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SPECIAL EDITION

MEDICAL WRITING

THE BACKBONE OF CLINICAL DEVELOPMENT

2017

Medical Writing: The Backbone of Clinical Development


Special Edition 2017



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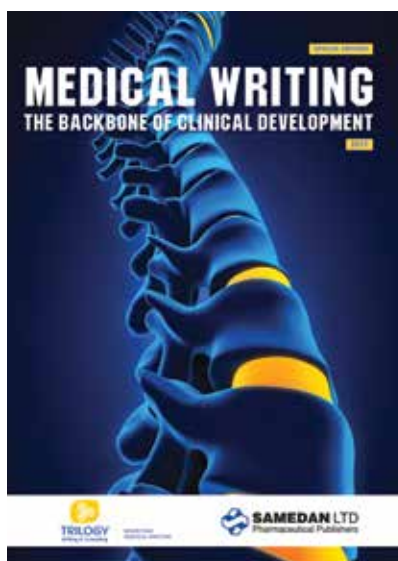
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Publisher's Introduction



Welcome to our special edition of *International Clinical Trials*, specifically created to address the important topic of medical writing.

ICT, in partnership with Trilogy Writing & Consulting, have gathered medical writing experts from around the world to help create a definitive guide to medical documentation and the various challenges of developing it. The carefully selected and esteemed contributors are thought leaders from across the pharmaceutical and medical writing sector. Their articles raise much-needed awareness of what is required and how best to go about producing accurate, well-written documentation.

Whether you already are or intend to become a medical writer – or if you simply need your medicinal product or clinical trial documented – we hope that you will find valuable advice and practical tips in these pages, and wish you to keep it as a handy reference.

We would like to thank Julia Forjanic Klapproth, a former President of the European Medical Writers Association and a Senior Partner at Trilogy Writing & Consulting, for her contribution as Chief Editor. Trilogy has played a crucial role in suggesting, sponsoring, coordinating and editing this special edition. By doing so, they have once again confirmed their deserved reputation as a leader in this industry.

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International Clinical Trials



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Foreword

By Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research at the FDA

The health of Americans is the first priority of the FDA's Center for Drug Evaluation and Research (CDER). CDER protects and promotes health by ensuring that human drugs are effective and adequately safe, and that they meet established quality standards. Excellent communication is critical to both developing and properly utilizing drugs.

Good medical writing and careful documentation factor into each stage of the drug evaluation and review processes – from the first phases of clinical research, through the application and review process, and during the post-approval monitoring of marketed drugs. Through effective communication of drug risks and benefits, we provide healthcare professionals and patients with the information they need to use medications safely and avoid medical errors. All of these efforts require excellent medical writing and consistent documentation. We collaborate with many stakeholders to make sure that the most reliable clinical, scientific and regulatory information is disseminated.

In this special edition of *International Clinical Trials* magazine, leaders in the field tell us about the importance of good medical writing in a complex regulatory environment; how to write for different audiences and publications; and critical tools, tips and tricks of the trade. They also share ways to overcome challenges and avoid common pitfalls, among other key topics. We welcome their contributions and guidance in this effort.



A handwritten signature in black ink, appearing to read 'Janet Woodcock'.

Janet Woodcock, M.D.

Director of the Center for Drug Evaluation and Research at the FDA



Foreword

By Melanie Carr, Head of Stakeholders and Communication Division at the EMA

Medicines and knowledge are two principal outputs of pharmaceutical endeavours. The twin yields – one tangible and the other more abstract – have to work hand-in-hand to maximise health benefits. Huge effort goes into making medicines fit for use, being subjected to rigorous standards for demonstrable quality and that all-important positive balance between their benefits and risks. The European Medicines Agency welcomes the attention now being directed at that other crucial component of effective healthcare and decision-making: the presentation and dissemination of knowledge.



Knowledge is vital at every stage of a medicine's lifecycle – from that first glint in the scientist's eye at their origin, to the delivery of a medicine to patients with detailed instructions on their safe use. And at each stage, this knowledge is passed on in writing. Clear, accessible and accurate writing underpins the dissemination of precious and cumulative knowledge. Continual advances to improve a medicine must run alongside enhancements in composing the associated knowledge, so that the scientific and clinical communities as well as the public at large fully benefit from it.

This special edition of *International Clinical Trials* magazine prompts reflection on what makes medical writing effective and why it is so important. Coherent, logical and appealing documentation aids decision-making, while poor-quality writing can hinder it and run the risk of drawing flawed conclusions. From the regulator's perspective, better quality documentation is likely to foster better and more timely evaluation. At the user's end, well-written information means that the patient receives the right medicine, at the right dose and with the right instructions on how to take the medicine.

The adoption of clear writing principles is becoming important for another emerging reason: the march towards open and accessible information as pioneered in the EU region. Many reports and documents written to meet regulatory requirements have so far not been open to the public gaze. But now, those compiling these documents will see how their work will be accessible to academics, clinicians and the public. A medical writers' expertise and professionalism will need to be deployed more than ever to come up with documents of the highest quality, which demonstrate sound science and good practice of the bodies behind these documents.

The principles of good medical writing are becoming embedded in the world of medicines regulation; enthusiasm over good writing and the sharing of ideas across the whole pharmaceutical spectrum will benefit patients, the health community and society at large. The experience and skills of the authors of this special edition encompass the fundamentals of clear, concise and accurate writing.

Melanie Carr

Head of Stakeholders and Communication
Division at the European Medicines Agency

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Foreword

**By Julia Forjanic Klapproth, Senior Partner
at Trilogy Writing & Consulting**

Dear Reader,

If you are reading this special edition on medical writing, it is very likely that you are at least one of the following: someone interested in becoming a medical writer, someone who is already a medical writer or someone who has worked – or intends to work – with a medical writer in the future. The idea for this special edition is to provide you with useful information, regardless of which group you belong to.

I had the good fortune of discovering medical writing some 20 years ago and it was love at first sight. It is a career that challenges one intellectually, but also pulls on numerous facets of training gained at university. In addition, when a good medical writer is in full swing, they pull a team together and push them to achieve documents that truly help expedite drug approval, which is professionally gratifying. Medical writers are people managers, idea miners, mediators, communicators and document wizards. Their experience gives teams a measure of confidence when things get stressful, and helps keep them focused on pulling the right information together and communicating what is needed for a particular document's purpose.

Anyone who has worked with a good medical writer knows the value they bring to a writing team, yet many people in the pharmaceutical industry still do not understand their role. The biggest and most common misunderstanding is that 'anyone can write', meaning that a medical writer does not need any special training – or any training at all. As a result, numerous people are employed as medical writers who, sadly, know nothing about the documents they are working on and do not have the skillset to advise their teams on the directions to be taken. Teams who have worked with these untrained medical writers also know how this can hinder the process. Expecting an inexperienced medical writer to work miracles with a document is like expecting an inexperienced surgeon to work miracles with their surgery. Excellence comes from practice and training, and it is worth making the effort to find a professional to do the job.

That is why it is important to evangelise the industry about the value and importance of high-end medical writing. This issue of *Medical Writing: The Backbone of Clinical Development* brings together authors who are industry thought leaders in the world of medical writing. With articles ranging from the basics to the specific, the goal is to raise general awareness about the importance of producing well-written regulatory documentation. The articles explore how to overcome and avoid hurdles that are reducing efficiencies when preparing these documents, and make clear the benefits of using experienced professionals.

In my ideal world, authoring teams of the future will comprise well-trained experts who bring their experience in their respective domains; weaving the input from the clinical perspective together with that from statistics, pharmacovigilance, regulatory and medical writing. In this world, teams will be able to better communicate throughout the lifecycle of a product, ensuring that investigators and patients properly understand what needs to happen during clinical studies. Companies will consequently obtain more consistent and robust data from those studies, and agencies will better understand the implications of medicinal benefits and risks for the products they are required to assess. Ultimately, clear and effective documentation can streamline the whole process of drug development, which would enable us to get new medicines and therapies to patients who need them sooner and with less cost. Now *that* is a goal worth striving for.

Julia Forjanic Klapproth
Senior Partner at Trilogy Writing & Consulting



The Need for, and Benefit of, Good Medical Writing

The job of a medical writer involves authoring and editing a wide range of documents that reach a variety of audiences. The main concern of the medical writer is the clear communication of scientific information, which inevitably involves specific tailoring of that document for the target audience. This task necessarily requires a special skill set, which allows the medical writer to craft this message. In this article, we introduce the skills that a professional medical writer brings to a project and the ways that this expertise can benefit a document and, more broadly, a clinical programme. We also discuss how other team members can best assist a medical writer to produce high-quality documents.

By Karry Smith and
Ann Winter-Vann
at Whitsell
Innovations, Inc.

Communicating Science

Science, admittedly, can be difficult to read and to understand. At best, poorly written information confuses the reader; at worst, it leaves its audience misinformed. According to the 1990 article by Gopen and Swan, the goal of all text is that the “majority of the reading audience accurately perceives what the author had in mind” (1). Simply stated, medical writers write about medicine and health. Whether they author publications, develop educational materials, or compile an entire regulatory submission, medical writers are responsible for clearly communicating complex scientific information.

What Is Medical Writing?

Medical writers are professionals with a broad expertise in communication, who are skilled at presenting complex information in a manner that is clear, logical, and attuned to the needs of a particular audience. Medical writers often have formal training in science, which provides a solid foundation for gathering and evaluating medical information. Professional medical writers contribute much more, however. They understand ethical standards and contribute a wide range of skills in project planning and management. Altogether, the skills of a medical writer contribute to improving each document they write and helping each team they support. The broadly defined skills we present in this article support the contributions illustrated in Figure 1.

Grammar and Writing Skills: The Foundation of Medical Writing

At the simplest level, word choice can have a critical effect on how well a message is communicated. Words that are inaccurate or unfamiliar to those outside the field can obscure the message and discourage the reader. The rules of grammar govern the construction of sentences and dictate how words, phrases, and clauses are combined; a failure to follow the rules will distract or confuse the reader. More subtly, the location

of words and phrases within a sentence can drastically alter the perceived message (1). At a less granular level, a medical writer weaves sentences together into paragraphs that form the body of a document. The manner in which sentences are arranged leads us to the next skill – organisation.

Organisation

The skill of organisation overlaps, in part, with grammar and writing. Medical writers use organisational principles (with the reader in mind) to construct sentences that convey accurate information. On a less granular scale, organisational principles govern the construction of paragraphs and the flow of information within a document. For example, in scientific publications, background information must be presented and organised in such a manner that it leads seamlessly to the research question at hand. In educational documents, introductory information must sufficiently prepare the reader to understand the subsequent information. The ability of a medical writer to organise information ties in closely with the ability to collect and critically review data.

Gathering and Analysis of Information

Medical writers are information managers. They must both gather and analyse information at every step in the writing process, before eventually determining which pieces of information are incorporated into the final document. Gathering information can involve research in the form of literature reviews, or collating information from team members, including statistical outputs.

Analysis involves breaking information down into its constituent elements and using this as a basis for discussion, interpretation, or examination of relationships. Analytical writing, therefore, involves describing these ideas with the written word. Medical writers comb through the statistical outputs from a clinical study to identify relationships between adverse events, medical history, and laboratory toxicities;

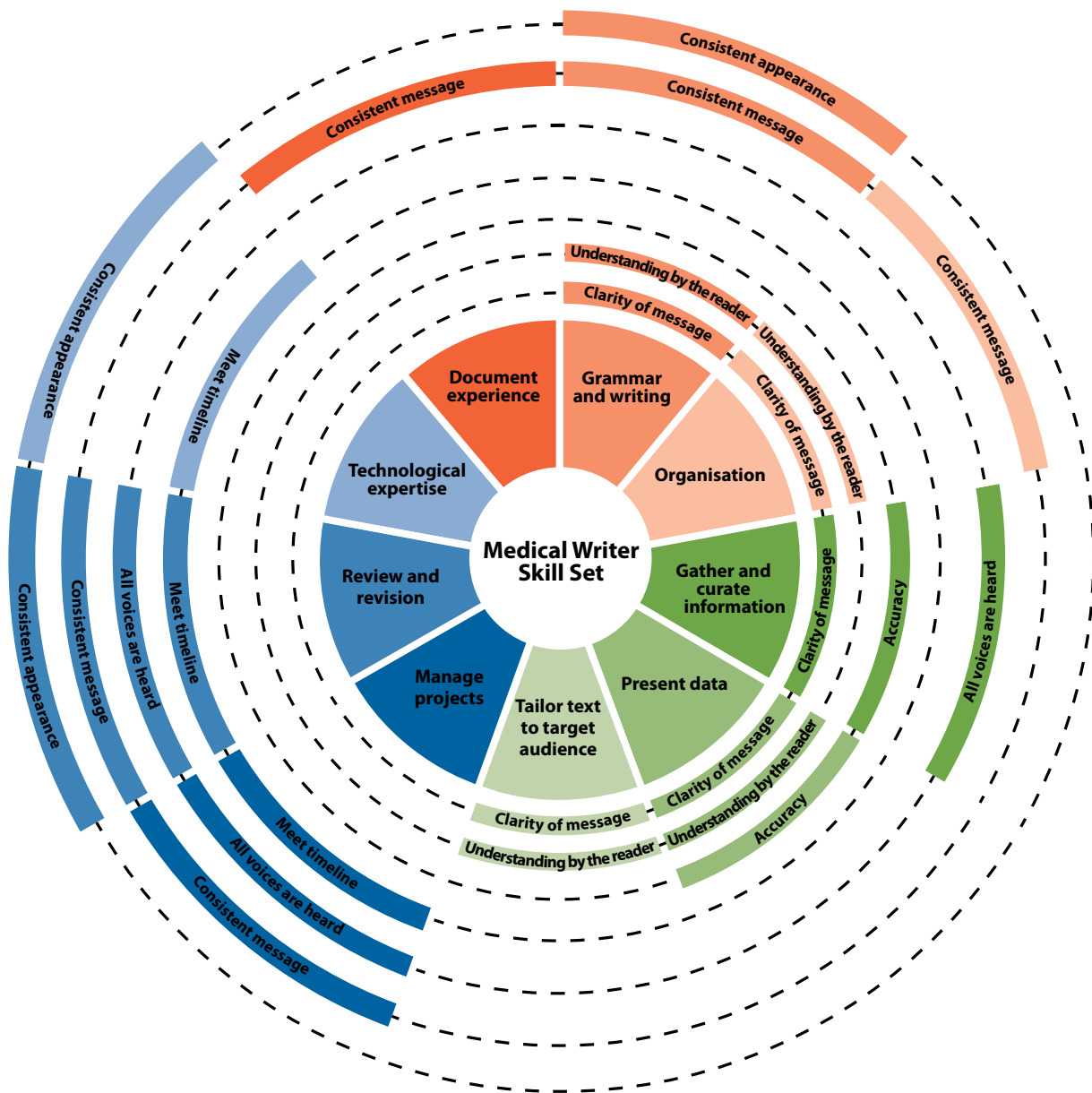


Figure 1: Skills and areas of expertise of medical writers

compare and contrast the results of different treatment groups; and describe key information from the tables, listings, and figures. They carefully determine which information supports and accurately conveys the study data. Not every table or figure will find its way into a final clinical study report; the sheer volume of the statistical outputs would bury critical information in a pile of less informative data. Writers must review all of the available information and determine what goes into the text to tell the story. In order to accomplish this, writers must have a solid understanding of statistics, which allows them to curate and present the data appropriately. In educational writing, analytical writing skills allow medical writers to determine the organisation and flow

of information so that it makes logical sense. This includes drawing comparisons and analogies between ideas to assist the reader in understanding key points. When information has been gathered, analysed, and curated, the next step is to determine how to present the data.

