firm commitment to pursuing the objective of full transparency regarding clinical trial data. The Agency will continue to monitor progress in the court cases brought by two pharmaceutical companies against the Agency and the on-going discussions on the new European clinical trials legislation. It recognises the need for consistency in the general approach to access to documents by European Union (EU) institutions and bodies, while recognising the specificity of documents in the possession of the EMA and the Agency's primary duty to protect and foster public health.

The Agency's draft policy has prompted broad debate among an unprecedented range of stakeholders, including the important focus on the benefits to patients, and more generally to society of giving access to clinical trial data and on the best approach to achieve this. It has been the catalyst for various initiatives from the pharmaceutical industry, funding bodies, and academia centres in this direction.

The Agency has embarked on developing its plans for the proactive publication and access to clinical-trial data because it believes that the release of data is about establishing trust and confidence. The Agency is also firmly of the opinion that wider availability of data broadens the scientific knowledge base, fosters innovation, and encourages investment in the development of medicines and ultimately benefits public health.

European Medicines Agency and US Food and Drug Administration strengthen collaboration in pharmacovigilance area

The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have set up a new 'cluster' on pharmacovigilance (medicine safety) topics. Building on the experience of previous regular videoconferences between the EMA and the FDA in this area and the recent creation of the EMA's dedicated committee for pharmacovigilance, the Pharmacovigilance Risk Assessment Committee (PRAC), this cluster will provide a forum for a more systematic and focused exchange of information on the safety of medicines.

Clusters are regular collaborative meetings between the EMA and regulators outside of the European Union which focus on specific topic areas that have been identified as requiring an intensified exchange of information and collaboration. The EMA and the FDA have already set up such clusters to discuss issues related to biosimilars, medicines to treat cancer, orphan medicines, medicines for children, and blood-based products, among other topics. Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) are also involved in some of these clusters.

'In an increasingly globalised pharmaceutical market, collaboration between medicines' regulators is essential', explains the EMA's Executive Director Guido Rasi. 'Medicines' regulators are interdependent: any action taken in one territory has repercussions on the rest of the world. International cooperation is a key area of work for the Agency'.

'The work of protecting the health and safety of the American people cannot be done in isolation', says Janet Woodcock, Director, M.D., director of the FDA's Center for Drug Evaluation and Research. 'It is part of a larger collaborative global effort between the FDA and its international regulatory partners to ensure the health and safety of all our citizens'.

As part of the new cluster, discussions on any pharmacovigilance issue will now take place between the agencies on a monthly basis by teleconference. This increased degree of interaction will allow the agencies to work swiftly in the area of the safety of medicines and to coordinate communication activities.

The creation of this cluster is the latest step in the EMA's and FDA's wider approach to expand and reinforce international collaboration. The information exchange is covered by the confidentiality arrangements between the EMA and FDA.

Canadian and Japanese regulatory authorities will participate in the meetings of the cluster on pharmacovigilance as observers.

Regulatory information – use of eSubmission Gateway and web client extended to new procedure types from 1 April 2014

From 1 April 2014, the EMA will extend the use of the eSubmission Gateway and web client to all referral procedures, veterinary medicine submissions, and paediatric submissions.

This will allow companies to submit their documentation to the EMA securely over the internet, thereby improving efficiency and reducing costs

for applicants. Applicants who wish to use the eSubmission Gateway or web client need to register on the EMA's eSubmission website. Applicants who have already registered and used the eSubmission Gateway or web client for electronic Common Technical Document (eCTD) submissions for the centralised procedure or PSUR single assessment (PSUSA) procedure submissions do not need to register again.

Submissions on physical media (CD/DVD) for referrals, veterinary submissions, and paediatrics will continue to be accepted as an alternative method for the time being. However, it is essential that applicants only use one submission method and do not submit duplicate submissions on physical media or Eudralink as this might lead to a negative technical validation and cause a delay in processing the application.

Applicants are invited to register to use the eSubmission Gateway or web client solution as soon as possible.

The Agency launched the eSubmission Gateway in 2012 as an electronic submission channel for all types of eCTD applications for human medicines. The eSubmission web client was launched in January 2013 to complement the Gateway and is aimed at applicants with lower transmission volumes.

The use of the eSubmission Gateway or web client will be mandatory for all eCTD submissions through the centralised procedure from 1 March 2014.

Statements of non-compliance with GMP now publicly available in EudraGMDP

The EMA has launched a new version of the EudraGMDP database which includes, among other changes, the publication of statements of non-compliance with good-manufacturing practice (GMP).

Regulatory authorities conduct inspections of manufacturing sites and issue GMP certificates when they conclude that a site is GMP compliant. When inspectors conclude that a site is not GMP compliant, a statement of non-compliance with GMP is issued and regulatory authorities enter the document in EudraGMDP. These non-compliance documents are now publicly accessible as well as the positive GMP certificates.

Statements of non-compliance contain information on the nature of the non-compliance and the actions taken or proposed by the issuing authority in order to protect public health. These statements aim to establish a coordinated and

harmonised response by the network of EU medicines regulators.

EudraGMDP is a database operated by the EMA that supports the exchange of information on GMP compliance and non-compliance, as well as on manufacturing and importation authorisations, among European regulatory authorities and regulators outside the EU.

As of April 2013 the database also includes information on good-distribution-practice compliance, as well as registrations of active substance manufacturers, importers and distributors, and wholesale distribution authorisations.

Most information contained in EudraGMDP is publicly available. Information of a commercially or personally confidential nature is not made public. The decision on which information to make public is taken by the medicines regulatory authority in the EU Member State that adds the information to the database.

Charging for access to publication correction notices: Right or wrong?

Imagine buying a faulty product and then being asked to pay the same amount again for its repair. That's more or less the scenario if you buy an article published by ACS (American Chemical Society) Publications that subsequently requires corrections, as one synthetic chemist blogger recently discovered.[1]

Writing on the Just Like Cooking blog, 'See Arr Oh' presented two tweets, one an indignant message to ACS Publications, the other the publisher's nonchalant reply:

See Arr Oh @SeeArrOh

Dear @ACSPublications, I am not giving you $35 to access a *%$&$% article CORRECTION. These are *not* publications; they should be free #grr

ACS Publications @ACSPublications

@SeeArrOh Corrections are considered additional materials, but we appreciate your feedback and will take it on board.

Additional materials? Are you kidding me?! This is information that should have been correctly presented in the original article, not some kind of bonus or upgrade.

Picking up on the story, the excellent Retraction Watch blog polled the views of its users.[1] At the time of writing, 386 of the 463 voters (83%) thought that all correction notices should be freely available. Only 11 voters (2.4%) did not agree that all corrections should be freely available, while a significant minority felt that only those relating to significant errors ('not spelling errors and the like') should be gratis. This last option puzzles me. Can you imagine paying to read corrections to spelling?

As Retraction Watch points out,[2] the Committee on Publication Ethics (COPE) recommends that all retraction notices be 'freely available to all readers',[3] but has not apparently issued an equivalent statement for correction notices. I feel strongly that all such notices should be free to all; publishers profiting from mistakes in their journals is hard to swallow.

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English Grammar and Style

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Some more four-letter words

I published a series of articles in *The Write Stuff* on short words frequently used in the medical and scientific context between Volume 16(3) 2007 and Volume 18(4) 2009. Since then, at training courses and in email enquiries, I have been asked questions about the usage of some further short words not covered earlier.

Wide

Wide is an adjective (a *wide* band), an adverb (*wide* awake; we could see nothing far and *wide*), and a noun, but only in the mysterious world of cricket (Note: Oxford English Reference Dictionary: 'a ball judged to pass the wicket beyond the batsman's reach and so scoring a run'). Its use as a single-word adjective is clear and needs no special explanation. *Wide* frequently crops up in our texts as part of the terms *worldwide* (used to represent all three terms below), *companywide* or *countrywide*, where it means *affecting the whole*. The most frequent question here is, do you need a hyphen before *wide*? You can adopt a couple of approaches:

- Never put a hyphen before *wide* whether you are using *world wide* as an adjective – *the world wide incidence of*; or an adverb – *we observed an increase of 23% world wide*. I do not agree with leaving a space before wide.
- Many would prefer hyphenation: *the world-wide incidence of* and *we observed an increase of 23% world-wide*, because here *world-wide* is being used as a 'compound modifier' and the hyphen shows that the word *wide* is linked to the word *world*.
- The simplest alternative that needs the least checking is to always write worldwide as one word: *the worldwide incidence of* and *we observed an increase of 23% worldwide.*

I use the style described in the second or third point and try to remain consistent in one text.