Data Presentation

The order and manner in which data are presented affect the ease with which a reader comprehends this information. Gopen and Swan use the example of reversing the order of columns in a table to drive this point home: the reader can more easily interpret information when it is presented

in a format that the reader anticipates or is used to seeing (1). Many times, information is better presented in a figure than in text. Franzblau and Chung list three advantages that graphs have over text (2):

- They portray complex information and comparisons in a way that is easier to interpret and understand;
- They reduce reading time by summarising and highlighting key findings; and
- They reduce the overall word count

The medical writer is often responsible for pulling out important figures or tables from datasets that contain hundreds of figures and tables. Once incorporated into the document, the medical writer must then highlight the key data in text.

When authoring publications, medical writers frequently help design figures. A classic reference by Edward Tufte outlines how good graphs communicate data – with clarity, precision, and accuracy (3). If a figure is ambiguous, confusing, or misleading, the medical writer will suggest revisions.

For educational documents, medical writers create flowcharts, choose which text to convert into short, bulleted points, and pull in images to drive home key points to the audience. The ability to clearly present data is important in making sure the information can be understood by the target audience.

Tailoring Text to the Target Audience

Different audiences have different needs for background information, word use, sentence structure, and information. Proper grammar, word choice, organisation, and presentation all contribute to making a document clear, simple, and easy to understand. We must ask ourselves: “What message should the audience take home when they are done reading our document or presentation, and how can we help them reach that conclusion?” Using the example of an educational document detailing the discovery of a new drug, a research scientist may be most interested in the mechanism of action, whereas a doctor might be more interested in efficacy, the side effect profile, and potential drug-drug interactions. The lay audience will likely require more background and simplified (or more generalised) information than those who are experts in the field. Reviewers at regulatory agencies would be most interested in the safety and efficacy data.

Project Management

Whether authoring a regulatory document or drafting a lay summary, medical writers are, first and foremost, skilled at writing. However, their contributions to a document go beyond grammar and data presentation, because their

responsibilities include more than just writing. Medical writers are often project managers: creating timelines, meeting deadlines, and managing input coming from multiple sources. Because of their organisational skills, medical writers are able to keep multiple documents moving forward, make accurate edits and updates, and ensure that all team members are heard.

In its *Guide to the Project Management Body of Knowledge*, the Project Management Institute describes a framework for project management (4). This framework includes five processes that have been defined and applied to publications writing by Auti *et al* but are equally applicable to the regulatory and educational writing arenas: initiation, planning, execution, monitoring and control, and closure (5).

In regulatory writing, initiation might involve developing a scope of work and hosting a kick-off meeting. The next process, planning, begins by assigning project roles, gathering a core team, and creating an agreed-upon timeline for the project. Execution involves many standard procedures – drafting text, managing review cycles, resolving comments, gathering necessary information from team members, and preparing a final draft for team review. Monitoring and control of the project involves defining risks that could impact timelines and creating solutions to these problems. The fifth and final process is closure, which involves delivering the final

Do's and Don'ts of Medical Writing

Do:

- Let the writer know if you will be on vacation or unavailable for a period of time
- Provide text as requested (by the deadline)
- Keep the writer informed of any changes to the programme that might affect the document
- Use the agreed upon review system
- Provide actionable comments
- Provide specific references and source documents
- Meet deadlines for review of the document
- Consolidate comments by functional area (eg statistics, safety, regulatory)
- Decide upon preferred styles and wording early in the process. This step is particularly important for large submissions so that the full set of submission documents can be consistent in style and presentation

Don't:

- Ignore questions or forget to respond to the medical writer
- Send multiple versions of a document to the entire team; this can lead to version control issues
- Focus on minor wording issues and miss the “big picture”
- Get distracted by findings that do not pertain to the study objectives and endpoints
- Skip comment review meetings
- Wait until the final draft to actually read the document

product, completing any final documentation required by company standard operating procedures, and in some cases, reviewing how the project went in order to further streamline the activity the next time.

Review and Revision: Creating the Final Document

We indicated in the introduction that the main concern of the medical writer is the clear communication of scientific information. The final form of this information is a document that, after weeks, months, or even years of work, reaches its intended audience. Each document passes through multiple stages of review and revision. New data might become available or a new advance in the field might affect the science that supports the document. Because scientific fields evolve rapidly, and because many individuals contribute, the review and revision process ensures that the project is completed and that all input is considered: all voices are heard. To accomplish this, medical writers work with team members to resolve conflicting comments, revise the document, and keep record of changes to the document over time. Because documents often change in real time, soliciting resolution and a final approval from the team are key steps in completing a document.

Technological Expertise

Medical writers are experts in the tools of document writing, adept at using software such as Microsoft Word, Excel, and PowerPoint, and Adobe Acrobat. Their expertise includes an advanced knowledge of the powerful functions of these programmes that make a document consistent in formatting and style, navigable, and stable – even in documents that are hundreds of pages long and include dozens of tables and figures. These highly formatted, stable documents eliminate the need for tedious and time-consuming revisions by the publisher.

Depth of Experience

Because writers work with many teams across different therapeutic areas and different stages of clinical development, they add depth and breadth of experience to each project. Experienced medical writers understand how various documents fit together throughout the lifecycle of a clinical programme: well-written protocols allow the collection of data to support the objectives and endpoints of a study. Clinical study reports present those data with a clear, consistent message that is then conveyed to the public through posters, presentations, and publications. The messages are combined across a clinical development programme to support the eventual submission.

Getting the Greatest Benefit from Adding a Medical Writer to Your Team

It should be evident by now that the medical writer is a key contributor and coordinator of any regulatory writing,

publications, or educational writing team. The medical writer necessarily interacts with all members of the team.

To get the most from this interaction, we recommend some “Dos and Don’ts” that will assist the medical writer in producing high-quality, on-time documents (see previous page).

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What you Need and When – The Key Documents in the Drug Lifecycle

Clinical development is a complex and expensive undertaking, involving many years of research that culminate with clinical trials, the objectives and results of which all have to be documented. This article provides a pathfinder to which documents need to be prepared, when they are needed, and who they need to be submitted to.

By Julia Forjanic Klapproth at Trilogy Writing & Consulting

Throughout the lifecycle of a medicine, documents are the key means for designing, conducting and reporting trials in human subjects, as well as for monitoring the quality manufacturing, packaging, labelling, safe usage and performance of drugs once on the market (see Figure 1). The ICH guidelines – particularly ICH E6 – provide a unified standard for the EU, Japan and the US to facilitate the mutual acceptance of clinical data by regulators within these jurisdictions, laying out the essential documents required to proceed through the clinical lifecycle and meet regulatory requirements (1).

Many of the documents needed are relatively straightforward forms that need to be completed with the appropriate information. Some, however, are more complex and require the efforts of multifunctional teams to pull together the information needed. In particular, experienced medical writers bring value to the process of weaving it all together in a way that effectively communicates the intentions and

objectives of each document. This article aims to provide an overall summary of the documents that medical writers can, and should be involved in, as expert communicators who can ensure the documents are fit for purpose across the lifecycle of clinical drug development, approval and marketing. It will focus on the key documents required at each stage of the drug lifecycle, describing their content, purpose, audience, and deadlines for submission.

Documents Required Before the Start of a Clinical Trial

Prior to testing any new medicine or therapy on human subjects in a clinical trial, the drug developers must apply for permission to run clinical studies by submitting an Investigational New Drug (IND) application in the US or an Investigational Medicinal Product Dossier (IMPD) in any of the EU Member States (see Figure 1). For the initial human studies, these applications summarise manufacturing information, all

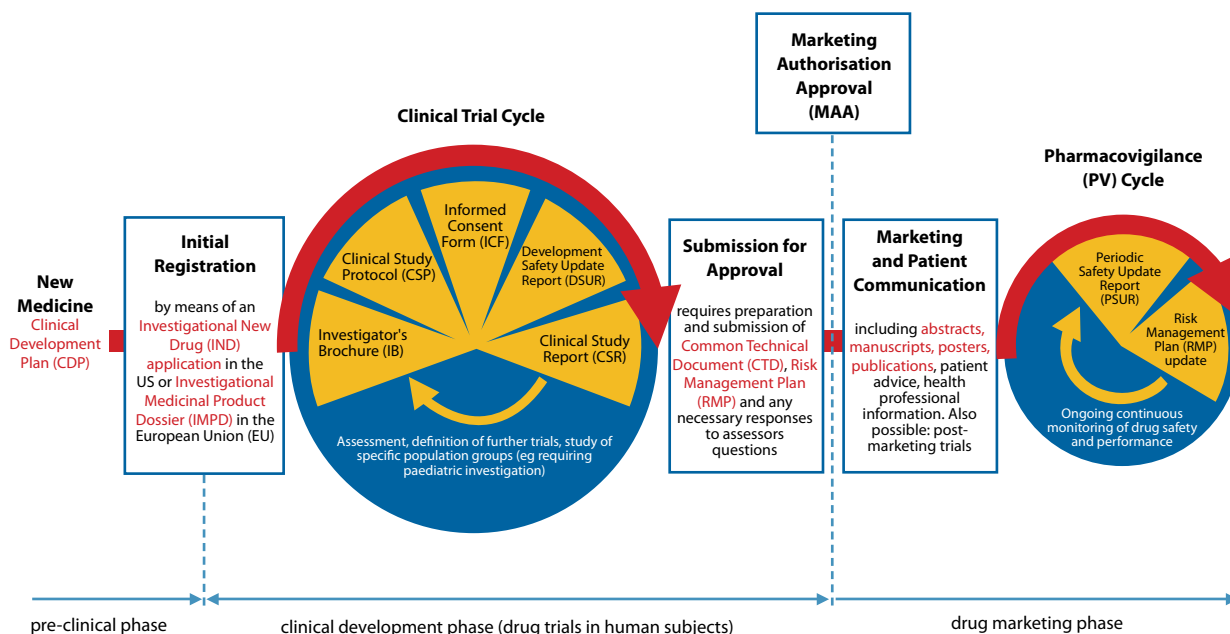


Figure 1: Documents in the drug lifecycle

| EU documents | US documents | Nature and purpose |
|--|--|--|
| Investigational Medicinal Product Dossier (IMPD) | Investigational New Drug (IND) Application | An application for permission to use an investigational product in a clinical trial with human subjects. A separate IND or IMPD is required for each product used in a trial (including placebo). These documents may need updating for the approval of each new clinical trial, if the known information about an investigational product changes significantly |
| Investigator's Brochure (IB) | Investigator's Brochure (IB) | A compilation of all the relevant clinical and medicinal data of an investigational new drug or medicinal product, as relevant when studying the medicine in human subjects |
| Clinical Study Protocol (CSP) | Clinical Study Protocol (CSP) | A document that lays out strict guidelines for the performance of a clinical trial. Based on the most current data about the disease under treatment and the medicine being tested, the protocol lays out guidelines for diagnosis, prognosis, handling of subjects, dosage of medicines and risk/benefit considerations, providing decision options and their expected outcomes |
| Informed Consent Form (ICF) | Informed Consent Form (ICF) | A document to be signed by all subjects who are to take part in the clinical trial – to confirm that they understand and accept the objectives, methods and risks involved |
| Paediatric Investigation Plan (PIP) | Pediatric Study Plan (PSP) | A development plan that is required if the investigational product is to be licensed for use in children. It describes how clinical data will be obtained safely in clinical studies with children |

Table 1: Documents needed to start a clinical trial

data available to date from animal studies including toxicity data, the clinical study protocols (CSPs) for the planned clinical studies and information about the investigators who will run the studies. As the development programme proceeds, the IND or the IMPD must be updated for each new study, adding new data from animal and human research available at the time the new study application is made.

There are a number of key documents that need to be written to be able to run the clinical studies, as explained in detail in ICH E6. The most important of the documents defined by ICH E6 are the CSPs, the informed consent forms (ICFs) and Investigator Brochures (IBs) (see Table 1 and Figure 1). The purpose of these is to:

- Lay out clearly the scientific information available about the product (in the IB)
- Explain the rationale for performing each study (in the CSP)
- Provide a detailed investigational plan and describe the analyses to be made to achieve the objectives of a study (in the CSP)
- Explain the details and intention of the trial in lay language for subjects participating in the trial (in the ICF)

These documents are often complex collections of thoughts that need to build on each other to tell a clear story of what the trial hopes to achieve and how. The coordination and writing of these documents warrants the use of an experienced writer who knows how to pull together input from the many stakeholders involved in the authoring process, and to make sure their ideas are consolidated into a consistent reflection of the planned studies.

It should be kept in mind that the complexity of these documents tends to increase as the development programme proceeds. Clinical development begins with Phase 1 clinical trials that are conducted with just a few human subjects to assess the safety and pharmacokinetics of the medicine. Phase 2 clinical trials follow, in which initial efficacy assessments are made in subjects with the target

disease and dose finding studies are made to identify the optimal dosage of the medicine. Ultimately, large-scale Phase 3 trials are performed to unequivocally demonstrate the efficacy of the product at the planned dosage and to better understand the safety profile.

As a result, the CSPs of Phase 1 and simple Phase 2 studies often have few assessments, are small and less complex, and can be written quickly with only a few drafts. In contrast, a complicated Phase 2 or 3 CSP that has several objectives (eg efficacy, safety, pharmacokinetics and quality of life), assessment of multiple dose groups or treatment regimens, and perhaps includes sub-studies, may take months of discussion and consideration to develop. This means there will usually be numerous drafts and multiple rounds of revision as various stakeholders are asked to contribute their opinions on the design and activities to be performed.