I think you can apply this to *countrywide* and *companywide*. The addition of *wide* in this way does not seem to have pervaded English very far. It is not generally acceptable to tag *wide* onto the end of words to indicate *affecting the whole*. We do not seem to have invented laboratory-wide, organ-wide, club-wide, school-wide, party-wide, or university-wide yet, with or without a hyphen, although hospital(-)wide and nation(-)wide are in common use.

Is there a difference between *broad* and *wide*? Do you talk about *wide* or *broad* bands in a chromatogram, or a *wide* or *broad* bandage? These questions illustrate nicely that sometimes words are interchangeable and sometimes they are not. A band in a chromatogram can be *broad* or *wide*, and the reader will understand the same whichever adjective is collocated with *band*. But a margin and a bandage are almost exclusively collocated with the word *wide*. Nobody could claim, however, that a broad margin or a broad bandage was incorrect or that they would be misunderstood: they just do not sound right.

Long

As with *wide*, *long* used as a single-word adjective poses no problems. Do not be tempted to use *lengthy* instead, unless you are talking or writing more informally or even jocularly. *Long* is also a noun, even though you may not recognise it as such (the *long* and the short of it …; it didn't take us *long* to realise that she was …). It is when *long* is tagged onto the end of another word, such as *hour*, that a similar problem to that with *wide* emerges: *hour long*, *hour-long*, or even *hourlong*?

I definitely come out in favour of the hyphen with *long* and no other solution. Comprehension of the written word relies entirely on the visual effect of strings of letters and punctuation, and *hourlong*, *weeklong*, and *lifelong* just do not look right. So I would always go for … *a month-long course of XXX* or *a year-long sabbatical*. Adding *long* to the end, can, of course, be avoided by saying a *1-month course of XXX* or a *1-year sabbatical*, and I really do feel that these alternatives are better, and that '*-long*' formulations should be avoided in our type of writing. Except for *life-long*: try expressing the

idea of a *life-long disability* in so few words without using *life-long*.

Long is also a verb and should find only rare use in our context, as it means *to yearn for*, and not *to lengthen*. I attended a course on understanding ECGs quite a few years ago now, and the course leader kept saying '… notice how the QRS complex *longs* …' and '… again we see *longing* of the QRS complex …'. I just sat there *longing* for her to talk normal English.

Grow

You can *grow*:

- plants
- old
- angrier and angrier
- a new leg if you are a newt
- and antlers if you are a deer

but, as far as I am concerned, you still cannot *grow* your:

- assets
- organisation or
- involvement in a project.

This may be evidence of a somewhat old-fashioned streak (it took me a long time to drop the *out* after *sort*, as in *that has been sorted*), but the older I get the more progressive I get, so there is hope for me yet.

Ones

Here we are concerned with the use of the word *one* as a noun, rather like a pronoun.

When making a verbal presentation about the results of a clinical study or in a conversation about the results, it would be quite normal to say something like this: *As you see, the patients in Group A, who were given antibiotic prophylaxis 24 hours before dental surgery, didn't develop infection. The ones in group B, however, who didn't have any prophylaxis, all developed infection.*

Instead of repeating *patients* in the second sentence, many of us would use *ones* in this way. This sounds fine when you are speaking. Here is another example: *Here are the eggs our hens laid today. The ones they laid yesterday were broken before I could bring them to you.* Again *the ones* sounds perfectly acceptable and is what most people would say.

Substituting *one* or *ones* for previous words like a quasi-pronoun does not work in our types of text. It sounds too informal or spoken: *Metabolism of exogenous substances and some endogenous ones is mediated by enzymes.* Or: *We were able to confirm the results in mice, but not the ones in rats.* Or: *This was the effect we saw in rats; the one we saw in rabbits was different.*

So how do we deal with this?

The simplest solution is to repeat the word that *one* or *ones* replaces. Hence: *Metabolism of exogenous substances and some endogenous substances is mediated by enzymes.* Using *those* or *that* often does the trick, hence: *We were able to confirm the results in mice, but not those in rats.* Or: *The effect in rabbits was different from that in rats.*

To avoid *ones*, some authors may opt for the following solution to the first sentence in the previous paragraph: *Metabolism of exogenous and some endogenous substances is mediated by enzymes.* This is acceptable when the distance between the adjective before *and* (exogenous) and the noun it modifies after *and* (substances) is very short, which is the case in this sentence – lengthened only by one very short word, *some*. Any further apart is a source of annoyance for the reader. Writers whose first language is not English sometimes leave too long a distance in such formulations because it is more acceptable to do so in their first language.

However you solve this, avoid using *one* and *ones* as quasi-pronouns in our types of text.

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The Webscout

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What happens pre-approval?

The theme of this issue made me wonder what it is that happens before approval of a new medication. Of course, it is clinical development, notably phase II and phase III studies. But many years have already passed before a drug reaches this particular development phase and many drugs have failed on the way to that point. Only 1 out of 5000 to 10 000 development compounds makes it to the market and this process can take up to 15 years.

http://www.innovation.org is a project of the pharmaceutical industry in the USA with the mission to create awareness and encourage discussion about the pharmaceutical development process, its challenges, and its future promise. On their website you can download a brochure on drug discovery and development from

http://www.innovation.org/drug_discovery/objects/ pdf/RD_Brochure.pdf.

or alternatively learn about the process by watching this video:

http://www.innovation.org/index.cfm/ InsideDrugDiscovery/Inside_Drug_Discovery.

When I was looking for a good presentation about pre-clinical research, I came across this piece of work:

http://altweb.jhsph.edu/altex/30_3/FFTHartung. pdf.

The author critically reviews the relevance of pre-clinical studies for drug development and considers different aspects of the pre-clinical phase. He addresses issues such as the limitations of animal testing for toxicity assessment, the predictive value of animal disease models, the non-reproducibility of basic research results, and the shortcomings of *in vitro* testing.

Pre-clinical development planning is a complex task. What kinds of pre-clinical studies and data are required for drug approval? For a first impression, you can have a look at the requirements of the submission dossier, the CTD (common technical document):

http://ec.europa.eu/health/files/eudralex/vol-2/b/ update_200805/ctd_05-2008_en.pdf.

Pre-clinical data go into Section 2.4, the non-clinical overview, and Section 2.6, the non-clinical summary. From Section 2.6, you can already get some idea of the kind of pharmacology, pharmacokinetics, and toxicology data that is required and how it should be presented.

You can find a basic overview on pre-clinical study types, their objectives, and aspects such as duration and outcome measures at

http://www.pacificbiolabs.com/tox_regulatory.asp.

Good pre-clinical planning will avoid potentially harmful and costly clinical trials. The following slideshow summarises some important points to consider in early development:

http://www.powershow.com/view1/74134-ZDc1Z/ Points_to_Consider_in_Preclinical_Development_ powerpoint_ppt_presentation.

If you want to gain a broader insight into drug development, this free online course is a wonderful resource:

https://www.coursera.org/course/drugdiscovery.

It covers the whole process from the bench to the patient. It will give you a basic understanding of research approaches and regulatory requirements.

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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Gained in Translation

Science at the multilingual crossroads

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Medical translation: Pondering equivalence at word level

The concept of equivalence in translation has long been hotly debated. Thus, it has been argued that 'equivalent' means 'virtually the same thing' and that equivalence in translation is therefore an 'illusion'.[1] Alternatively, equivalence has been described as being 'the conceptual basis of translation'[2] or as something 'artificial, fictive, something that has to be produced on the level of translation itself'.[3]

Every source-text author is deeply rooted in his or her cultural and linguistic environment with its rules of usage, readership expectations, and aesthetic and formal determinants. At least equally important, every author is shaped by his or her world knowledge, outlook on life, experiences, and attitudes. The same is true for the translator. Every translation assignment, therefore, brings together a unique pair of distinct personalities pursuing a specific purpose in their respective environments – resulting in myriad possible ways of achieving 'equivalence' in translation. This makes equivalence a rather elusive phenomenon. Yet, as Mona Baker put it, we have used it 'for the sake of convenience – because most translators are used to it rather than because it has any theoretical status'.[4]

In her textbook on translation, *In Other Words*,[4] Baker explores equivalence in translation at several levels, differentiating between equivalence at word level, grammatical equivalence, textual equivalence, and pragmatic equivalence.

Equivalence at word level may seem to be the easiest to produce. However, true equivalence – or invariance – is rare even at this most fundamental level.

Standardised speech

Invariance is often achievable in areas where standardised nomenclatures are available. The purpose of such classifications, such as the *Terminologia Anatomica*,[5] the international standard of anatomical terminology, is to increase the precision of medical language and facilitate communication.

The need for the harmonisation of anatomical terms became prominent in the late nineteenth century, at a time when one and the same anatomical structure was referred to by different names, depending on vernacular and medical traditions. The *Terminologia Anatomica*, the first edition of which was published in 1998, contains about 8000 anatomic terms composed of about 600 basic terms – 400 of Latin and 200 of Greek origin. Regardless of their origin, the terms are treated as if they were Latin words. Translations into other languages are therefore not necessary – ensuring invariance.

Some standardised terminologies, however, are themselves translations from one source-language version into several target languages, such as the International Classification of Diseases (ICD) or the Medical Dictionary for Regulatory Affairs (MedDRA). ICD-10 is available in 6 official and 36 other languages.[6] MedDRA has also become available in a number of translations of the original English version, including French, German, Hungarian, Italian, and Spanish.[7]

Translation always carries the risk of introducing non-equivalence. Indeed, looking at the German translation of MedDRA, the medically adept translator will notice a number of rather unusual renderings.

For example, the MedDRA system organ class (SOC)[8] '025 – Pregnancy, puerperium and perinatal conditions' is translated into German as *Schwangerschaft, Wochenbett und perinatale Erkrankungen*, making it sound as if 'pregnancy' and the 'puerperium' were themselves medical disorders. This is because 'pregnancy' and 'puerperium' in the English original are used as adjectives, whereas the German translators treated them as nouns. Also, translating 'puerperium' as *Wochenbett* ('childbed') introduces an unnecessary change in register.

The SOC '026 – Reproductive system and breast disorders' is translated into German as *Erkrankungen der Geschlechtsorgane und der Brustdrüse*. Here, 'reproductive system' is translated using the subordinate term *Geschlechtsorgane* (genitals), although truly equivalent German terms are available, i.e. *Fortpflanzungssystem* or *Reproduktionssystem*, which, unlike *Geschlechtsorgane*, do not only cover the anatomic but also the functional aspect of this SOC. 'Breast' is likewise translated using a

Table 1:   Selected MedDRA preferred terms (PTs) and their official versus suggested German translations

MedDRA PTs English source	Official German translation	Comment	Suggested German translation
Swelling face	*Schwellendes Gesicht*	*Schwellendes Gesicht* is unidiomatic and sounds as if the face were in the process of swelling; not a standard medical term.	*Gesichtsschwellung*
Feeling abnormal	*Gefühl anomal*	*Gefühl anomal* is an unidiomatic phrase that does not exist as a medical term.	*Fehlempfinden Gefühlsstörung*
Gravitational oedema	*Ödem der Gravitation folgend*	The German *Ödem der Gravitation folgend* sounds as unusual as would the English phrase 'oedema following the gravitation'. This translation is all the more disconcerting as a perfectly adequate German term is available.	*Gravitationsödem*
White blood cell count decreased	*Leukozytenzahl erniedrigt*	This is an inadequate collocation, with the primary meaning of the German *erniedrigt* being 'debased' or 'humiliated'. The proper adjective to use in this collocation is *vermindert*.	*Verminderte Leukozytenzahl*

subordinate term, namely *Brustdrüse* (mammary gland), leaving the breast's stromal components unaccounted for.

Looking at some of MedDRA's preferred terms (PTs), 'hypersensitivity reaction' in the German MedDRA translation becomes *Übersensibilitätsreaktion*. *Sensibel* in German is generally used in psychological contexts to describe a person who is empathetic and perceptive, and the German *hypersensibel* describes persons who are thin-skinned, vulnerable, or easily hurt. *Sensibel* does not generally refer to being 'abnormally susceptible physiologically to a specific agent (as a drug or antigen)',[9] as implied by 'hypersensitivity reaction', which should have been translated into German as *Überempfindlichkeitsreaktion*. Additional examples are provided in Table 1.

Fortunately, each MedDRA term is assigned a unique non-expressive code. Therefore, even if a particular translation is in fact non-equivalent with its original, the code will allow disorders, diseases, or conditions to be unequivocally matched and coded across languages. For language purists, however, the bad news is that such non-equivalent translations as are part of MedDRA are increasingly finding their way into medical texts translated into German, most importantly into summaries of product characteristics (SPCs), which use the MedDRA terminology.

General speech

If equivalence is difficult to obtain in standardised technical language, it is even harder to produce in non-standardised general speech. Languages, rather than capturing the outside world in an objective manner, emphasise certain aspects that appear to be particularly relevant to the people who speak them. What follows are some situations in which producing equivalence at word level may be a challenge and selected strategies to resolve them, as initially outlined by Baker.[4]

Culture-specific words

One group of concepts that can be difficult to translate are those that are culture-specific. A text that provides a plethora of examples in this respect is 'Alice's Adventures in Wonderland.' For example, in Chapter 1, Alice, while falling down the rabbit hole, asks herself:

'I wonder how many miles I've fallen by this time?' she said aloud. 'I must be getting somewhere near the centre of the earth. Let me see: that would be four thousand miles down, I think —'

The translation by Franz Magnus Enzensberger, one of the most popular translations of 'Alice's Adventures in Wonderland' into German, uses a cultural substitution for the second occurrence of 'miles' and converts the actual distance into kilometres:

'Wie viele Meilen ich wohl schon gefallen bin?' sagte sie laut. 'Weit kann es nicht mehr sein bis zum Erdmittelpunkt. Das wären dann, ja: sechstausend Kilometer wären das, ungefähr wenigstens —'

Thus, one way of producing equivalence is to bring a text closer to the reader by using a cultural substitution. The substitution may not have the same meaning, but it should have the same effect in the target culture or convey a similar image in the reader's mind.

The terminology of political, legal, administrative, health care, or educational systems is also replete with culture-specific terms. For example, the German or Austrian *Assistenzarzt*, literally an 'assistant physician', could also be translated using a cultural substitution, e.g. 'resident' for an American audience, 'specialty registrar' for a UK readership, or 'senior house officer' in many Commonwealth countries. In certain contexts, however, using *Assistenzarzt* as a loanword in translation and describing *Assistenzarzt* as a person with a medical degree receiving in-depth training in a medical

speciality and practicing medicine under the supervision of a licensed physician may be more appropriate.

Even the term 'summary of product characteristics' (SPC, SmPC) – a ubiquitous term in the medical writer's world – may pose a challenge in translation. It may be translated into German either literally as *Zusammenfassung der Produktmerkmale* or by another term used in both the German and Austrian Medicines Acts, i.e. *Fachinformation*. With both terms referring to the same document, which is more appropriate? Again, this depends on the context. Thus, whereas *Zusammenfassung der Produktmerkmale* is generally used in the context of applications for marketing authorisation, *Fachinformation* generally refers to already marketed medicinal products.

This distinction is supported by the translation of the German Medicines Act (Arzneimittelgesetz, AMG) into English provided by the Language Service of the German Ministry of Health.[10] It translates the German *Fachinformation* into English using the loan translation 'expert information', and reserves 'summary of product characteristics' to instances where the AMG specifically refers to *Zusammenfassung der Produktmerkmale*, i.e. only in the context of dossiers submitted to obtain marketing authorisation.

Differences in expressive meaning

Many verbs do not only have a propositional meaning, they also have an expressive meaning, and this should be matched in the target language. This is often difficult – as in the following example:

> *Of 991 families interviewed, in 88 percent of them a parent acknowledged <u>shouting, screaming or yelling</u> at the kids at least once […] in the previous year.*[11]

> *Von den 991 befragten Familien gab in 88 Prozent ein Elternteil zu, die Kinder zumindest ein Mal […] im vergangenen Jahr <u>angeschrieen oder angebrüllt</u> zu haben.*

The original English text uses three expressive words, each eliciting distinct nuances of meaning. Thus, 'shout' refers to a sudden loud cry, 'scream' implies a sharp loud cry, and 'yell' refers to a loud piercing sound. Finding three German words with an equivalent expressive meaning is difficult – particularly the piercing, high-pitched aspect appears to be missing from the German vocabulary available to describe such situations. Therefore, rather than adding a third verb that would sound unusual in this context, 'does not move the text forward or may merely distract the reader from what's really important',[4] it may be more appropriate to translate by omission without loss of meaning.

Differences in form

Some word forms in the source language have no direct equivalent in the target language. For example, one characteristic of the English language is that it tends to turn nouns into verbs, such as 'to email', 'to mastermind', 'to text-message', or – 'to verb'. This often does not work in other languages and may call for a paraphrase, such as *eine SMS-Nachricht senden* for 'to text-message' or *ein Verb bilden* for 'to verb'.