Likewise, an IB needed in later stages of clinical development is a much more difficult document to write. The intention of the IB is to inform investigators who will be running studies about all available information on the PK profile, efficacy and safety of the drug being tested. By Phase 3, there is a wealth of clinical data available that needs to be condensed and consolidated into a brochure that is still easy and quick for the investigator to read. This takes much more skill and experience as a writer than the early editions of an IB. Thus, the demands on the team as a whole – but particularly on the medical writer – increase considerably with the rising complexity of documents in later stages of development. It is, therefore, important to ensure that the experience and skill of the medical writer is carefully matched to the demands of the documents in these different phases.

For investigational products that will be licensed for use in children, it is necessary to write a development plan focused specifically on the studies to be performed in children. This Paediatric Investigation Plan (PIP) in the EU, or Pediatric Study Plan (PSP) in the US, describes how clinical data will be obtained in studies involving children to support the

| Document | Nature and purpose |
|--|--|
| Development Safety Update Report (DSUR) | A comprehensive annual review and evaluation of safety information relating to drugs under development, which must be revised annually as necessary |
| Clinical Study Protocol (CSP) amendment | Revisions to the original CSP that reflect changes in the design or investigational plan, eg due to practical problems in running the study or unexpected outcomes |
| Investigator's Brochure (IB) updates | Prior to the start of any new clinical trial, the IB must be updated with any data from prior studies; at a minimum, updates are required at least annually to reflect any changed information |
| Pregnancy prevention plan or programme (PPP) | A document laying out a set of interventions intended to reduce the likelihood of pregnancy during treatment with a medicinal product with known or potential teratogenic effects |
| Statistical Analysis Plan (SAP) | A detailed description of the statistical analyses to be performed on the data collected during the clinical trial, based on the statistical analyses described in the CSP. This includes the rationale and references for why particular statistical methods are appropriate for the planned analyses |

Table 2: Documents to be authored during the conduct of clinical trials

authorisation of a medicine for them. These are not trivial documents, as they must provide detailed background information about what is known about the disease in children and what treatment options are already available; describe the measures to adapt the medicine's formulation to make its use more acceptable in children (eg use of a liquid formulation rather than large tablets); and address how the studies will cover the needs of all age groups of children (from birth to adolescence). Teams often underestimate the amount of time they will need to discuss, develop and agree on the content of their paediatric plans and it is important that the writing timelines plan for sufficient time to develop the document properly.

Documents Needed During the Conduct of a Clinical Trial

Once the clinical trials are running, the writing activities are far from over. Several documents need updating or writing throughout the course of a clinical programme, and many of these are written during the conduct of clinical trials (see Table 2). There are often amendments to the CSPs, which describe changes to the planned study or analyses, frequently because the original study design proves to be impractical, and the activities need to be adapted to make them more feasible or to increase patient recruitment.

Pharmacovigilance data that are collected during the conduct of a clinical development programme needed to be reported in a cumulative, ongoing manner in the annual Development Safety Update Report (DSUR). Updates to IBs need to be generated in preparation for the start of upcoming studies. The final statistical

analyses of the trial data need to be defined in advance of looking at the data, and these are described in the Statistical Analysis Plan (SAP). It is important that clinical teams have all these documents on their radar to plan for them accordingly. There is nothing more frustrating than recognising a week before a new study is meant to be submitted that an important document, such as an updated IB, is not available. By mapping out the preparation of all these documents relative to the ongoing clinical studies, writing resources can be planned out well in advance and delays in starting new studies can be avoided.

Documents Needed after Completion or Termination of a Clinical Trial

Following completion of a trial, a comprehensive clinical study report (CSR) must be written that provides a detailed description of the results of the study, whether positive or negative. In addition to describing the methodology of how the study was run (including changes to the original plan according to the CSP), all of the information collected during the study needs to be reflected in this report. Again, depending on the clinical phase of development, a CSR can be a relatively short document (eg summarising a small Phase 1 pharmacokinetic [PK] study) or immensely complex and long (eg for a Phase 3 study with numerous assessment parameters and in a particularly complex therapeutic area). While the former may only take a few weeks to write, the latter can take 6 months or more for a team to craft and develop the storyline. Often it is simply the sheer amount of data that everyone has to wade through and digest that slows the process. However, it is important to give teams the time to do this properly – taking time to think ideas over and refine the messages through

“ Once the clinical trials are running, the writing activities are far from over. Several documents need updating or writing throughout the course of a clinical programme, and many of these are written during the conduct of clinical trials ”

| Document | Nature and purpose |
|-----------------------------|---|
| Clinical Study Report (CSR) | A mandatory report covering the objectives, conduct and outcomes of the clinical trial. Note: the EU has recently defined a clinical trial report as a CSR pertaining to an interventional (rather than non-interventional) study |
| Clinical Trial Summary | A summary of a CSR, including a summary understandable to a layperson, to be uploaded onto a publicly available clinical trial registry (eg www.clinicaltrials.gov in the US or www.clinicaltrialsregister.eu in the EU) |

Table 3: Documents needed after clinical trials have ended

a couple of iterations – since well-written text and more complicated thought processes take time to hone.

It is now obligatory to post a summary of the clinical trial results for studies performed in the US or EU on online databases for access by the general public. This summary must be submitted within 1 year of completion of the trial (ie last patient last visit, as described in FDAAA 801 Requirements in the US, and the detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the EU (2,3)). From the writing perspective, it is important to know that the reports posted on these public databases may not include any information that allows identification of any subject in a study, as outlined in the EMA policy 0070 (4). Hence, the medical writer should help their authoring teams understand potential implications of the information included in a CSR to avoid unnecessarily large efforts for redaction when creating these summaries (see page 63 for more detail about the EMA policy 0070 and its implications for public disclosure).

Documents Needed to Apply for Marketing Authorisation

After completion of the clinical development programme, the data collected need to be pulled together in a dossier that will be submitted as an application for marketing authorisation. These dossiers consist of summary documents written according to the guidelines of the common technical document (CTD). The clinical part of the CTD dossier comprises Module 2.5 (the clinical overview) and Module 2.7 (summaries of clinical pharmacology, biopharmaceutics, clinical efficacy and clinical safety) (see Table 4).

Writing these dossiers is the pinnacle of the medical writing challenge to synthesise numerous ideas and data points into a cohesive description of what is known about the medicinal product. The documents need to be written so that the regulatory reviewers can quickly understand what data are available from the clinical programme, and what these tell us about the PK profile, efficacy and safety of the drug, and the nature of its relative benefits and risks. Depending on the complexity of the product and the indication for which it is to be used, writing Modules 2.5 and 2.7 can take anywhere from 6-12 months (the writing and coordination of CTDs is discussed in more detail on page 32).

As part of the application dossier, the sponsor must plan for how any potential risk associated with use of the medication

will be monitored for and minimised. This plan is laid out in the Risk Evaluation and Mitigation Strategies (REMS) document in the US (which is only required on request of the FDA) or the Risk Management Plan (RMP) in the EU (which is mandatory). As the name suggests, the document draws on all previous experience and reports of the drug to assess the main risks and to consider what would be appropriate precautions for ensuring appropriate monitoring and mitigation of those risks. The RMP also requires a summary for the layperson – ensuring that patients have full access to information about the risks of treatments they are being prescribed.

Documents Needed during Marketing (Phase 4)

In order to make health authorities, physicians, health practitioners and patients aware of a new drug – including its potential benefits and risks – the data gathered during the clinical studies are published in the form of posters, abstracts, manuscripts, patient information sheets and informative websites. There are very strict compliance rules around how marketing may be conducted, and what claims may be made in these documents.

In addition, specific material, including that derived from specially designed post-marketing (Phase 4) clinical studies, may be collected for the purpose of Health Technology Assessment (HTA) to gain specific knowledge about particular safety aspects of the drug, or to understand its performance in certain patient populations. HTA is the process by which national health authorities aim to assess the affordability of new drugs – comparing their benefits against their costs and that of alternative treatments.

Once a product is on the market, all records of reported safety events must be collated and assessed on an ongoing basis. This is done in the form of the periodic benefit-risk evaluation report (PBRER, previously the Periodic Safety Update Report, PSUR), as described by ICH E2C (R2) (5). The purpose of the PBRER is to harmonise the worldwide reporting of safety experience of a medicinal product after approval. Since the timing of when these reports must be submitted each year is regulated, preparation of these documents is often done under extreme time constraints between obtaining the data summaries for a reporting period and producing the final report. Since much of the data being assessed is in a similar format each time, it is possible to standardise the production and presentation of these data, which can go a long way to streamlining the writing process by allowing teams to focus their efforts on looking for safety signals, rather than agreeing on how to present the information.

| Document | Nature and purpose |
|--|--|
| Module 2.5: Clinical Overview | A short (up to 40 pages) critical assessment of the clinical data culminating and a benefit/risk assessment of the product |
| Module 2.7.1: Summary of Biopharmaceutic Studies and Associated Bioanalytical Methods | A summary of the formulation development process, the <i>in vitro</i> and <i>in vivo</i> dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence and <i>in vitro</i> dissolution profile database |
| Module 2.7.2: Summary of Clinical Pharmacology Studies | A summary of the clinical pharmacology studies that evaluate human PK, pharmacodynamics and <i>in vitro</i> studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes |
| Module 2.7.3: Summary of Clinical Efficacy | A summary of the programme of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought |
| Module 2.7.4: Summary of Clinical Safety | A summary of data relevant to safety in the intended patient population, integrating the results of individual CSRs as well as other relevant reports, such as the integrated analyses of safety that are routinely submitted in some regions. The aim is to clearly describe the safety profile of the product |
| Risk Evaluation and Mitigation Strategies (REMS) in the US or Risk Management Plan (RMP) in the EU | To succinctly describe how the risks of a product will be prevented or minimised in patients, provide plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine, identify risk factors for developing adverse reactions, and to explain how the effectiveness of risk minimisation activities will be measured |

Table 4: Key clinical documents prepared to apply for marketing authorisation

Summary

Throughout the clinical lifecycle of a medicinal product, a myriad of documents are needed to effectively plan, run and then assess and communicate the outcome of the clinical studies performed. Many of these documents are complex compilations of data and thoughts, and also function in conjunction with other documents – meaning they all need to tell a consistent story.

It is important to have experienced stakeholders on the authoring teams, including a medical writer who has the experience with the document types to know how to advise teams on the needs of a particular document and to guide authors through the review and revision process. Planning well in advance and ensuring enough time is given to the authoring teams to allow them to think about, discuss and craft documents that accurately reflect what the data have to say, will ensure that these documents are fit for purpose while making the writing activities less arduous for everyone involved.

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“ It is important to have experienced stakeholders on the authoring teams, including a medical writer who has the experience with the document types to know how to advise teams on the needs of a particular document and to guide authors through the review and revision process ”

About the author



After receiving her PhD in Developmental Neurobiology, **Julia Forjanic Klapproth** started her career as a medical writer in the regulatory group at Hoechst Marion Roussel (later Sanofi) in 1997. Since then, she has been president of the European Medical Writers Association twice. In 2002, Julia co-founded Trilogy Writing & Consulting Ltd, a company that specialises in providing regulatory medical writing. In addition to managing the company as Senior Partner, she writes a wide array of clinical documents including study protocols, study reports, and the clinical parts of CTD submission dossiers.

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Writing for Different Audiences

Medical writing is a wide-ranging discipline catering for a variety of audiences, from regulatory experts and healthcare professionals to the lay public. All medical writing must clearly communicate often complex facts and concepts, and this is underpinned by the fundamental principle of knowing your audience.

By Kerry Walker and Nicola Evans at Insight Medical Writing

Introduction

As a discipline, medical writing encompasses everything from the preparation of confidential clinical and regulatory documentation to lay summaries. In all medical writing, facts and concepts must be communicated in a clear, concise fashion. However, information can only be effectively communicated by use of language, style and content that is appropriate to the target audience. No reader likes to be faced with impenetrable wording. Equally the informed reader will not appreciate over-simplistic text.

The importance of telling a story is often overlooked in scientific writing; however, leading the reader through a logical, structured argument is more effective than simply listing facts. Good writing uses rhythm and pace to engage the reader. Although judicious use of short sentences can be effective, overuse can feel abrupt and disjointed. Conversely, long, overcomplicated sentences can be difficult to follow. Precision, as well as consistency in terminology and presentation, is also crucial in helping the reader understand key points and conclusions.

The target audience can be divided into three broad categories:

1. Regulatory bodies and pharmaceutical experts
2. Healthcare professionals (eg doctors, nurses and pharmacists)
3. The lay public not otherwise involved in the pharmaceutical or healthcare professions (eg patients)

While there are specific considerations and techniques that distinguish writing for each audience, many areas overlap (see Figures 1 and 2). For all audiences, however, the key to successful and appropriate writing is to be CLEAR (see table below). This article will discuss the techniques and requirements to effectively write for each audience.

Regulatory and Pharmaceutical Audience

Preparing regulatory documentation provides a fascinating challenge to the writer. While these documents are primarily for assessment by regulatory authorities, they represent the culmination of years of drug development on behalf of the sponsor. This considerable investment in time and cost is ultimately judged on the data and documents submitted. Thus, the production of high-quality documents is critical and can ensure smooth progress through submission and beyond.

Writing for regulatory assessment is distinct from writing for other audiences in that it involves the production of large submission packages that provide comprehensive information for in-depth review by regulatory authorities. While established guidelines and templates ensure that documents conform to predefined structures, the challenge is to craft an effective presentation of large bodies of data, highlighting benefits while maintaining transparency of potential risks and limitations. It is critical that content is presented in a clear, accurate and objective fashion. Effective cross-referencing is also essential to facilitate both navigation across documents and location of sources.

Linguistically, regulatory writing adopts a formal, scientific style, outlining the purpose and objectives of each document. Text, tables and figures should facilitate effective review by regulators. Appropriate scientific and regulatory terminology that is routinely accepted and/or standard practice should be used. A well-recognised example is the use of the Medical Dictionary for Regulatory Activities (MedDRA) instead of colloquial terms to describe adverse events.