Also, the English language makes ample use of suffixes that carry part of the word's meaning, such as in the pairs 'payer/payee' or 'trainer/trainee'. The ending '-ee' derives from the French passive participle and refers to 'a person who is/has been (verb)-ed'. In banking, for example, a 'payee' is someone to whom money is paid. Other languages, such as German, may have less efficient tools of word formation at their disposal and will have to explain or paraphrase the source-language word. Thus, 'payee' becomes *Zahlungsempfänger* ('payment recipient') and 'payer' may be rendered as *Zahlungspflichtige(r)* ('individual liable to pay') or *Auftraggeber(in)* ('individual commissioning a payment'). Note that, unlike English, German differentiates between male and female payers by using a suffix.

By contrast, 'trainer/trainee' have entered the German language as loanwords. Whereas the German *Trainer(in)* has long been used to refer to sports coaches, *Trainer(in)* in the sense of 'course instructor' is a fairly new meaning of the word. The English loanword *Trainee* has entered German 'corporatese' only recently and with a slight change in meaning. Thus, whereas the English 'trainee' refers to anyone being trained for a job – which in German has been referred to as *Praktikant* –, *Trainee* in German refers to university graduates hired by international corporations with a view to advancing into a managerial position. Such pseudo-loanwords – words that are borrowed from another language but having acquired a different meaning in the borrowing language – call for particular caution during translation because they may easily be overlooked as requiring translation. Other examples of English pseudo-loanwords in German are *Handy* ('mobile phone' or 'cell phone'), *Smoking* ('dinner jacket' or 'tuxedo'), or *Messie* ('compulsive hoarder').

Another instrument of word formation in the English language is the morpheme '–ese' describing a type of language that is difficult for non-experts to

understand or typical of a particular profession and has a slight pejorative touch, such as in 'journalese', 'medicalese', 'legalese', or 'technicalese'. In German, this highly expressive morpheme again has to be rendered using an explanation or a paraphrase. Whereas 'journalese' could be rendered as something like *Journalistensprech*, 'medicalese', 'legalese', or 'technicalese' could all be translated as *Fachchinesisch* ('technical chinese').

Neologisms

Particularly in rapidly advancing areas such as science and technology, new word creations, or neologisms, are a common phenomenon. Once coined in one language, however, it may take some time until they have been lexicalised in other languages. Several strategies are available to transfer such neologisms into other languages, such as using a more general word, a paraphrase, a descriptive translation, a loanword, or a loan translation (calque).

Some 100 years ago, one such neologism was the German term *Dämmerschlaf* – a type of light general anaesthesia obtained by the subcutaneous administration of a combination of scopolamine and morphine introduced at the end of the nineteenth century and later refined and widely introduced into surgical medicine.

This neologism came to be translated into English as 'twighlight sleep' – a calque which adequately captures not only the effect these drugs have on the patient, but also the expressiveness and vagueness of the original German term. The internationally renowned gynaecologist HJ Boldt, professor emeritus at the Post-Graduate Medical School of Columbia University and honorary member of the *Deutsche Gesellschaft für Gynäkologie und Geburtshilfe*,[12] held a different opinion. In 1915, he wrote a letter to the editor of *The New York Times* about the inaccuracy of the term, which he identified as an 'improper loan translation from the German *Dämmerschlaf*' that he suggested be translated as 'semi-narcosis' or 'semi-narcosis with hydrochloride of scopolamin and morphin' (see Box 1).[13]

Despite Boldt's suggestion that *Dämmerschlaf* be translated into English using a descriptive, and certainly less expressive, term that belongs to a different register than the loan translation, the expressions are still around in both languages – as colloquial umbrella terms covering a wide range of different types of analgosedation brought about by a variety of agents other than scopolamine. Although Boldt's criticism remained unheard at the time, the fact that he stood up to raise awareness of the importance of the meaning of words is to be cherished.

Box 1: Twilight sleep

> **"TWILIGHT SLEEP."**
> An Inaccurate Translation of the German Daemmerschlaf.
>
> *To the Editor of The New York Times:*
> Much has been written about "Twilight Sleep," for the production of painless childbirth, both in the lay and in the medical press. I want to protest against this term, since it is a misnomer. There are a number of idioms in any language which cannot be directly translated into another language without changing their meaning. While in the German tongue "Twilight Sleep" may be accepted as a term to be used for the semi-narcosis in use by the administration of scopolamin and morphin, yet to translate the word "Dämmerschlaf" into "Twilight Sleep" is likely to cause more harm than good.
> As an illustration, permit me to cite the word "Kriegsherr," which in the direct translation would mean "War-Lord." As a matter of fact, however, the idiom should be translated in its actual meaning—"Commander in Chief." Therefore, it would seem to the best interests of all hereafter, when it is desired to use the word "Dämmerschlaf," to make use of the exact meaning of the word and not translate the idiom by the actual word, but use the word "semi-narcosis," and for a fuller description of the semi-narcosis — as to how it is brought about—it ought to be "semi-narcosis with hydrochloride of scopolamin and morphin."
> I may add, for the information of those who may have been under the impression that the scopolamin-morphin narcosis is something new, that this is a misconception, as it has been used in service in Germany, where it was first made use of and published for the benefit of mankind, for more than ten years, and I personally know of one surgeon who has used it for that period of time in this city. But to say that scopolamin-morphin narcosis can be used indiscriminately, or left to one whose judgment is not to be absolutely relied upon, would be a serious mistake. It requires great discrimination and good judgment to benefit thereby. H. J. BOLDT.
> New York, Feb. 5, 1915.

An example of a modern-day calque that has really gone awry is the German translation of a term that was newly coined in the 1990s[14,15] – evidence-based medicine. The most common, yet seriously misleading, rendering of 'evidence-based medicine' in German is *Evidenz-basierte Medizin* – a fine example of a false friend. The mistranslation derives from the misperception that 'evidence' and *Evidenz* mean the same thing – when in fact they have opposing meanings. Thus, whereas the English 'evidence' in a scientific context refers to something we rely on whenever access to the truth would otherwise be difficult,[16] the German word *Evidenz* refers to absolute certainty based on irrefutable facts – to something whose truth can be

'grasped in an utterly direct, unmediated way'.[16] In fact, in the presence of *Evidenz*, little or no 'evidence' is needed.

Several German-speaking authors have rightly criticised the unfortunate rendering of 'evidence-based medicine' in German[17–20] and have instead proposed *auf wissenschaftlichen Erkenntnissen begründete Medizin*, *nachweisorientierte Medizin*, or *nachweisgestützte Medizin* – all paraphrases of the English original that elegantly and, perhaps more important, correctly characterise the concept of evidence-based medicine. Whatever the strategy to overcome this instance of non-equivalence, a loan translation into German will not work here (see Box 2).

Box 2: Evidence-based medicine: False friends do not make good company

Modern methodologies to establish evidence in biomedical research were pioneered by the Canadian research group around Gordon Guyatt and David Sackett. In 1992, the term 'evidence-based medicine' was first used in the medical literature by Guyatt *et al.*,[15] and in 1996, Sackett *et al.*[14] explained what they thought evidence-based was and what it was not. The most common, yet seriously misleading, rendering of 'evidence-based medicine' in German is *Evidenz-basierte Medizin* – a classic example of a false friend.

An important distinction in the philosophy of science is that between proof and evidence. Proof is the availability of an argument in support of the truth of a proposition. Certain areas of research are capable of providing such irrefutable proof. For example, the Greek philosopher–mathematicians were able to provide proof for the truth of many of their theorems, particularly in algebra and geometry.

In other areas of human enquiry, such as in biomedical research, there is less certainty. This is where evidence comes in. We generally rely on evidence whenever access to the truth would otherwise be problematic.[16] Evidence may be described as allowing one's views 'about what is the case or what ought to be done to be guided by evidence, as opposed to (say) the typically distorting influences of ideological dogma'.[16] As (groups of) individuals collect evidence (i.e. the results of their observations), their views will 'increasingly converge over time: as shared evidence accumulates, consensus tends to emerge with respect to formerly disputed questions'.[16]

Evidence had formerly been taken to precede theory. For example, for Hume science relied on observations and inductive ('bottom-up') reasoning. This view is now generally rejected, because it is appreciated that theories – or plausible hypotheses – play an essential role in determining what type of evidence should be collected. This view is exemplified in Popper's falsification model of science (although other models of science, in addition to disconfirming evidence, also allow for confirming evidence). In Popper's model, science is a deductive ('top-down') process. Scientists formulate hypotheses that cannot be verified and confirmed, but they can be falsified and rejected – or tentatively accepted if corroborated in the absence of falsification.

To make his point, Popper used Hume's example whereby all swans are white simply because all of the swans we have seen so far are white. There is no proof, however, that all swans are white. We can merely hypothesise that they are – and a single black swan would be enough to refute this hypothesis. In other words, if our null hypothesis is that all swans are white and we cannot reject the null hypothesis, this does not necessarily mean that the null hypothesis is true – we simply do not have enough evidence to reject it.

The basic principle of evidence-based medicine is that treatment be based on 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients'.[14] This evidence is provisional only. The more evidence we gather in support of a given practice, the more confidence we can have that this practice actually makes sense – but we cannot prove that it does.

The German *Evidenz* has a fundamentally different meaning. It signifies *unmittelbare und vollständige Einsichtigkeit* ('immediate and complete insight'), *Gewissheit* ('certainty'), *unumstößliche Tatsache* ('irrefutable fact'),[21] *das dem Augenschein nach unbezweifelbar Erkennbare* ('that which is undoubtedly discernible based on what we see and perceive').[22] Several German-speaking authors have rightly criticised the unfortunate rendition in German for the reasons outlined above[17–20] and have

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proposed that 'evidence-based medicine' be referred to as *auf wissenschaftlichen Erkenntnissen begründete Medizin, auf empirisch erbrachten Nachweisen basierende Medizin, nach-weisorientierte Medizin*, or *nachweisgestützte Medizin* – all elegant paraphrases of the English original. In fact, in the presence of *Evidenz*, little or no 'evidence' is needed.

In 2000, the German term *evidenzbasiert* even found its way into German legislation,[23] and the centre branches of the Cochrane Collaboration in German-speaking countries likewise use the translation which actually misrepresents the very mission of The Cochrance Collaboration, which is to 'promote evidence-informed health decision-making by producing […] synthesised research evidence'.[24]

Could the cause against diluting the meaning of *Evidenz* have been lost already? If we agree with Werner Koller, as quoted by Anthony Pym,[3] that 'translators are ultimately the people who say what should or should not be proposed to the receiver as an equivalent', let us take to heart Hans-Martin Gauger's plea in *Forum Sprachkritik* of the *Deutsche Akademie für Sprache und Dichtung*: '*Trennen also, bitte, zwischen* Evidenz *einerseits und* Beweis *andererseits. Oder retten wir unsere, sagen wir, kontinentale* Evidenz. *Sie ist ein semantischer Reichtum*'.[17]

Summary

This article provides some examples of situations in which producing equivalence in translation may be a challenge, e.g. when faced with culture-specific words, differences in expressive meaning between languages, differences in form, or words not (yet) lexicalised in the target language.

Some of the strategies of overcoming non-equivalence – or producing what the translator considers equivalence – include using a cultural substitution, a loanword, a loan translation, a less expressive word, a paraphrase, or an explanation. The translator may even choose to omit an aspect of meaning which, if transposed into the target language, would merely distract the reader from the key message.

In some situations, then, equivalence in translation may be easily achieved. In others, the translator will have to make a choice as to which aspects of meaning to convey in translation to offer to the target-language reader a text which the translator thinks represents the most effective trade-off between readability and precision.

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Medical Writing Jumble # 10

1. Re-arrange the jumbled letters to get a meaningful word related to medical writing.
2. Next, take the circled letters from each word and make two new words that will answer the riddle in the cartoon. Hint: The answer is probably a pun.
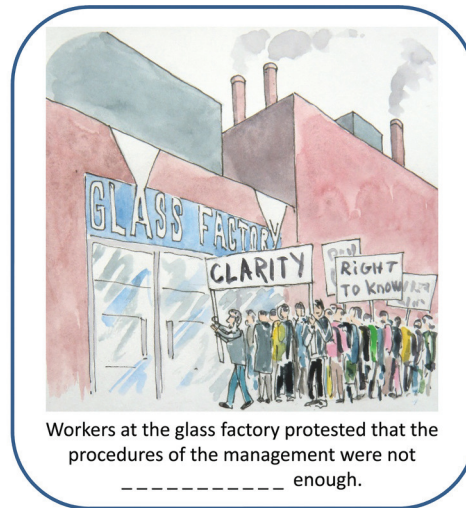3. Use British English.

by Anuradha Alahari

Illustration: Anders Holmqvist

TRIPN

NATIR

FAYEST

UORNEN

Workers at the glass factory protested that the procedures of the management were not _____ enough.

Answer:

See page 170 for the answers.

Out On Our Own

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Editorial

Our gathering in Budapest last month was, as always, fun and this time a little different. We welcomed you to a new-look Freelance Business Forum (FBF) after polling you in February on what you hoped to gain from FBF attendance and your preferred meeting environment. Refreshments fuelled an informal atmosphere and, with experienced freelance colleagues in circulation, we were able to inject some dynamism and creativity into our discussions on common issues that affect us all. Between us, we conjured the FBF that you wanted. How do we know that? You told us so in a straw poll at the end of the meeting. We will try this format again, so next time, be sure to come along and join us at the Florence FBF in November 2014.

In this June issue of Out On Our Own (OOOO), we continue Alistair Reeves' and Susanne Geercken's English language resources series. This time the duo explore printed and Internet punctuation resources and, more generally, Internet language resources.

PCG, 'the voice of the freelancer' in the UK continues to inform us on a practical level, this time with tax-related issues, in the second article in the series. Michelle Storm Lane keeps us on the right side of the taxation tracks.

Alysia Battersby, a relative newcomer to freelancing, takes a light-hearted look at combating loneliness when working from home. Kathryn stands in for Raquel as Tool Box guru in her review of online document storage facilities, while Anne McDonough provides a touch of humour in 'Freelance Foraging'.

We hope you enjoy this issue's varied content; do keep your ideas and articles flowing in!

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A writer's 'best friends' – recommended language resources for (medical) writers (2)

Susanne's part of this article in this series is dedicated to punctuation:

Experience has told me that for many native and non-native speakers of English – and medical writers are no exception – punctuation feels like a tedious and confusing business. At least this was how I felt before I attended my very first EMWA workshop many years ago, which happened to be 'Punctuation' by Alistair Reeves. Does not this tell us something about the sustainability of EMWA workshops? For those of you who do not have the time or opportunity to attend a punctuation class, let me recommend some 'good friends' again.

Eats, Shoots & Leaves

Yes, this IS a book on punctuation,[1] despite the somewhat quizzical title (for an explanation, see: http://en.wikipedia.org/wiki/Eats,_Shoots_%26_Leaves). As you might guess, this book by Lynne Truss is not an ordinary language resource. Ever since it was published in 2003, it has met with quite some public attention in the English-speaking world and has sparked discussion unusual for a book on the rather mundane subject of punctuation.[2] So what is so special about it? Her book gets you thinking about punctuation, your own attitude towards it, and the wonders and beauty of (the English) language. Lynne Truss takes a journalistic approach to punctuation. I particularly recommend the book to those of you who rather try to avoid dry language textbooks and stern grammar talk. Lynne Truss talks about the impact of (modern) life on punctuation and about the impact of punctuation on life: apart from an overwhelming array of everyday-life poor punctuation examples, she gives several intriguing historical stories on the impact (poor) punctuation can have on politics. She even reports about a comma that became a matter of life and death. I should not withhold the fact that, interspersed

among the anecdotal information, the book does feature punctuation rules, but dished up in a form that I think even those allergic to grammar will survive. Last but not least, I recommend this book because Lynne Truss, like many of us language lovers, has a passion for punctuation and good grammar, and I find her enthusiasm contagious.

The Penguin Guide to Punctuation

For those of you who want no journalistic fuss, I recommend this book[3] as a down-to-earth alternative to Lynne Truss. I appreciate The *Penguin Guide to Punctuation* because it provides clear and practical guidance on each of the punctuation marks, focussing on the basic rules, and avoiding too much detail. The book even includes a brief section on abbreviations and on the most important rules for capitalisation. I particularly appreciate the fact that R. L. Trusk – who grew up in the United States and later studied and taught linguistics in England – refrains from taking sides when explaining the difference between British and US punctuation usage. The *Penguin Guide to Punctuation* is best suited for writers looking for an introduction to English punctuation.