Strategic document planning should commence early in the development process while always focusing on the final regulatory submission. Involvement of an experienced

| |
|--|
| C oncise, with an appropriate level of detail |
| L ogical, enabling the reader to follow the facts and arguments presented |
| E vidence-based, for scientific integrity |
| A ccurate, avoiding data or text errors |
| R eadable, by the target audience |

Key attributes of successful writing

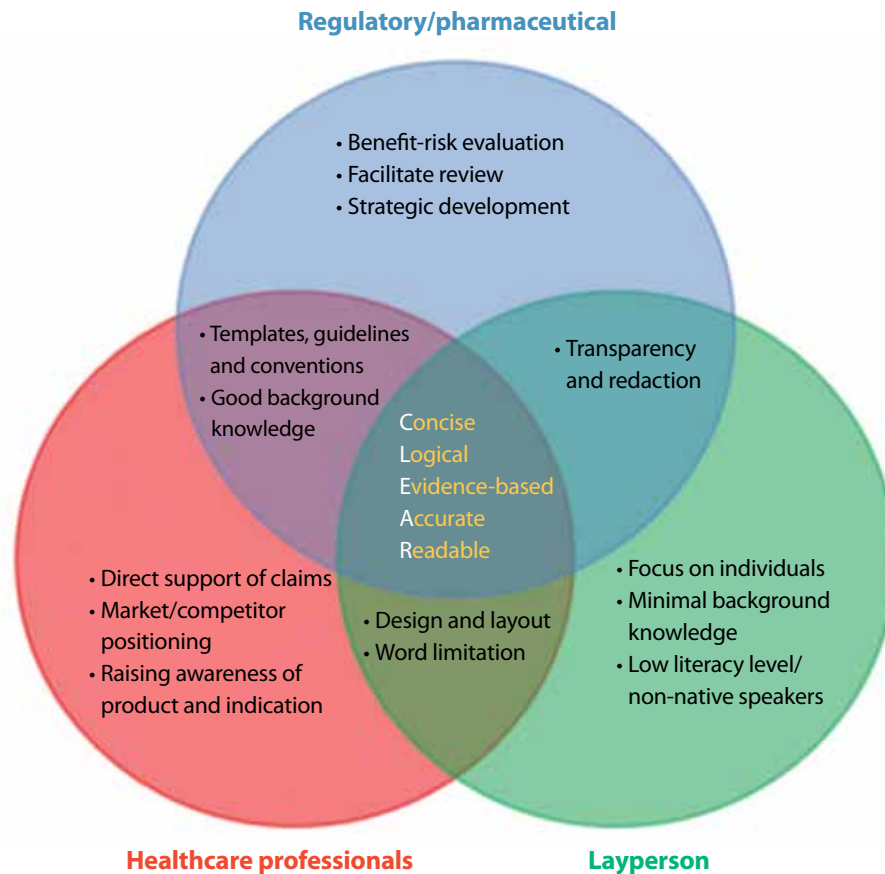


Figure 1: Writing considerations for different audiences

medical writing team can greatly enhance this process. For example, a well-designed and written protocol not only assists the running of the study and reduces the need for amendments, but also facilitates writing of the clinical study report (CSR) and ultimately the submission documents. Each document in the dossier should be written using a consistent style and approach to ultimately feed into the regulatory package.

Guidance

International guidelines, which suggest appropriate content and structure for regulatory documents, are an essential resource for every medical writer. Since submissions may be made to one of numerous competent authorities, awareness of national and international guidelines is vital. For example, the EU-specific Risk Management Plan (RMP) is defined in guidance from the EMA (1), and a template for the Canadian Product Monograph is provided by Health Canada (2).

While guidelines are not intended to be absolute requirements, their detailed nature means that, in practice, document templates tend not to deviate significantly from the format provided. Associated clarifications and work aids may also assist with interpretation of the original guidance. A notable example is the CSR guidance, ICH E3, which has recently been evaluated by the European and American

Medical Writer’s Associations together with other contributors. This initiative resulted in development of the Clarity and Openness in Reporting: E3-based (CORE) Reference user manual, which incorporates ICH E3, subsequent clarifications published in 2012, and suggestions to facilitate public disclosure of clinical trial results (3). An article specifically discussing this initiative is provided elsewhere within this supplement (see page 28).

For all dossiers submitted to the EMA since 1 January 2015, submission documents including the CSR, Clinical Summary, and Clinical Overview will serve two purposes (4). While still primarily intended for regulatory assessment, they are now to be made publicly available following redaction of information that is either commercially sensitive or might identify individual patients. Content for redaction is agreed in advance with the EMA; however, the medical writer will play an important role in the process. As anticipated in the CORE Reference, the challenge for medical writers will be to produce a ‘primary use’ CSR for regulatory review that pre-empts the need for later redaction by retaining data meaning and context, while anonymising patient information. Such a proactive approach will minimise the efforts needed to produce the ‘secondary use’ CSR intended for public disclosure, thereby improving both efficiency and transparency.

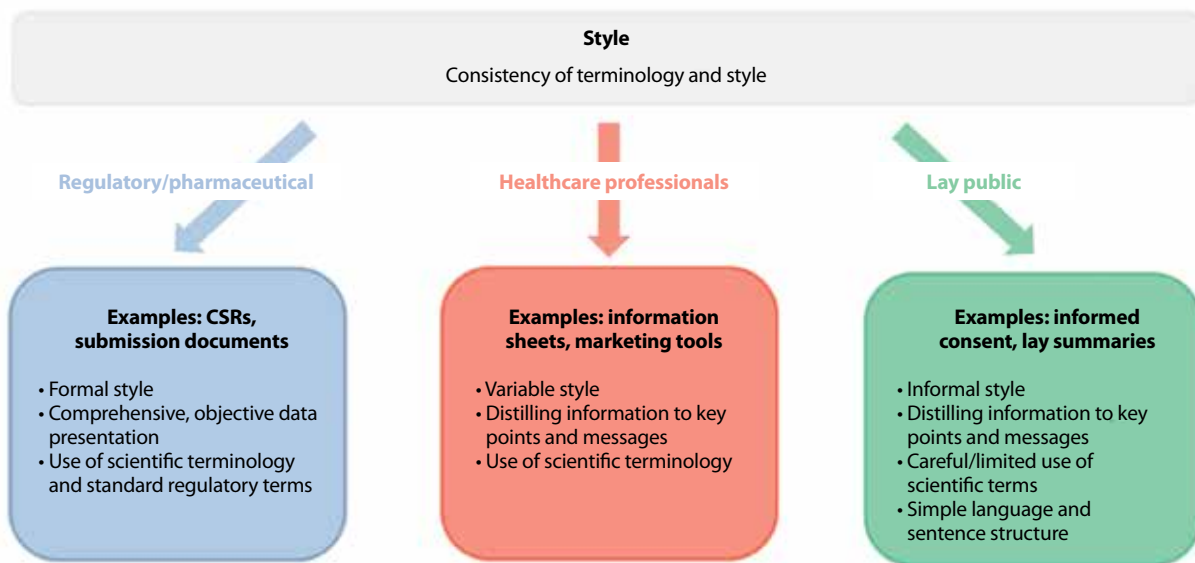


Figure 2: Writing style for different audiences

Healthcare Professional Audience

Effective communication between the pharmaceutical industry and healthcare professionals provides prescribers with the most recent, accurate information, and ensures that medicines are used safely and appropriately for maximum patient benefit. Successful product approval is of limited benefit if healthcare professionals remain unaware or unconvinced of its potential utility. While the best writing raises awareness and knowledge of new treatments, poor quality writing can mean that key messages are lost.

Similar to regulatory documentation, writing for healthcare professionals targets an ‘expert’ audience who will critically assess the information provided. Technical language is appropriate and the emphasis should be on accuracy. However, in contrast to regulatory documentation, information presented to healthcare professionals is necessarily abbreviated. Although publications in scientific journals must comprehensively discuss specific studies or data, information is ultimately constrained by word limits and can rarely be presented in the context of the overall clinical development programme. Direct marketing materials for healthcare professionals present an even greater challenge, as they must effectively convey key data to an audience that typically devotes a relatively small amount of time to communications from pharmaceutical companies. Writing for healthcare professionals therefore requires key data

to be communicated concisely to a time constrained audience, while providing sufficient detail for adequate assessment.

Industry Codes of Practice

It is widely acknowledged that trust in the pharmaceutical industry has declined in recent decades. Scepticism of pharmaceutical companies is reflected among healthcare professionals for a variety of reasons, including under-reporting of negative results (5). When presented with trials of hypothetical drugs, doctors downgraded the rigour of an industry-funded clinical trial and had less confidence in the results compared to a similar quality trial with no funding disclosure or with support from the National Institutes of Health (6). Restoring faith in communications to healthcare professionals is central to rebuilding industry trust. To this end, guidelines outlining good practice for healthcare communications are available.

In the US, many major pharmaceutical companies are signatories to the Pharmaceutical Research and Manufacturers of America (PhRMA) Code on Interactions with Healthcare Professionals (7). Central to the code is that promotional materials should be accurate and not misleading, claims should be substantiated, and information should both reflect the risk-benefit balance of the product and be consistent with other FDA requirements governing communications. These principles are also reflected in the Association of the

“ Although publications in scientific journals must comprehensively discuss specific studies or data, information is ultimately constrained by word limits and can rarely be presented in the context of the overall clinical development programme ”

British Pharmaceutical Industry (ABPI) Code of Practice, which indicates that communication materials must be "... appropriate, factual, fair and capable of substantiation and that all other activities are appropriate and reasonable" (8). The code also includes detailed criteria for the content and structure of pharmaceutical advertising.

Given the condensed nature of direct marketing materials, providing sufficient information for assessment of risk-benefit as required by the PhRMA and ABPI codes of practice may be daunting. However, the scientific knowledge inherent in this audience may be exploited to minimise unnecessary explanation. Lengthy paragraphs can be reduced to short bullet points and 'call out' text can highlight key data. The widespread use of electronic devices allows key data to be supported by further detail that can be accessed when required; however, high-level summaries must be self-contained and remain accurate when more detailed information is not displayed. Good design and layout are critical, and close collaboration between experienced writers and designers can ensure appropriate emphasis is given to the information presented.

In contrast to direct marketing materials, articles in scientific journals must provide detailed information that is sufficient for replication of the reported work. Guidance to ensure legally compliant, ethical and transparent publication of company sponsored research is provided by the *Good Publication Practice* (GPP) guidelines, developed by the International Society of Medical Publication Professionals and first published in 2003. The latest iteration (GPP3) was published in 2015 and key principles include the reporting of clinical trials in a "...complete, accurate, balanced, transparent, and timely manner", avoiding duplicate publication, appropriately reflecting the collaborative nature of research, and defining author and sponsor responsibilities (9). The GPP guidelines have been widely adopted by medical journals, and updates include changes to the criteria for authorship and clarification of the role of professional medical writers.

Information for comprehensive reporting of randomised clinical trials, as required by GPP3, is specified in the Consolidated Standards of Reporting Trials (CONSORT) Statement and checklist (10). Although adopted by many medical journals, compliance with the CONSORT checklist is frequently lacking in published articles (11). Increasingly, supplementary information is made available online to provide the required detail and transparency. Nevertheless, inclusion of CONSORT-required information while adhering to journal word counts and maintaining readability is often challenging. It is perhaps unsurprising that the involvement of professional medical writers may assist in achieving this (11).

Scientific posters and publications share common ground with regulatory documents and direct marketing materials. As for regulatory documents, comprehensive information should be presented using a formal style. However, like direct

marketing materials, the primary constraint is word limit. The assumption of good scientific knowledge allows text to focus on concepts and details that may be particularly relevant to a specialist field. Figures and tables are used not only to summarise, but also to highlight key data.

Lay Audience

Historically, writing for the lay public has included patient education materials, package leaflets, informed consent and medical journalism. In all cases, text should be sensitive to the needs of the reader while remaining engaging and interesting. To account for variations in literacy levels and understanding, simple language should be used and scientific terms, acronyms and jargon avoided or explained.

Package leaflets and informed consent forms are documents traditionally written for the layperson. However, there is evidence that even these well-established documents may be written at too high a reading level and may be improved to increase patient understanding (12,13).

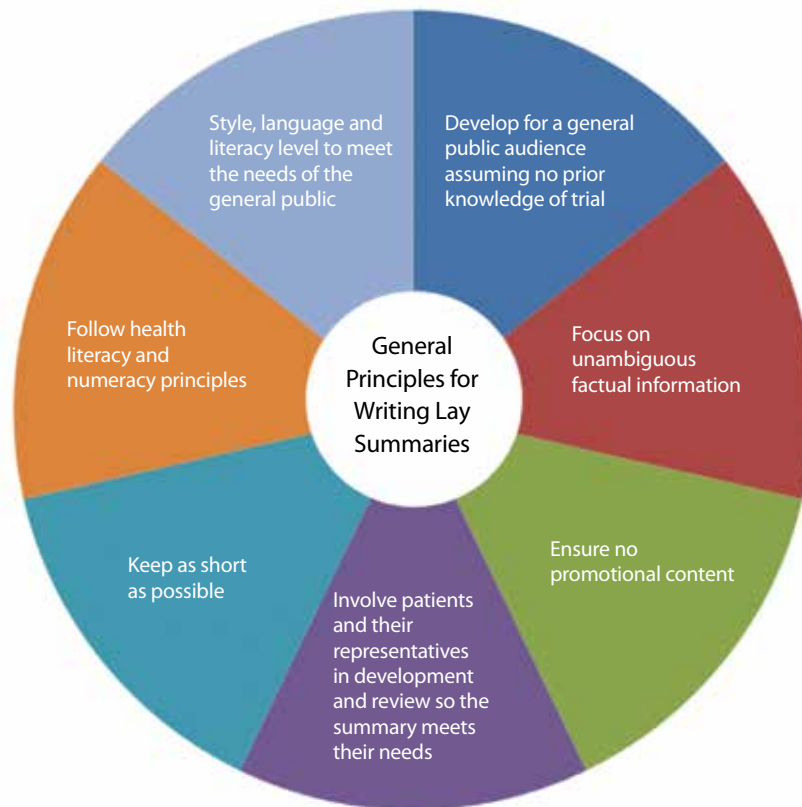
Alongside the more traditional writing for lay audiences, the rapid development of web-based information sources has resulted in greater patient demand for healthcare information. In recent years, regulators and the pharmaceutical industry have increasingly recognised the importance of making information on healthcare products accessible to the general public. Stakeholders and patient organisations have indicated that although participants are interested in the outcomes of the studies they entered, they receive little if any subsequent information following study completion. Notably, however, the most recent iteration of the Declaration of Helsinki stipulates that "All medical research subjects should be given the option of being informed about the general outcome and results of the study" (14).

Guidance

In the last decade, legislation in the US and EU has provided for the dissemination of clinical trial summary data within the ClinicalTrials.gov and EU Drug Regulating Authorities Clinical Trials (EudraCT) databases, respectively, and has also specified the production of clinical data lay summaries for European RMPs and clinical trials.

Building on content outlined in European legislation for clinical trials, a position document published by the European Patient's Forum proposed that the clinical trial lay summary should also include (15,16):

- Details on study limitations, including steps to address bias
- Description and rationale for study endpoints
- Protocol modifications
- Details of any patient engagement in the setting of research priorities



Source: Summary of clinical trial results for laypersons (17)

Figure 3: General principles for writing lay summaries recommended by the EU expert group on clinical trials

In 2016, the expert group on clinical trials provided a consultation document outlining recommendations and templates for those producing lay summaries for the EU database (17). The general principles established in this document are presented in Figure 3.