Chicago Manual of Style

When I look for help with more sophisticated punctuation problems, I like to turn to The *Chicago Manual of Style*,[4] a reference work that many of you (at least those who work with American English) may know of or have heard about. Among many other details on style, the book contains valuable guidance on trickier aspects of punctuation like the use of the comma with adverbial clauses and phrases, or the correct usage of different types of brackets and dashes in complex sentences. You will find a section on 'hyphenated compounds' and detailed advice on hyphenation with pre- and suffixes. My own volume is bookmarked in the sections on bulleted lists (capitalisation, punctuation within enumerations), quotations, and on the correct abbreviation of names, titles, and academic degrees. While the recommendations to be found in The *Chicago Manual of Style* should not and cannot be regarded as universal truth, I have often been glad to obtain guidance on controversial issues of style and punctuation in this widely recognised work.

AMA Manual of Style

The same is true for the *AMA* (American Medical Association) *Manual of Style*.[5] Medical writers will find an abundance of guidance on issues of style and punctuation relevant to our field: punctuation and capitalisation of the different table headings (column headings, row headings); hyphenation and capitalisation of words preceded by numerals, Greek letters or per cent signs; recommendations on the spelling of eponyms (e.g. whether 'Graves disease' should be spelt with or without the apostrophe), the correct spelling of expressions like '2.5-fold' and suggestions for punctuation in enumerations and bulleted lists.

While both the *Chicago Manual of Style* and the *AMA Manual of Style* are relatively expensive (around 30–35 Euros) to buy new, both volumes can be easily obtained second hand at a lower price.

Let me close by reminding you that The *Write Stuff* (*TWS*)/*Medical Writing* itself has published a number of contributions on punctuation in previous issues, notably Stephen de Looze's wonderfully creative, entertaining, clever, and educating article about the slash[6] and Alistair's numerous comments on controversial aspects of punctuation in the 'Myths about English' series (This series exploding 50 myths about English ran in The *Write Stuff* (*TWS*) from Vol. 15(1) in 2006 to 17(1) in 2008 and was followed up by three further articles that can all be found in the *TWS* and *MEW* Archive on the website.), and the 'comma issue' (Vol. 16(2) of *TWS* in 2007 was devoted to the use of the comma) of *TWS*.

In the last issue, Alistair restricted himself to paper resources. He has three Internet resources to recommend this time:

Once, in the days before the Internet, deciding whether to write 'pleural *space*' or 'pleural *cavity*' (as I had to recently), or making similar choices between terms, meant much laborious research in journals, dictionaries, textbooks, and glossaries. Of course, you could always ask a few experts, but in many cases this had unsatisfactory results because of personal, regional, and even institutional preferences. I was once emphatically told by a consultant in a London teaching hospital (X) that the correct term to use for 'congestive heart failure' was 'a low-output state' because 'it is much more precise'. A few months later, I was editing an article on congestive heart failure for a fellow opinion-leader (Y) and suggested that we use 'low-output state' because X had said that this was a more precise term. 'Oh! You don't want to listen to what X says', said Y, 'He has all sorts of funny ideas'.

Writers, editors, and translators often kept card index collections that gradually grew as 'correct' or 'most appropriate terms' were found or decided upon, and they transferred these into electronic databases as soon as the Internet became available.

Many of these collections have been turned into useful – and sometimes very large – searchable glossaries dealing with specialist areas of science and medicine for which there were no other resources.

Let me start with *Springer Exemplar*.

A frequent approach to finding the right terminology nowadays is to use search engines – primarily, of course, Google – to search for terms and compare how many hits there are for similar terms. One of the problems with this is that the whole of the search engine is searched, including every URL and document that happens to contain the string being searched regardless of its source – and most websites have never seen anything like quality control (QC), so many are teeming with automatic translations, inconsistencies, and errors. Searches can be refined in certain ways, e.g. putting a minus sign before words that you _do not_ want to search. Or, for English terminology, you can search only pages from the USA, UK, Ireland and Australia, and other English-speaking areas. But whatever you do, in Google at least, searching for 'time-table' also returns hits for 'timetable' and 'time table'. So this sort of search is not suitable for deciding whether a term should be written as one word, with a hyphen, or without a hyphen. And decisions should be based on the number of hits only if there is a really clear difference – often you have to decide between a 60–40 or a 70–30 split, for example, which with small numbers is not wide enough to decide that you have found the right term. Also, a comma separating two words is disregarded, which means that the number of hits includes those where the words in your term happen to follow each other separated by a comma.

A more reliable database to search in is the Exemplar archive set up by Springer Science & Business Media and the Center for Biomedical and Health Linguistics called Springer Exemplar (http://www.springer-exemplar.com). Exemplar searches over 1900 journals and close to 4000 books from Springer's collection to find published examples of how a word or phrase is used in the following areas: life sciences, medicine, engineering, mathematics, computer science, business, and law. It is continuously updated with new content.

They offer what they call a 'snippet search' which enables you to enter a string and see how many hits are returned. It still does not differentiate between 'time-table' and 'time table', for example, and also ignores commas, but is much better than Google for several reasons:

- Every hit is returned in context with the number of hits. You can click on any of the

hits to see the source it was retrieved from. This also brings up the option to obtain the entire content at a price or download it if you already have an account with Springer.
- You search only in the subject areas given above – mainly life sciences and medicine.
- Many of the documents are peer-reviewed, properly edited, and undergo QC, so the content you are searching in is much more reliable than that of general search engines.

The results for the pleural *cavity* or *space* search were 1943 hits for pleural cavity and 1702 for pleural space, so the outcome was pretty clear: I decided the terms are interchangeable and chose cavity to be consistent with other terminology used in my text.

The site also includes other information primarily of interest to writers and linguists – for example, the year the term was first found is also displayed, and a breakdown of the subject areas is also given, which is useful when deciding whether accepted terms or fixed phrases (which are actually medical and scientific collocations) are more frequently used in one speciality than another.

Exemplar is on offer as a free beta version at present, so I am encouraging as many people as possible to use it as frequently as possible so that it is not discontinued because of underuse. Let us also hope that it remains a free service. Anyone who worked as a writer or editor before the days of the Internet will realise what a fantastic resource this is.

Dictionaries and glossaries

As so often with the Internet, I recently came across the patient.co.uk site by accident while clicking around, as usual looking for a particular term. What caught my attention was that they have a section called dictionaries and glossaries under http://www.patient.co.uk/directory/dictionaries-and-glossaries which, it says 'provides links to websites explaining medical terms, phrases and words'. No editor can resist the temptation to follow such links.

From its name, the aim of the site is obviously to provide information for patients, but it gives access to a large number of dictionaries (also in the USA) and glossaries which will certainly be of use to anyone working in the medical writing and communications business. The link above takes you to the dictionaries and glossaries landing page, and as an example, clicking on MediLexicon Medical Dictionaries takes you to the http://www.medilexicon.com site, where, amongst other things, you

find a dictionary of medical abbreviations, a medical dictionary based on Stedman's, and an enormous dictionary of medical equipment and surgical instruments which must cover every possible medical device, with an explanation of each.

The dictionaries and glossaries site also offers access to the Glossary of Health, Social Care and Information Technology compiled by the NHS Care Records Service, which in turn provides links to webpages and factsheets for keywords and will do a direct Google Search for each keyword.

I am still exploring what this site has to offer – so all I can say is visit it for yourself and see where it takes you!

In the next quiet moment you have, search Google for 'Dictionaries Glossaries Medical Scientific' and be amazed at what is retrieved: a vast amount of helpful resources awaiting discovery.

Oxford Dictionaries website

Apart from providing information on all the dictionaries and reference works that the Oxford University Press has to offer and a wealth of information and curios about the English language, the Oxford Dictionaries website has a whole area with writing advice under http://www.oxforddictionaries.com/words/better-writing, covering grammar, spelling, punctuation, writing help, abbreviations, and much more. The explanations are simple and 'matter-of-fact' with plenty of good examples. The layout is such that you can either read through it

systematically like a book, search for specific items, or ask questions, either serious or fun ones, such as 'Apart from "angry" and "hungry", what other common English word ends in "gry"?' (you will have to go to the website to find the answer). Click to the 'Spelling' and 'Usage' sections for explanations and help with lists of 'grey areas' or common errors and questions, such as 'words ending in –ance and –ence', 'words ending in –able and –ible', 'shall or will', 'he or she versus they', 'double negatives', and 'may or might'.

Readers are encouraged to let us know about their favourite language resources for future issues.

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Getting savvy with tax: Five questions to ask yourself

You may be familiar with the words that Benjamin Franklin wrote in 1789: 'In this world nothing can be said to be certain, except death and taxes'.

One could say that human discovery has made greater progress in delaying the former than solving the latter – 225 years on we are still certain to receive the dreaded tax bill!

However, what is less certain is, 'just how much tax must we pay?'.

Large companies have whole departments geared up to answer this question. Freelancers do not have that luxury, which means that it can become a tedious and confusing chore. The confusion is compounded by the fact that freelancers sit in a rather nebulous gap, neither employer nor employee, which can make tax planning all the more complex.

Nevertheless, it is critical to get it right. There have been cases of freelancers finding that they owed hundreds of thousands in retrospective tax,

interest and penalties, because they did not understand how the rules applied to them.

Conversely, when you hit upon legal and ethical ways to save a lot of money, tax suddenly becomes a great deal more interesting!

Here are five questions to help you reflect on your current tax situation:

1. Am I clear about my employment status?

Across EU member states the law is set up to police the border between employment and self-employment. The authorities seek to identify cases of 'sham self-employment', where someone who claims to be freelance works in such a way that they might as well be their client's employee.

These laws exist for two reasons. The first is to protect workers from being forced into self-

employment and losing their employment rights against their wishes. The second is to protect governments from reduced tax revenues; the tax for employees can be higher than for the self-employed and in some isolated cases people have gone into 'sham self-employment' purely as a tax-avoidance measure. The unfortunate consequence is that freelancers who are legitimately running their own businesses can still be treated with suspicion by the authorities.

All EU member states have legal tests to establish a worker's employment status. This decides whether you should be treated as employed or self-employed for tax purposes.

In the UK, for example, the tests focus on three areas:

- *Direction and control*: does your client supervise you in the way a boss would?
- *Personal service*: are you obliged to do the work yourself at all times, rather than appointing a substitute if you so wish?
- *Mutuality of obligation*: is the client obliged to keep offering you work and are you obliged to accept it?

If the answer to these is 'yes', then you could be 'deemed employed', which means that the UK tax authorities would seek to recover additional tax and national insurance. Who they choose to recover the tax from depends on your chosen business structure. If you are a sole trader, your client would be liable whereas if you invoice via your own limited company, your company would be liable under the terms of Britain's IR35 legislation (for details please see http://www.pcg.org.uk/IR35).

Most EU states use various ways to establish the degree of 'subordination', in other words, the ability of an employer to 'control' an employee. Other rules vary from state to state. For example, in Spain, freelancers who invoice more than 75% of their income to one client are required to draw up a contract with the client specifying that they are 'financially dependent' on that client.

It is therefore very important to understand the rules in the country (or countries) where you operate, so as not to land yourself, or your client, in an expensive mess!

2. Am I using the most effective legal form?

Most countries offer the choice between operating as a self-employed person (also known as a sole trader or autonomous worker), or incorporating as a

company. Other forms, such as partnerships, could also be appropriate.

The pros and cons of each choice vary from country to country. In the UK, for example, setting up a limited company can be a commercially sound, tax efficient decision, as long as you are not liable under IR35. A company is very quick to set up and there is no minimum capital requirement.

In Germany, on the other hand, it would not make sense for a freelance medical writer to form a capital company, such as a GmbH or UG. As a medical writer with an academic background it is usually possible to be accepted by the German fiscal authorities as a 'liberal professional'. Liberal professions or 'freie Berufe' do not pay trade tax and avoid a great deal of bureaucracy. As a liberal professional you can still achieve the 'limited liability' advantage of a limited company by taking out liability insurance and having the appropriate contractual provisions.

3. Which taxes am I liable for?

The basic principles apply across Europe. As a business you pay tax on your profits (total turnover minus allowable expenses). This can either be as an individual, a company, or a mixture of both, depending on your chosen legal form.

Some countries have additional levies. Germany, for example, has a particularly complicated tax system. Businesses that are not accepted as liberal professions have to pay trade tax, a communal tax that varies from town to town. A sole proprietor in Munich would pay 3.85% on all 'trade income' above 25 500 euros, along with the normal income tax.

On top of this there is the solidarity surcharge applicable since German unification, which is 5.5% of the income tax. Church members pay another surcharge of 8% or 9%, depending on the federal state they live in. German business owners have to pay a TV and radio levy, once as an individual, and once for each company they own. Every business owner who places orders with journalists or artists (including web designers) has to pay a levy of 5% on top of the payment made directly to the journalist or artist.

Most German businesses are also required to charge their clients 'Umsatzsteuer', or value added tax (VAT), which is passed on to the government. This is normally 19%, although writers can usually charge a reduced rate of 7%. This only makes your services more expensive to customers who cannot redeem the VAT paid. You can also redeem the VAT that you pay on services that you use.

In the UK, you are not obliged to charge VAT until your turnover crosses £79 000 (UK VAT registration threshold for tax year 2013–2014) in any 12-month period, although you can register voluntarily before that. If your turnover is less than £150 000 you can also join the Flat Rate Scheme, designed to simplify VAT accounting for small businesses. Many freelancers find this works in their favour.

4. How should I handle social security?

Across the EU, social security payments, or national insurance contributions as they are known in the UK, are used to build up your entitlement to key state benefits such as a pension and healthcare.

How much you pay depends on whether you are self-employed (a sole trader or autonomous worker) or if you are an employee of your own limited company. If the latter, you would pay the 'employee' rates, which can be as high as 40% in some tax jurisdictions.

If you are self-employed in the UK, you normally have to pay Class 2 national insurance contributions at a flat rate of £2.70 per week. You also pay Class 4 contributions of 9% on annual profits between £7755 and £41 450, plus 2% on any profit over that amount (UK Class 2 and Class 4 rates for tax year 2013–2014).

In Germany, it is obligatory to have health insurance, but self-employed persons can choose to switch to private cover if they wish. If you stay in the statutory system, your minimum monthly contribution is 350 euros. You also have the option of joining the statutory unemployment insurance scheme, which varies geographically between 68 and 81 euros.

Pension contributions are currently obligatory only for certain professions in Germany, although the government is in favour of extending obligatory cover to all self-employed professions.

5. Am I making the most of the professional support available?

Freelancer Steve Aspin recalls: 'When I first went freelancing… I didn't have any advice, I didn't use an accountant, I did everything myself, and let's face it, it was an absolute mess. I really recommend getting advice from day one'.

Taxation is a complex, ever-changing field, particularly if you are part of the growing number of freelancers who work across borders. Investing in qualified professional support can help you not only to stay on the right side of the law, but also to save time and money. Many accountancy and bookkeeping providers have innovative online or app-based solutions that can revolutionize the way you handle your finances.

Bear in mind that the type of professional support you need also varies by country. For example, in the UK it is usual to obtain tax-planning services from an accountant, whereas in Spain it would be a fiscal lawyer.

A good starting point for advice is the national representative body for freelancers in the country where you are based. For example, PCG in the UK has a register of accredited accountants who have been specifically trained in the complexities of tax for freelancers.

Other organisations that represent freelancers across Europe are provided in Table 1.

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Andreas Lutz is CEO of VGSD, the representative body for freelancers in Germany. You can email him at lutz@vgsd.de.

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Table 1: European associations representing freelancers

Association	Country	Website
FediPro: representing iPros from every discipline	Belgium	http://www.ipros.be
Aprotrad: representing translators and interpreters	France	http://www.aprotrad.org
FedAe: representing auto-entrepreneurs from every discipline	France	http://www.federation-auto-entrepreneur.fr
VGSD: representing self-employed persons, freelancers, and small businesses with typically less than ten employees	Germany	http://www.vgsd.de
ACTA: representing autonomous workers from every discipline	Italy	http://www.actainrete.it
ANITI: representing translators and interpreters	Italy	http://www.aniti.it
PZO: a representative body for freelancers, organised as a collective of networks focusing on specific professions	Netherlands	http://www.pzo-zzp.nl
PCG: representing independent professionals from every discipline	UK	http://www.pcg.org.uk

The Loneliness of a Freelance Writer

Pre-freelance naivety?

When I decided to be a professional freelance writer 2 years ago, I drew up a long list of the challenges that lay ahead. The list included setting up a limited company, a business bank account, a website, and a social media profile. It never occurred to me that loneliness was a challenge that should feature on my list. In fact, I was looking forward to working on my own. The thought of having nine uninterrupted working hours a day filled me with eager anticipation. I had been sharing an office with other people and unless I worked outside office hours, there was never really a moment's peace. Inevitably one of us would be talking with a visitor and we often chatted amongst ourselves. As jovial as this was, I could not help feeling that I was not focused enough because of the background noises and distractions. Another attraction of working alone was not having to sit through lengthy group meetings or get involved in office politics. Looking back I do not think anyone could have embraced the singleton working life more emphatically than I did when I started freelancing.