Healthcare literacy is possibly the biggest challenge in presenting clinical data to the layperson. The expert group recommendations indicate that text should be aimed at an International Adult Literacy Survey proficiency level of 2-3 (ie low to average levels of literacy), corresponding to a Flesch Reading Ease test score of 70 or higher, or a Flesch-Kincaid Grade Level as close to 6th grade level as possible. Language should be made accessible by avoiding complex sentences

and technical terms. Nevertheless, balancing accuracy and understanding remains key in maintaining text that is readable for the layperson. For example, when describing neutropenia, an important safety concern for many drugs, directly translating to 'reduction in white blood cells' may not be sufficient. It may be necessary to explain that white blood cells are responsible for fighting infection, and therefore a reduction in these cells will make a patient more prone to serious infection.

Of note, the recent EMA guidelines on the EU RMP (18), anticipated to come into effect shortly, specifically indicate that although the summary section "...should be written and presented clearly, using a plain-language approach..." this

“ Alongside the more traditional writing for lay audiences, the rapid development of web-based information sources has resulted in greater patient demand for healthcare information. In recent years, regulators and the pharmaceutical industry have increasingly recognised the importance of making information on healthcare products accessible to the general public ”

does not mean that technical terms should be avoided". This guidance may seem contradictory to the perceived wisdom that scientific terminology and jargon should not be used. However, patients may benefit from understanding the medical term that describes their condition and from awareness of terms they may hear during medical consultations. In such cases, a scientific term may be followed by a brief explanation. Thus, writers should focus on avoiding excessive or unnecessary use rather than eliminating all scientific terms.

Contrary to documents written for 'expert' audiences, use of the active voice is appropriate in lay summaries (ie 'doctors treated patients' rather than 'patients were treated by doctors'). Crucially, sentences must also maintain neutral, non-promotional language. The European expert group recommendations on lay summaries cite guidance from the Multi-Regional Clinical Trials Center of Harvard and Brigham and Women's Hospital Return of Results Toolkit, produced to facilitate writing result summaries in lay language (17,19). The Toolkit also contains a suggested template, and clear guidance on neutral language, which is reproduced in the recommendations.

Summary

The constant evolution in the requirements for healthcare communication means that medical writers are continually required to present vital information to an ever broader range of readers. In targeting different audiences, a medical writer must be able to adapt language, terminology and presentation to communicate complex concepts and data to the particular requirements of the reader. However, while writers must be aware of the distinct differences in style and content required, a commitment to clarity, accuracy and quality is essential for effective and regulation-compliant medical writing, whatever the audience.

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Clinical Study Protocols: How to Write to Solve Problems Now and Avoid Big Ones in the Future

Too many protocols are poorly written – wrought with inconsistencies in endpoint descriptions, timing of assessments, approaches to gathering data – and lacking consistency across the programme. The identification of different responsibilities, under the clear leadership of the medical writer, is necessary to improve the quality of clinical study protocols – to prevent problems and mistakes that can result later, during conduct of the clinical trial, or afterwards, when reporting on trial results.

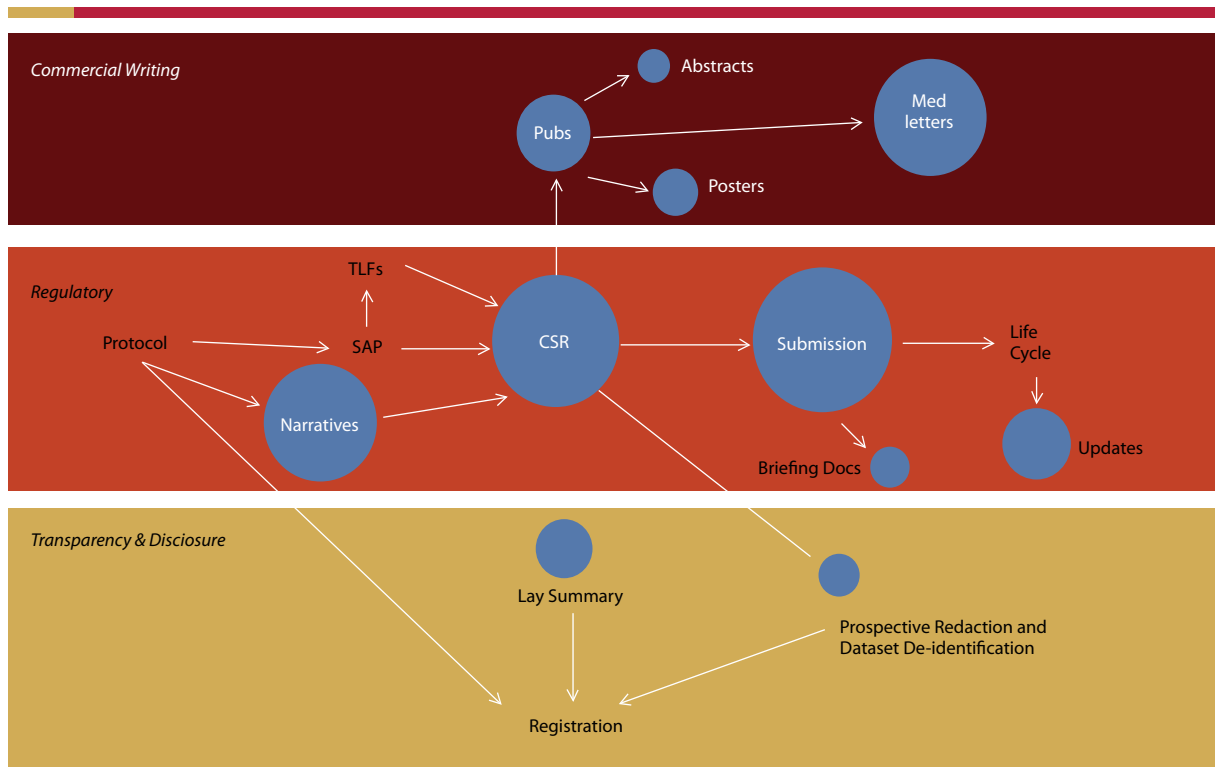
By Kelley Kendle
at Synchrogenix

Historically, protocol generation has been the responsibility of clinical and operations teams, who are understandably focused on ensuring that the appropriate data are identified for collection to support the study objectives and that the study is initiated as quickly as possible, often with the mindset that any inconsistencies will be corrected in future amendments. These poorly written protocols present challenges both during the study, when site personnel try to understand the requirements of an inconsistent document, and after the study, when clinical study report and submission document writers try to understand, and are often forced to re-write inconsistent study design and assessment descriptions.

In addition to these existing challenges, the growing requirements for disclosure and transparency are driving the need for additional thought and care in protocol development to ensure that the value of the information obtained in a study is balanced with the patient experience. Protocols, historically unlike any other regulatory document, have various audiences such as the Private Investigator, study coordinator, regulator and the patient at heart. Writing protocols consistently and clearly, from the first version, requires ownership of the process that understands the various goals of a protocol document and can provide the consideration, quality, and leadership that will ensure that these downstream challenges

| | |
|----------------------------|---|
| Strategy and design | The protocol accurately reflects the objectives of the study. It is clear and consistent and has the correct assessments to determine the success of the study |
| Ethics | The protocol has been drafted with ethical considerations in mind. The study takes into consideration the patient experience and the concerns or reservations of individual patients both for ethical reasons and to ensure feasibility of recruitment |
| Re-usability | The protocol is optimised for re-usability in downstream documentation. From registration of the protocol to the extension of the protocol into the statistical analysis plan and clinical study report, relevant considerations have been explored to address how the protocol is being written for the ease of the next steps in documentation (eg description and selection of endpoints) (see Figure 1) |
| Process/controls | Process and controls have been agreed upon and implemented. Decisions regarding where the protocol will “live,” who owns the core protocol and amendment, strategies and technology solutions for maintaining version control, and the process for obtaining approval have been made and are being followed |
| Alignment | The protocol is aligned with all relevant company standards and associated documentation. It is consistent with applicable style guidance, similar approaches and descriptions within the same programme, the informed consent form (ICF), and the CRF. The protocol should be able to function as the starting point for the lexicon for the entire programme, which should carry all the way through to marketing application |
| Innovation | The protocol includes thoughtful input from multiple functions regarding both the design and assessments as well as relevance of that design and those assessments across the clinical programme (eg leveraging ideas across therapeutic areas and programmes, reducing the tunnel vision of the clinical teams, exploring new tolerances by the regulatory health authority (eg modelling and simulation to support some objective and end points), collecting certain data that will be valuable to contribute to a future bridging analysis etc) |
| Time | Everyone on the protocol team has had the opportunity to spend the necessary time and focus on performing the tasks that bring their highest value |

Table 1: Fundamental goals of protocol writing



Source: Certara, 2015

Figure 1: Protocols are the foundation of the clinical programme

are minimal, re-usability of the content is high, and rework, including additional clinical interpretation, is low.

“The first step in any clinical study is the protocol; if that first step is organised, well-placed, and developed with the downstream activities in mind, the rest of the journey will go that much more smoothly”

Jen Moyers, Protocol Workstream Lead

Protocol creation, including document standards and drafting processes, is part of an ongoing and lively debate that generally exists between two camps: the clinical and operations functions and centralised medical writing. The clinical and operations functions own the content of protocols and tend to prioritise study design elements and consistency with other downstream documents (eg the case report forms (CRFs) and risk monitoring plans), with a goal of initiating the study as quickly as possible. In contrast, the centralised medical writing functions tend to focus on internal document consistency, clarity of thought, downstream re-usability in other areas of the dossier, and adherence to company standards. As always in these kinds of debates, the two sides tend to focus on either/or solutions, where one side is right and the other wrong, when a better solution can usually be found somewhere in the middle. Ensuring that the fundamental goals of the protocol remain the focus throughout protocol development will help ensure that a quality protocol is generated, from the first version. These fundamental goals include those listed in Table 1.

With all of these fundamental goals to consider, it is clear that there needs to be an understanding of the ownership and value of each. The owners of process and content knowledge are usually the medical writing or regulatory functions. The clinical and operations functions are focused on selecting the optimal design and getting the study started, as they should be. However, the coordination of efforts necessary for protocol creation, in addition to the time commitment required, is often more than the clinical and operations functions can handle in addition to their existing priorities. Therefore, when these functions are also the owners of a process, that process is frequently cut short in an effort to progress the document, often leading to unnecessary amendments and issues downstream in the reporting phase. This can result in a study that generates inconclusive data, extension of study timelines to collect additional measurements, inconsistencies that require explanation to health authorities, and more involved quality assurance activities, all requiring additional costs and potentially putting the programme at risk.

With the rise of patient centricity, there is also a need to engage the patient community and advocates to enhance feasibility and to get perspective on the key objectives and the measures to which we are willing to go (or not to go) to collect them. The role of clinical operations is critical to drive this process, engaging with the patient community and focusing on getting the clinical sites up and running. Clinical trials are increasingly more complex, often weaving collection of data for biomarkers, imaging biopsies,

| |
|--|
| Strategy and design |
| Ethical obligation and consideration |
| Coordination of the ICF and CRF |
| Alignment across programmes |
| Process and style |
| Lifecycle and communication of changes |
| Cross-functional review: transparency and disclosure |

Table 2: Responsibilities to be assigned when preparing protocols

“ In the past few years, we have seen an organisation go from clinical and operations protocol ownership and resistance to medical writing participation, to fully embracing of the role of a medical writer in the process, to finally creating their own writing team focused on protocol creation and lifecycle ”

pharmacokinetics, etc into the classic objectives of a study. For this reason, the clinical operations team needs to focus on ensuring the planned activities of the study are feasible, can be adhered to by study staff and participants, and align with study goals. The medical writers will ensure these activities are clearly and consistently communicated in the protocol. It is imperative that both sides work together as a cohesive team, trusting and relying on each other to provide their respective inputs in the areas of their particular expertise.

In the past few years, we have seen an organisation go from clinical and operations protocol ownership and resistance to medical writing participation, to fully embracing of the role of a medical writer in the process, to finally creating their own writing team focused on protocol creation and lifecycle. This not only shows the value of the medical writer contribution to improving clarity and the ability to meet timelines, it also shows that including perspective outside of the study team can bring valuable insights and innovation to the study design and conduct.

In addition, the integration of a medical writer into protocol writing often includes the review of the ICF and CRF, and cross-functional reviews including a transparency/

disclosure representative. This bridges the strength that a medical writer can bring to the table (clarity, consistency, adherence to process, coordination of reviews, balance of objectives of speed and completeness, and creation of the building blocks for downstream documentation) while allowing the clinical and operations functions to be critical reviewers, owning the design and feasibility, bringing in the patient perspective and understanding of the disease, and focusing on the training and set up of sites. This also allows for coordination across studies if amendments are needed once a study has been started.

Regardless of your organisation's size, it is critical that you clearly define the necessary responsibilities and owners. Consider who in your organisation would be considered the owner of the responsibilities listed in Table 2.

For most protocols, a combination of functions/ roles is responsible and accountable for each of these responsibilities. Determining the owners of each and realising that these fundamental elements will carry through the programme for the length of its existence is critical. Focusing on the fundamental goals for your protocol, defining responsibilities, and identifying owners will ensure that quality protocols are generated, without the need for amendments... solving problems now and avoiding them in the future.

About the author



A long-tenured executive with Synchronix and a strategic regulatory solutions provider, **Kelley Kendle** possesses a keen understanding of the regulatory landscape, coupled with a strong focus on client relationships. She has been instrumental in developing solutions to address the industry's needs. With over 15 years of experience in drug development, Kelley is both an internal and external subject matter expert. As President, she is responsible for driving Synchronix's strategic growth, including mergers and acquisitions, business process, and organisational dynamics.

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Streamlining Clinical Study Protocols and Reports

Recent pharma initiatives have been established to help ensure that clinical study protocols and reports are always presented in a similar way, making for easier assimilation and assessment. This article discusses these initiatives, and outlines their key recommendations.

By Sam Hamilton at Sam Hamilton Medical Writing Services and Julia Forjanic Klapproth at Trilogy Writing & Consulting

As we have seen in earlier articles in this magazine, ICH guidelines help ensure that the same critical types of information are included in appropriate clinical documentation (including clinical study protocols [CSPs] and clinical study reports [CSRs]), but they do not guarantee that this information is always presented in a similar way. This means that regulatory reviewers have to interpret numerous documents about all kinds of medicines, which may differ not only because of their specific therapeutic area content requirements, but also because information requirements that are common across programmes are presented in different ways. It is therefore difficult to gain a clear understanding of the data generated across an industry. The effort needed to extract and compare data from one programme to the next – even within a single therapeutic area – can be enormous. Despite this, the reviewer must assess if each new drug would be a valuable addition to the existing armamentarium of medicines.

In the past 12 months, two initiatives have come to fruition that will help streamline the writing of CSPs and CSRs. These are the TransCelerate Common Protocol Template (CPT) and the

CORE (Clarity and Openness in Reporting: E3-based) Reference. Both aim to produce CSPs and CSRs of common structure and layout, with standard information in just one, consistent place. They aim to simplify the review task enormously and improve transparency, making it immediately apparent if information is missing or incomplete. The goal is to save time in developing documents and in drug development generally, as writing teams dispense with discussing options for the structure of the standard elements of a particular document, and focus on content. So is this a pipe dream?

TransCelerate Common Protocol Template

The new CPT was issued by TransCelerate in December 2015 (1). The TransCelerate group is a collaboration between industry stakeholders and regulators who had the idea of producing a definitive template for the CSP, regardless of the type of treatment or therapeutic area being studied. Each company approaches CSP writing slightly differently: should the description of all the variables be in the statistics section

What is the TransCelerate CPT?

The CPT is a detailed protocol template, including pre-prepared headings and draft text, in Microsoft Word format. It is intended to be used directly by authors of CSPs for any kind of clinical study, involving any kind of medical condition or therapy. The goal is that all protocols present equivalent information in a similar manner. The Word template contains sections marked as common text or text that may be employed across CSPs with little to no editing if the author so chooses. Clearly, the use of the template is at the discretion of the author.

For the preparation of a CSP, the CPT implementation toolkit includes the resources listed in the table below (2):

| Resource | Description | Comments/value of using |
|---|---|--|
| Word CPT Guidance for use | A detailed Word document that contains instructions and brief videos demonstrating selected steps in the use of the technology-enabled edition of the CPT | Provides understanding of the functionality found in the technology-enabled edition of the CPT |
| Frequently asked questions | Frequently asked questions and responses about the CPT, how it was developed and how it will be maintained | Access to responses on common questions |
| Mapping exercise – instructions and worksheet | A tool to facilitate comparison of an existing protocol template to the CPT | Allows for section-by-section identification of differences in headings and content to aid in assessing impact of implementation and possible mitigations needed |
| Stakeholder map | A customisable tool to assess the impact that implementation of the CPT may have on each stakeholder group | Allows those implementing to plan for appropriate training and communication needs |
| Text colour guide | Colour coding used within the CPT to distinguish common, suggested example and instructional text | Provides understanding of the meaning of colour coding used |

or in the investigational plan section? Where should details of the various parties involved in performing the clinical study appear – in an appendix, at the front or somewhere in the middle? As long as the information is there, its location is immaterial – as evidenced by the fact that CSPs are approved and the studies run, despite all this variation. So why not agree on one approach, and use the time saved to focus on other, more important things? Training medical writers would be less time-consuming; writing and review time would also be shortened.

So what does the TransCelerate CSP template give us? At a minimum, it offers a model CSP template defining a common structure and standardised language. Its intended use with libraries of common language in areas specific to patient populations and therapeutic areas means that the pre-crafted text proposals for many sections will be the same across CSPs. Ultimately, the industry can save the time spent pondering redundancies and instead focus on study-specific content. Co-author and end user review will be streamlined as familiarity with these standardised texts grows. Regulatory reviewers will more rapidly navigate to the meaningful, study-specific content and comparison of CSPs across programmes will be enhanced, such that the input from ethics committees/institutional review boards and regulators will be more focused. Investigators and study staff will more readily find the information they need, which may translate to efficiencies in terms of study performance.

CORE Reference

Another new tool – released in May 2016 for CSRs – is CORE Reference, designed to streamline the way the industry structures and populates a CSR. The international basis for CSR content is laid out in the 1995 ICH regulatory guidance document ICH E3 on the structure and content of CSRs (3), and the 2012 ICH E3 supplementary Q&As (4). However, any guidance or reference material is reflective of a static time point and, back in 1995, clinical studies were simpler than they are today. Modern clinical study designs often integrate pharmacokinetic, pharmacodynamic, pharmaco-economic and pharmacogenomic elements with a safety and efficacy backbone. Today's clinical studies need a fit-for-purpose reporting framework that may differ

What is CORE Reference?

CORE Reference is a user manual to help medical writers navigate guidelines as they create CSR content relevant for today's studies. It comprises a preface followed by the actual resource, which includes the following:

- Text from the original ICH E3 guidance document is shown in unboxed grey shading
- Text from the ICH E3 Q&A 2012 guidance document is shown italicised, grey shaded and boxed
- CORE Reference text is not shaded and not boxed

A separate mapping tool compares ICH E3 sectional structure and CORE Reference sectional structure. Together, CORE Reference and the mapping tool constitute the user manual (5).

“ So what does the TransCelerate CSP template give us? At a minimum, it offers a model CSP template defining a common structure and standardised language. Its intended use with libraries of common language in areas specific to patient populations and therapeutic areas means that the pre-crafted text proposals for many sections will be the same across CSPs ”

substantially from the more straightforward efficacy and safety studies of 20 years ago, which ICH E3 set out to support.

The ever-growing regulatory guidances dictate additional content requirements that must be worked into CSRs. The medical writer must be extraordinarily diligent and well informed to keep pace. Specifically, public disclosure of CSRs – now mandated in the EU – has profound effects on the way that we must write CSRs. EMA guidance on preparing clinical data for disclosure explains that because redaction alone will “decrease clinical utility of the data compared to other techniques”, it strongly encourages the move towards proactive anonymisation techniques (6). The impacts on the CSR are multiple and complex, and lessons will be learnt as CSRs are disclosed.

Key Areas in which CORE Reference adds to ICH Guidelines

CORE Reference makes content suggestions for the primary use CSR (the EMA term is 'scientific review version'). Comments are used to indicate individual report text portions that may potentially impact the secondary use CSR (the EMA term is 'redacted clinical report') and should, therefore, be considered for redaction in the secondary use CSR – for public disclosure.

CORE Reference mapping tool provides the sectional structure of CORE Reference, but the important areas where CORE Reference advises restructuring and greater granularity of CSRs are as shown in the table which follows:

| ICH E3 section | Key CORE Reference section differences |
|---|--|
| 8 – Study Objectives | New granularity: 8.1 – Objectives 8.2 – Endpoints |
| 9.4.1 – Treatments Administered | New granularity: 9.4.1.1 – Investigational Products 9.4.1.2 – Non-Investigational Products |
| 9.5.1 – Efficacy and Safety Measurements Assessed and Flow Chart | New granularity: 9.5.1 – Efficacy and Safety Measurements Assessed and Schedule of Assessments 9.5.1.4 – Safety – Adverse Events 9.5.1.5 – Safety – Clinical Laboratory Evaluation 9.5.1.6 – Safety – Vital Sign Measurements 9.5.1.7 – Safety – Physical Examination 9.5.3 – Pharmacokinetic and Pharmacodynamic Measurements 9.5.3.2 – Pharmacokinetic Parameters 9.5.3.3 – Pharmacodynamic Measurements 9.5.3.4 – Pharmacodynamic Parameters 9.5.4 – Other Measurements |
| 9.7.1 – Statistical and Analytical Plans | New granularity: 9.7.1 – Statistical Plans 9.7.1.1 – General Approaches 9.7.1.2 – Primary Efficacy Endpoint Methodology 9.7.1.3 – Secondary Efficacy Endpoint Methodology 9.7.1.4 – Other Efficacy Endpoint Methodology 9.7.1.5 – Safety Endpoint Methodology 9.7.1.6 – Pharmacokinetic and Pharmacodynamic Endpoints Methodology 9.7.1.7 – Other Endpoint Methodology |
| 9.8 – Changes in the Conduct of the Study or Planned Analyses | New granularity: 9.8.1 – Changes in the Conduct of the Study 9.8.2 – Changes in the Planned Analyses 9.8.3 – Changes Following Study Unblinding and Post-hoc Analyses |
| 11.1 – Data Sets Analysed (Efficacy Section) | Moved to 10.3 – Data Sets Analysed – new Study Subjects, Section 10 |
| 11.2 – Demographic and Other Baseline Characteristics (Efficacy Section) | Moved to 10.4 – Demographic and Other Baseline Characteristics – new Study Subjects, Section 10. New granularity added: 10.4.1 – Demography 10.4.2 – Baseline Disease Characteristics 10.4.3 – Medical History and Concurrent Illnesses 10.4.4 – Prior and Concomitant Treatments |
| 11.3 – Measurements of Treatment Compliance (Efficacy) | Moved to 10.5 – Measurements of Treatment Compliance in Study Subjects – new Study Subjects, Section 10 |
| 11.4 – Efficacy Results and Tabulations of Individual Patient Data | Becomes Section 11.1 – Efficacy Results |
| 11.4.1 – Analysis of Efficacy | Becomes Section 11.1 with new granularity: 11.1.1 – Primary Efficacy Endpoint 11.1.2 – Secondary Efficacy Endpoints 11.1.3 – Other Efficacy Endpoints 11.1.4 – Post-hoc Analyses |
| 11.4.6 – By-Patient Displays | Not included |
| 12 – Safety Evaluation | ICH E3 Section 12.1 – Extent of Exposure – becomes CORE Reference Section 10.6 – Extent of Exposure – new Study Subjects, Section 10 (Remainder of Section 12 renumbered accordingly; some additional granularity) |
| 12.2.4 – Listing of Adverse Events by Patient | Not included |
| 12.5 – Vital Signs, Physical Findings, and Other Observations Related to Safety | Becomes Section 12.4 due to renumbering (see above), with new granularity: 12.4.1 – Vital Signs 12.4.2 – Physical Examination Findings 12.4.3 – Other Observations Related to Safety |
| 13 – Discussion and Overall Conclusions | New granularity: 13.1 – Discussion 13.2 – Conclusions |
| Annexes | Annexes I, IIIa, IIIb, IVa, IVb, and VII adapted and moved into the document body |

In short, writers must create CSRs that support heterogeneous study design and cover all emergent content requirements, including public disclosure requirements. ICH E3 and the 2012 Q&A allow flexibility in CSR structuring to suit individual study design. Without a common approach, designing a logical CSR framework for individual studies inevitably results in variable report structures.

CORE Reference is an open-access “user manual to help medical writers navigate relevant guidelines as they create CSR content relevant for today’s studies” (5). It is not a template; rather, it presents the focused guidance-required content with other value-added insights, and organises it all into a logical presentational sequence. CORE Reference additionally suggests intelligent anonymisation approaches that will minimise redaction requirement in the publicly disclosed CSR, and pinpoints these within individual CSR suggested sections. In focusing on content and providing suggested common structure, CORE Reference facilitates a content-driven document that is as disclosure-ready as possible. With sufficient uptake, it has the potential to drive standardisation of CSR writing across the industry.

Collateral impacts on the overall drug licensure process from efficiencies gained on individual CSR structural planning and content considerations should positively impact time to market and development costs. Of course, any resource can only remain relevant if it is updated on an as needed basis. This is a stated aim for CORE Reference (7). Indeed, CORE Reference end users (including CROs and pharma) are beginning to report on the utility of CORE Reference to develop their existing CSR templates. The website supports sharing of disclosure feedback received from the EMA, and this will be fed back into the project to provide industry-wide insight on how best to make each CSR meet the EMA’s expectations.

Some four months after CORE Reference was launched, the US Department of Health and Human Services published the Final Rule on clinical trials registration and results information sharing – effective from 18 January 2017 – which mandates posting of clinical trial results information on CT.gov (8). Although the detailed requirements will not impact results reporting in CSRs *per se*, signposting to these requirements (as already done for similar EudraCT results posting requirements) in a future version of CORE Reference will add tangible value in managing registry postings alongside the writing of CSR results content.

Conclusion

In an industry crying out for standardisation of its documents, these two valuable tools will help streamline the production of two essential documents, the CSP and the CSR. Although in some quarters they may not be seen as perfect – because they break with long held convention

and culture – if we can overcome personal preferences and aspire to a higher goal of true standardisation, it could simplify processes, reduce the cost of developing drugs and accelerate getting them to market. This would be real progress that benefits patients.

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The Challenge of CTD Submissions and Responding to Questions from the Authorities

The Common Technical Document is an international standard for the summary documents needed to obtain regulatory approval of medicinal products.

These summary documents involve presenting key information drawn from a large body of data, with input from a range of stakeholders within a project team. The challenges involved in preparing a CTD submission are numerous, and for medical writers will vary according to dossier size, team experience, data complexity and time available. By having insights on all these aspects and proactively seeking pragmatic solutions to issues as they arise, medical writers can guide the project team towards the goal of delivering the final set of summary documents within the agreed timelines.

By Douglas Fiebig at Trilogy
Writing & Consulting

The Common Technical Document (CTD) is not a single document as the name implies, but an international standard published by the ICH that specifies the structure, content and format of summary documents used for obtaining regulatory approval of medicinal products.

The standard covers the entire spectrum of documentation to be included in a regulatory submission dossier, and provides guidance on how formulation and manufacturing information ('quality') as well as the results of non-clinical and clinical research should be organised and presented. The submission dossier is divided into five modules. Conceptually, the overall structure can be regarded as a pyramid, with study reports providing the most detail at the base and an increasing level of summarisation towards the apex (see Figure 1).

The highest level of summarisation is the region-specific prescribing information, the 'label', included in Module 1. The components included in Modules 1-5 vary according to the type of approval being sought, eg from a large, complex dossier for a new chemical entity to a small, straightforward dossier for a label change. From a medical writing perspective, the authoring involved in preparing a CTD submission is typically for the summary documents included in Module 2.

The electronic CTD (eCTD), which is based on the CTD, is the electronic standard published by the ICH for organising and submitting CTD documentation to regulatory authorities. From the medical writing perspective of the summary documents in Module 2, there is no difference between a CTD submission and an eCTD submission.