The reality

The solitude was wonderful at first. For over a year I rarely thought about my secluded working life. However, a couple of months ago, I noticed that I was getting quite chatty on emails with clients. I would sometimes end business emails with discussions about whimsical matters such as good places to go on holiday. Of course, I would delete the whole lot and condense it into a short concluding sentence such as, 'I hope the weather is nice where you are', and send the email off. This is when I realised that the isolation of freelancing had started to affect me. Was I missing the office chit-chat after all? Maybe the team meetings and politics were not as tedious as I had made them out to be?

Strategies to combat loneliness

I then considered various strategies for re-connecting with people. While I keep in touch with freelance writers around Europe through EMWA, and I also belong to an informal network for freelancers residing in the South West of the UK, I felt I needed to meet more local people. I had heard of freelancers going to the local café or pub just to be around other people and I tried this a couple of times. Although I enjoyed it, I could not resist the uplifting café lattes and enticing chocolate caramel shortbreads. My expanding waistline, therefore, put a halt to that venture! Besides, cafés are not the easiest place to meet like-minded people. So, I turned to the internet to locate an existing freelance writing community in Cardiff. This is when I stumbled upon Meetup (http://www.meetup.com), a website dedicated to organising local face-to-face meetings. I became a member and searched for writers' groups in my vicinity but found none. However, since any member can start a Meetup group, this is my next task. I'm hopeful that the Meetup group will ultimately bring together other freelance medical writers and it would be great to build such a community in South Wales.

Although I was certain that meeting local freelance writers would help to combat loneliness, I also found myself wanting to be part of an organisation. For this I had to look beyond cafés and online forums and decided to join the parent–teacher association at my daughter's school. This is not something I would have volunteered for a few years ago. Who wants to sit through another long meeting after a full day in the office? Well actually, someone like myself, who has not interacted with a soul the whole day. In fact, I find the meetings quite stimulating. I also volunteered to collect tickets for Santa's Grotto during the Christmas Fair and delighted in the bustle and activity behind the scenes. I cannot say I enjoyed the stress of facing long queues of irate parents waiting for their children to see Santa after their appointed time. However, I did like the challenge of improving the ticket system next year so that we could get more people into Santa's Grotto, raise more money, and reduce the waiting times.

Rekindled team spirit

Back at my desk I am still working on stand-alone projects but what has changed is that I feel part of a working community again. I have not established a local writer's group yet, but by joining the school association I have become part of a community with a common goal and regular face-to-face team work. Why was I suddenly enjoying committee meetings and team interaction? I now realise that my 'freelancer loneliness' was not about knowing too few people, but about missing the spirit of team effort. It goes without saying that the pub visits after the association's meeting are an added bonus!

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Tool Box

Document storage in the cloud
File storage

As medical writers we amass a lot of documentation – not only do we produce it but we also review, edit, and need it for reference purposes. Although I must confess to a propensity for printing off material to review and edit, I think it is safe to state that the large majority of the information we work with is produced and filed electronically. Not only do we have to consider where we store our documents and how we access them, we also need to think about having back-up copies in case we experience computer issues. Back-up copies may be stored on mobile hard drives and USB sticks, but we have to be able to keep these items secure plus it is another item to remember to take with us when we travel.

So in this electronic age of document production, how can we store our 'paperwork' securely yet ensure we have easy access?

What about online storage?

Online or 'cloud' storage is certainly an option to consider when having to store the large capacity of electronic data we now accumulate. Cloud storage can be defined as the 'storage of data on remote servers' and may be used for storing original material as well as back-up files. Some online storage providers also provide file sharing options to enhance collaboration within teams thus avoiding the need to send large, zipped files via email which can be slow and laborious.[1]

What are the pros and cons of online storage?

As with all document filing systems, there are advantages and disadvantages. Online storage providers will argue that storing data in this way minimises the need to carry important data around with you on a USB stick, portable hard-drive, or CD thus reducing the risk of your data being stolen or misplaced while you are travelling. This means of virtual storage may also reduce a loss of data due to damage to your computer or to portable 'physical' filing systems and if your computer does malfunction, your data should still be accessible via another device. Furthermore, traditional on-site storage devices may be more susceptible to corruption from viruses compared with online filing systems.[1]

Dropbox

Being new to Dropbox.com (http://www.dropbox.com) – one of the many online storage providers available – I have found it useful for storing copies of reference materials such as regulatory guidelines, disease area guidance, and literature references. I would also use it as a back-up solution to store photos and training materials. With Dropbox, you open an account and download the software onto your computer.

However, since your files are saved on a remote Dropbox server, you can still access these files from another computer on which the software is not downloaded because you can log-in to your account via the Dropbox website and access your
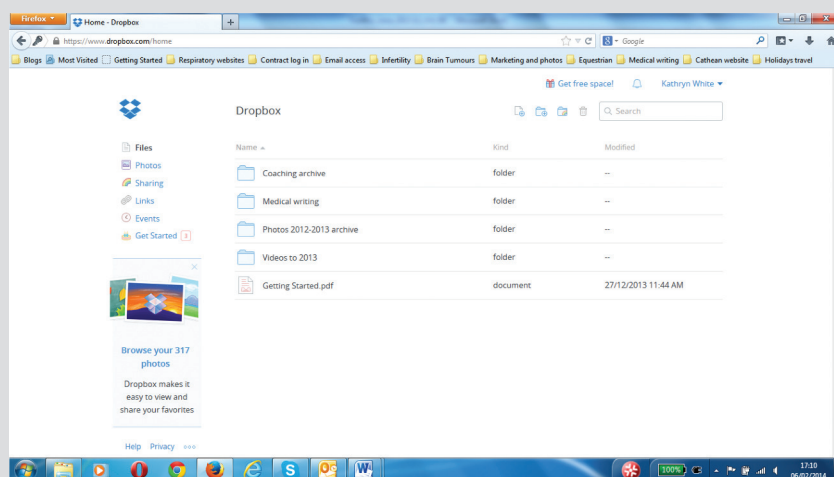

Figure 1: Dropbox.

folders that way. This is really useful if you are travelling or working from a client's office and want to access files that would otherwise be stored on your computer at home. Depending on your provider, you may also be able to access your files via your phone or tablet and synchronise your data across multiple devices.[2]

Security is, of course, a priority especially given the confidential nature of our work. Most companies encrypt the filed data using a system that is equivalent to the security used by your online banking service.[3] Despite this level of security, I, personally, would be reluctant to use 'the cloud' to store confidential client documents although one may argue that it may be more secure than carrying such data on a USB stick in my hand luggage when travelling.

Which online service to use

This is largely dependent on what service capabilities you are looking for and whether you use a PC or MAC. Some applications are primarily for syncing and sharing documents, while others are excellent as a back-up facility, enabling your computer to automatically copy your documents to your online folders. I chose Dropbox because it was reviewed in Writing Magazine, which I subscribe to, so I knew it was being used by writers, and I like its simplicity. However in the recent issue of Freelancing Matters[4] it was noted that Dropbox has experienced breaches of security. Generally, online storage providers offer a free package which gives you a certain amount of memory space (Dropbox for example provides up to 2 GB free of charge). Additional space may be purchased or you can upgrade to a service that provides a greater storage capacity and for these there is usually a monthly charge. Often, with the charge, comes increased security.

There are many online storage providers out there to consider and it is probably best to chat with colleagues about their experiences with such applications. Here are a couple of weblinks to articles that compare different online storage solutions to get you started:

PC Magazine: http://www.pcmag.com/article2/0,2817,2413556,00.asp

Online file storage: http://www.onlinefilestorage.com/what-is-online-file-storage

Disclaimer

The information contained within this article represents the opinion of the author based on limited experience of cloud storage. The information should not be used as the only resource for choosing an online storage provider and readers are recommended to seek advice and other information available. The author has no affiliation to Dropbox.com and does not recommend this product above any others.

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Freelance foraging

Anne McDonough sent in this poorly worded public health notice in the office of one of her clients. Anne says: 'Do I have to? I've heard smoking is bad for me!'.

The Light Stuff

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I love deadlines, I like the sound they make as they fly by

Douglas Adams, English writer, humorist & dramatist (1952–2001).
Illustration: Gemma Hobbs, Downham Market, UK.

Answers to Medical Writing Jumble #10:
PRINT, TRAIN, SAFETY, NEURON.
Workers at the glass factory protested that
the procedures of the management were not
TRANSPARENT enough.