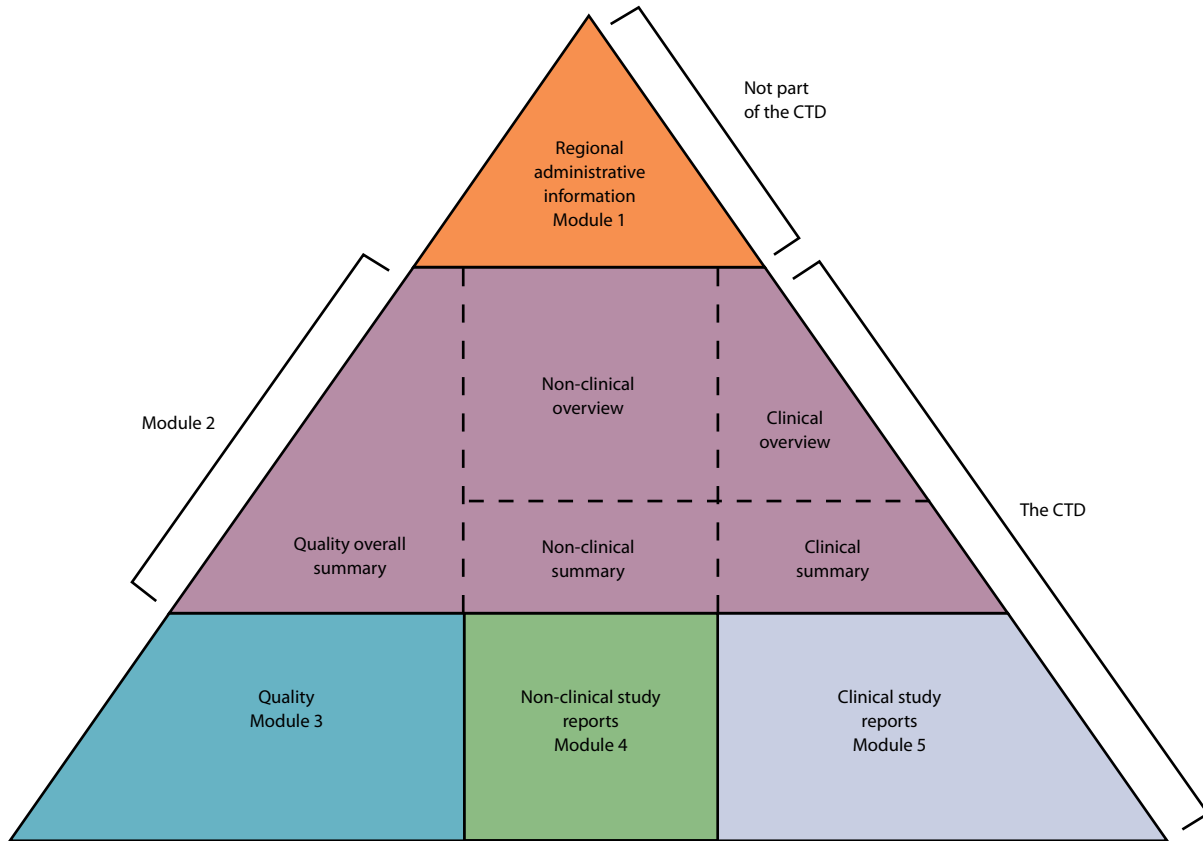
Preparation of a CTD is often regarded as the epitome of regulatory medical writing due to its complexity and the experience needed. The challenges involved are numerous,

and for medical writers vary according to dossier size, team experience, data complexity and available time. Typically, the challenges confronting medical writers preparing a CTD are similar irrespective of whether they are summarising manufacturing information (based on Module 3), non-clinical information (based on Module 4) or clinical information (based on Module 5). In all but the smallest dossiers, these areas will likely be covered by separate medical writers or separate teams of medical writers. The focus of this article is on medical writing needed for preparing and summarising clinical documentation, which typically constitutes the largest part of a submission dossier.

The Team Approach

Substantial hands-on experience of writing regulatory documents through to completion is an essential prerequisite for medical writers working on a CTD. To lead the medical writing effort, the writer must have substantial experience of writing CTDs (not just reviewing them), because this is the only way to gain the experience needed to visualise the finalised dossier and manage the multiple work streams required to achieve it. Support writers should, at least, ideally have had the hands-on experience of writing other regulatory documents, such as clinical study reports and investigator brochures.

For a larger dossier, the lead writer will typically need to assemble a team of writers with responsibility for writing various components of the clinical documentation. In this constellation, the clinical summaries (Module 2.7), encompassing the four key topics of biopharmaceutics, clinical pharmacology, efficacy and safety, may each require a separate writer. Each of these writers may also contribute to the clinical overview (Module 2.5), or the clinical overview may need a dedicated writer.



Source: www.ich.org/products/ctd.html

Figure 1: The CTD pyramid describing the organisation of a regulatory submission dossier

At this stage, it already becomes clear that the lead writer plays a key role in project logistics. The individuals on the writing team may each be interacting with different members of the project team as a whole (eg representing the clinical, clinical pharmacology, statistics, regulatory and non-clinical functions), and close coordination of the writing team is required from the outset to ensure scientific and technical consistency across the dossier. An example of the potential complexity of a CTD – including interconnectivity between documents and the overview that the lead writer needs to maintain throughout the process – is provided in Figure 2.

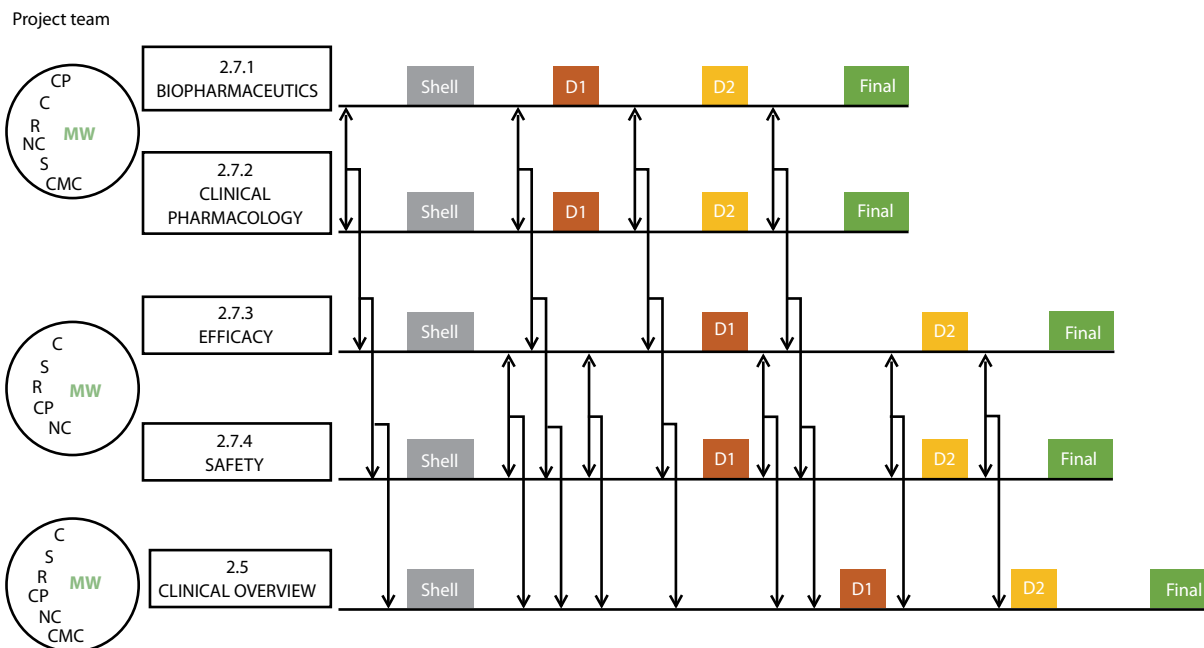
A first step in this coordination is a series of kick-off meetings, which aim to clarify details of the dossier and drive the design of the shells for individual summary documents. Medical

writers, whether leading or supporting, must understand the aims of the clinical programme in the context of the data available or expected, and must be in a position to advise the project team on interpretation of the regulatory guidance for writing CTD summaries. When the project team has little or no experience of submission dossiers, the medical writer’s experience can be crucial for advising on how to apply the guidance to achieve not only effective document structure and data presentation, but also an effective process for preparing the documentation.

Key Messages

As early as possible in the project, medical writers must ensure that the project team agrees on key messages and how these

“ Preparation of a CTD is often regarded as the epitome of regulatory medical writing due to its complexity and the experience needed. The challenges involved are numerous, and for medical writers vary according to dossier size, team experience, data complexity and available time ”



C = clinical; CMC = chemistry, manufacturing, and controls ("Quality"); CP = clinical pharmacology; D = draft; MW = medical writer; NC = non-clinical; R = regulatory; S = statistics.

Vertical lines indicate time points when consistency between documents is checked, depending on the status of their preparation. The figure provides only an example of interconnectivity between documents and is not definitive; the actual degree of interconnectivity between documents and the timing of ensuring consistency between documents is project-specific and will vary between submissions

Figure 2: Conceptual illustration of multiple work streams when preparing clinical summary documents for a CTD submission, including interconnectivity

can be effectively communicated. The correct time point for this will vary according to availability of data and between summary documents. Even when pivotal data have yet to be provided, key message scenarios can be developed in alignment with the envisaged prescribing information.

Key messages are akin to defining the destination of a journey. The challenge for medical writers is often to focus the project team on defining these sufficiently early so that the best route for reaching the destination can be mapped. While this sounds obvious, project teams are often surprisingly hesitant to commit to key messages early in a project, and often prefer to leave their options open for as long possible even when, with hindsight, this is rarely necessary. For medical writers, this form of procrastination can result in multiple changes in direction, with all the ensuing inefficiencies in document preparation – including a substantial drain on the team's ability to reflect on data and provide effective input.

Having aligned the project team on the issues above, the next challenge for medical writers is the practical task of crystallising out essential facts and interpretations from the mass of data included in the dossier. Starting at the base of the CTD pyramid, if the study reports are well written then they should include key messages regarding interpretation of the individual studies concerned. However, it is common for medical writers to have to revisit a poorly written report to establish exactly what the key message of the study is.

The clinical summaries (one level up from the study reports) are intended to summarise information from individual studies, as well as provide a perspective across studies. The approach needed varies across the four key topics in Module 2.7.

Take, for example, safety information: adverse events from the clinical studies may need to be summarised individually by study, together with an integrated analysis of the adverse events across these studies. The challenge for medical writers is to ensure that at the clinical summary level, only key facts relevant to supporting the prescribing information are included and that essential messages are not muddled by inclusion of unnecessary information. This can be a substantial challenge, because some teams are reluctant to prioritise facts, instead preferring to include as many facts as possible in a clinical summary to 'be on the safe side'.

The clinical overview (Module 2.5) – yet another level removed from the study reports that is intended to discuss strengths and weaknesses across the clinical programme to justify the prescribing information within a space of approximately 30 pages – should provide an even higher level of summarisation than the clinical summaries.

Medical writers often need to remind the project team that their audience for the clinical summaries and the clinical overview is primarily made up of regulatory reviewers



Medical writers often need to remind the project team that their audience for the clinical summaries and the clinical overview is primarily made up of regulatory reviewers charged with assessing suitability of the medicinal product for approval



charged with assessing suitability of the medicinal product for approval. In this context, every piece of information that is proposed to be included in these documents must be examined for its relevance in supporting the prescribing information. Not including a fact in a clinical summary is not synonymous with hiding that fact, because the study reports in Module 5 provide complete disclosure of all the data accrued in the clinical programme.

Planning and Review Workflows

The assembly of a writing team, coordination of writing activities and maintenance of writing standards provide the lead writer with a substantial logistical challenge. There is also a further challenge involved in planning and maintaining the timelines for reviewing CTD component documents, which must also take account of the interdependencies between these documents shown in Figure 2. The worst scenario is a timeline designed without the input of medical writers, especially the lead medical writer. Unless someone has actually written a CTD, they are ill placed to design the timelines for preparing a CTD, because they may not understand the critical nodes and knock-on effects of changes in the timing of individual components. The most effective approach is for the project planner to consult all document stakeholders in the project team – particularly the medical writers – while drawing up the timelines, and these should be regularly revisited and fine-tuned, with buy-in by all stakeholders as needed as the CTD progresses.

Even with the best planning, somewhere among all the moving parts there will almost certainly be delay beyond the writer's control, eg due to delays in planned analyses or the need for additional analyses. Time is always at a premium, and timelines are more likely to be truncated than extended. It is, therefore, crucial to ensure that the original plan is realistic, and buffers and mitigations for rate-limiting steps should be identified that can be used if and when the timelines need to be adjusted.

Having a project plan is one thing, but enforcing it can be quite another. For medical writers, the critical logistical aspects that are almost universally challenging while preparing CTDs are the timely provision of source information; an effective process to conduct the review within a single file; buy-in by all stakeholders that the reviews can and will be conducted within the agreed time slots; and a commitment to decide on the resolution of critical review issues as they arise to minimise

or eliminate the need to revisit such issues at a later stage. An essential element is effective planning of the reviewing time slots for all reviewers – including reserving time in calendars – so that a realistic amount of time is available for reviewing with a minimum of conflicts with other activities. If a member of the project team needs to review multiple documents within an unrealistic timeframe, the reviews will not receive the attention they deserve; issues will not be addressed appropriately; and unaddressed issues will stack up later in the document preparation process when the least amount of time is available.

A further challenge for medical writers is document review by senior management. In part, this is influenced by company culture, which can range between senior management having full faith in the project team and feeling the need to provide only minimal input to preparation of the CTD, to senior management providing extensive input. The quality and relevance of this input can vary considerably, and may or may not be helpful. For medical writers, the situation can become a substantial challenge when senior management input is added at the later stages of document review, especially when earlier decision-making is overturned. Medical writers with a wealth of experience can often sense when such a situation may arise, and will urge the project team to include senior management in early review rounds in an attempt to mitigate the situation.

Completing the Submission Package

Depending on the complexity of the submission, preparation of the CTD and the ensuing review cycles can be a lengthy process, but at some stage the summary documents must be finalised. In the later stages of preparation, medical writers play a key role in ensuring that all stakeholders are satisfied with the documents, and that these are factually correct and technically coherent. For the lead writer on the submission, the challenge is maintaining contact with project sub-teams across the four key topics of biopharmaceutics, clinical pharmacology, efficacy and safety, reviewing their documents through all stages of preparation. This ensures consistency of message and presentation across documents. In the final review round, the lead writer must ensure that all the CTD summaries are consistent between the individual clinical summaries (Module 2.7), and between these and the clinical overview (Module 2.5) as well as the proposed prescribing information.

“ **The questions posed by regulatory reviewers vary from straightforward technical queries to requests for new analyses or further interpretation of existing analyses. Questions regarding interpretation of data will usually require medical writers in the project’s rapid response team, with a central role in crafting responses and in coordinating input from the various stakeholders involved** ”

Irrespective of whether medical writers are responsible for the entire dossier or one or more component summaries, they are most effective when they operate in a role best summarised as ‘the glue that holds it all together’, ensuring that the various interests of all stakeholders are taken into account in the documents being prepared. Medical writers must ensure that all content issues have been resolved, and that the final document is delivered in a timely fashion.

Medical Writing after Dossier Submission

A common challenge for many project teams is their tendency to disband after the CTD dossier has been submitted. This is unfortunate, because often there is a substantial requirement for document authoring and preparation before a regulatory decision is received.

Almost all development programmes contain certain weaknesses or other issues of concern for regulators, generating questions during review of the dossier. In Europe, these questions come at predefined time points – 80 days after dossier acceptance for draft questions and after 120 days for final questions – while in the US, questions may come at any time after dossier acceptance.

The questions posed by regulatory reviewers vary from straightforward technical queries to requests for new analyses or further interpretation of existing analyses. Questions regarding interpretation of data will usually require medical writers in the project’s rapid response team, with a central role in crafting responses and in coordinating input from the various stakeholders involved. Ideally, the same medical writers and other stakeholders who prepared the CTD should also be available in the post-submission period, so that their legacy knowledge is available when a rapid turnaround is needed for responding to questions.

Thought should also be given soon after the dossier has been submitted to proactively assessing weaknesses in the clinical programme, and any potential questions that may arise even before they are raised. Time invested at this juncture can pay dividends when questions are received and responses are required in a short timeframe.

The challenge for medical writers is to focus the project team on providing input for addressing questions that have yet to be officially posed. Here, medical writers can facilitate the process by proposing pragmatic means of capturing thoughts on topics, eg via text or bullet points in a spreadsheet, together with other practical information such as the status or location of any additional analyses needed. Medical writers can also be effective in supporting the team in preparing materials (briefing documents and presentation slides) for an oral explanation meeting in Europe or an FDA Advisory Committee meeting in the US – events that can be instrumental for the decision on regulatory approval.

Conclusions

Medical writers, with their central role in preparing the summary documents needed for a CTD submission, face numerous challenges depending on dossier size, team experience, data complexity and available time. By having insights on all these aspects and proactively seeking pragmatic solutions to issues as they arise, medical writers can guide the project team towards their goal of delivering the final summary documents within agreed timelines. An overall challenge for medical writers is to remain focused and diplomatic at all times, understanding that they are likely not the only members of the team under intense pressure to complete the CTD on time.

About the author



With a PhD in Environmental Microbiology, **Douglas Fiebig** joined Hoechst (later Aventis) as a Medical Writer in 1996 and has since been involved in preparing the entire spectrum of clinical regulatory documentation. He co-founded Trilogy Writing & Consulting in 2002 and has

prepared regulatory documents for many large and small pharmaceutical companies. Douglas’ main focus has been on organising and writing CTD submission summaries, often also providing the medical writing support needed after the dossier has been submitted.

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Getting Clinical Research Results Published

The goal of clinical research is to provide doctors with a better understanding of treatment options and, ultimately, to improve medical practice. Achieving this depends on research results reaching policy makers, doctors, and other researchers via peer-reviewed journals. For many researchers, however, the path to successful publication is not clear, and the process can be time-consuming and stressful. In this article, we outline key concepts and steps in organising, preparing, and successfully publishing clinical research articles.

By Phillip S Leventhal
at 4Clinics and Stephen
Gilliver at TFS

To make good treatment decisions, doctors require a sound evidence base and therefore the complete, accurate, and timely reporting of medical research. Conversely, incomplete, inaccurate, misleading, or delayed reporting can damage the quality of healthcare.

Good Publication Practice (GPP), created in 2003 by the International Society for Medical Publication Professionals (ISMP), is the main ethical standard “for individuals and organizations that contribute to the publication of research results sponsored or supported by pharmaceutical, medical device, diagnostics, and biotechnology companies” (1,2). GPP3, the most recent version, recommends that the results of all clinical studies, even non-interventional studies, should be published in a peer-reviewed journal (2). This includes not only positive but also negative or inconclusive results, as well as all research on interventions that are investigational, licensed, or even have been discontinued or withdrawn from the market. GPP3 also insists that in cases where a study does not produce publishable data, the results should still be posted on a public website, such as ClinicalTrials.gov.

Start the Article off on the Right Foot with a Kick-off Meeting and an Organised Writing Process

Writing a publishable article is a challenge even for the most experienced writers, but just as challenging is keeping the entire process on track, on time, and on budget. Usually, publications are collaborative, multidisciplinary, multinational projects. In such a complex environment, a variety of communication problems can cause the project to go off track. Avoiding these problems requires an organised plan, not just for the writer but also for the whole team.

Start with a Kick-off Meeting

Kick-off meetings are time well spent. This is where the direction is set for the entire project. The kick-off meeting should include discussions and decisions about the key messages and data to include, how the writing process will proceed, who will participate and at which points in the

- Agree on messages/focus
- Discuss ideas for target journal
- Define roles
- Decide on timelines
- Organise review process

Figure 1: Agenda for a kick-off meeting

process, what journals might be targeted, and when different steps in the process should be completed (see Figure 1).

The Participants and the Venue

The kick-off meeting does not need to include everyone involved in the project, just the major players, typically the writer, the project manager, and the lead investigator or another knowledgeable investigator. More people can be added, but increasing the number of participants generally complicates decision-making and unnecessarily prolongs the meeting. Kick-off meetings can be via teleconference or web interfaces like WebEx and Skype for Business, although a face-to-face meeting can improve interpersonal relations and thereby help avoid miscommunication and conflicts between team members.

Present the Study Design and Results

In many cases, the lead investigator and main writer are not the same person. Frequently, a professional writer is involved. The kick-off meeting should therefore include a presentation by the lead investigator to help familiarise the writer with the study design and findings. Such a presentation also serves as the basis for a discussion of key messages and key data to be presented.

Discuss Ideas for the Target Journal

The kick-off meeting is an opportunity for the writer to ask whether the investigator and project manager have ideas for the target journal. As part of this, the writer should ask about the motivation for choosing a particular journal. An experienced writer can help ensure that the final target journal matches the novelty, impact, and interest of the article. The final target journal does not have to be selected during the kick-off meeting, but a discussion will help focus the selection.

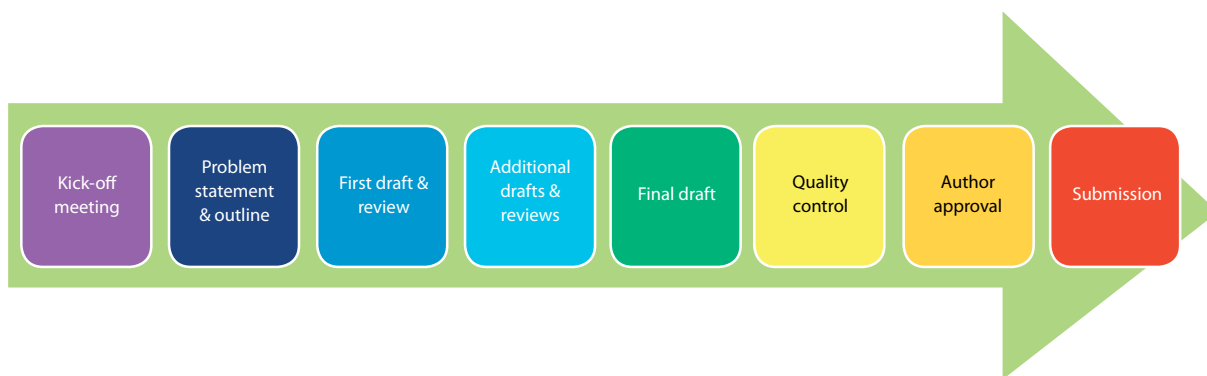


Figure 2: Recommended workflow for preparing an article for submission

Discuss Who Will Be the Authors

The kick-off meeting is also an opportunity to discuss who will be authors and who will therefore be required to participate in writing, reviewing, editing, and approving the article.

An experienced writer will be able to advise the team about who qualifies to be an author and who should instead be mentioned in the acknowledgments. The main guidelines for authorship are the International Committee for Medical Journal Editors (ICMJE) Recommendations (3), which state that all authors must have:

- Contributed substantially to conceiving or designing the work, or to acquiring, analysing, or interpreting the data; AND
- Written or edited the article or provided critical comments; AND
- Approved the final version of the article to be published; AND
- Agreed to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

These requirements mean that all authors need to be available to participate in preparing the article. As with selecting the journal, a final decision as to who will be authors does not need to be made during the kick-off meeting, but the list of authors should be agreed upon shortly thereafter to avoid conflicts, ethical issues, and lost time.

Discuss the Workflow and Who Will Be Involved at Each Step of the Project

Coming up with an organised workflow is an essential part of a kick-off meeting. This includes deciding who will take on what role and when during the preparation of the article, as well as how the article will be reviewed and revised. An effective plan for completing a publication based on a clinical study is shown in Figure 2. The writing starts with an outline, which should be reviewed and edited by the main author(s), usually the lead investigator(s). Once the outline is approved, the first draft is generated. At this stage, all co-authors should review the article and provide comments. This is important for ensuring that they all agree with the direction. Coming in with comments and changes at a later stage can create conflict and will result in additional and unnecessary drafts. Subsequent drafts can be kept to a minimum by clearly defining who should be involved (co-authors only

or others also, such as company management or intellectual property or compliance officers) and at which stage. To meet ethical guidelines and journal requirements, the final draft must be approved by all authors before it can be submitted to the journal.

Writing an Effective Article

An effective article needs to communicate and not just disclose. Disclosing means simply presenting information, which can be appropriate for a clinical study report, but not for an article. Communicating, in contrast, means making a link with the reader and convincing them of something. This implies that the article needs to be written so that the reader does not have to work to find information or grasp what it means.

Creating a Problem Statement to Clarify the Direction for the Article

After the kick-off meeting, the writer needs to start to determine exactly what the article will be about. This is not as simple as it seems, and it goes beyond any declared study objective. Determining what the article will be about can be accomplished by coming up with a “problem statement” (4).

A problem statement includes two parts, the first defining what problem the study was trying to solve and the second defining what the article does to address the problem. The problem statement does not need to be written down, but the writer should have one in mind when beginning the article. Here are two examples:

- Many candidate HIV vaccines have been developed, but results in animals have not been predictive of efficacy in humans. A reliable animal model for predicting the efficacy of HIV vaccines is needed. In this article, we describe a murine model of HIV that can be used to test vaccines.
- T-type lymphoblastic lymphoma, which mostly affects young men, has a poor prognosis. New and more effective treatment protocols are needed. In this article, we describe the results of a clinical trial on the efficacy and safety of a paediatric lymphocytic leukaemia-inspired treatment protocol.

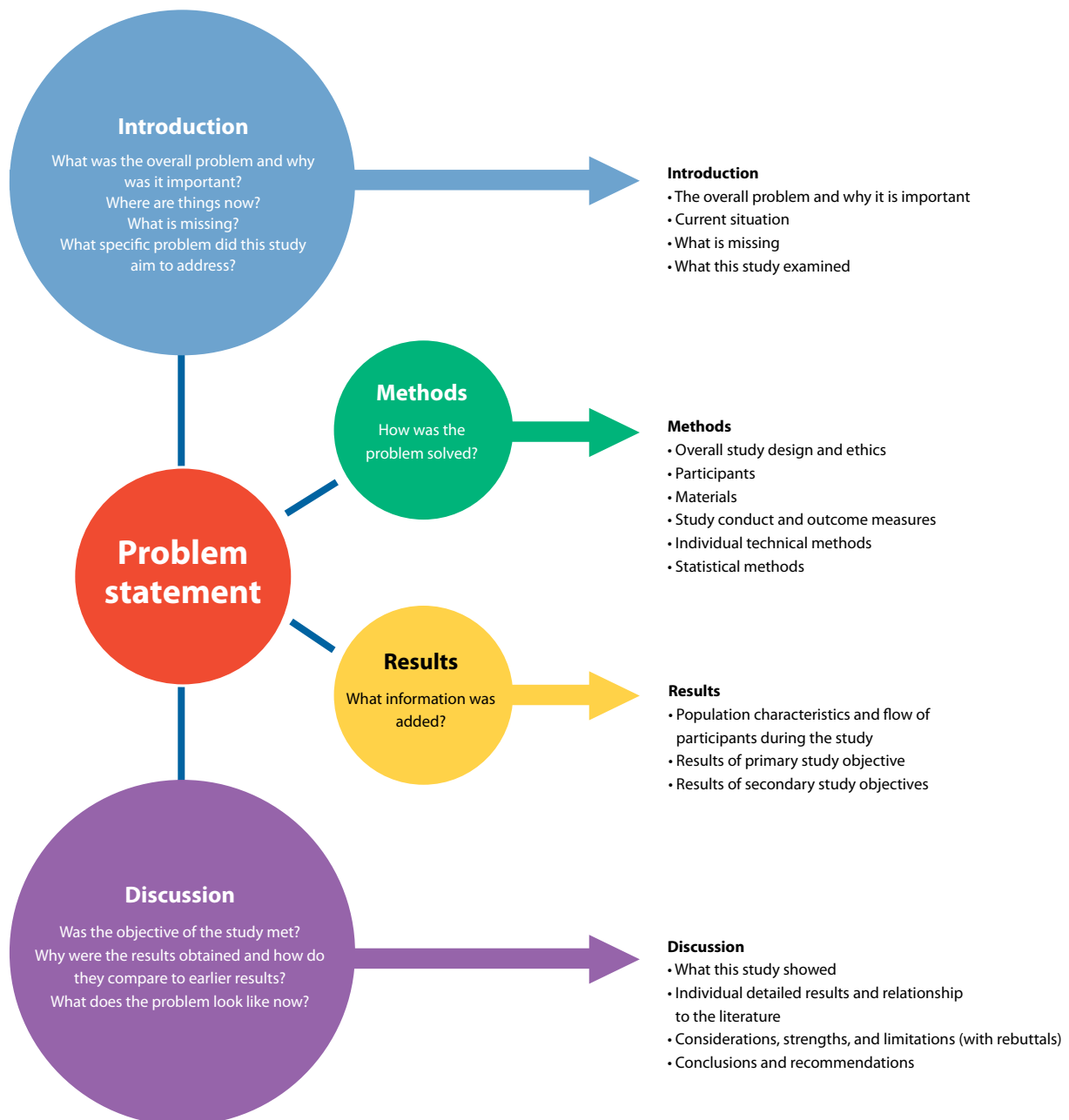


Figure 3: The problem statement and its relationship with different sections of an article

Use Outlining to Keep the Article on Track

An outline is a skeleton to organise thoughts and build the article around. Creating an outline helps keep the article from going off on tangents. It also serves as a starting point for discussing and confirming the intended content of the article. Creating a good outline saves a great deal of time later by allowing questions and problems to be dealt with early in the writing process.

Create a “Concept” Outline

With a clear problem statement, creating a concept outline is

simple. Start with a list of main bullet points or headings. All parts of the concept outline – and therefore the article – relate back to the problem statement (see Figure 3).

For example, the first part of the problem statement becomes the first half of the introduction, and the second part becomes the second half of the introduction. Subsequent bullet points or headings address:

- How the problem was solved
- What findings directly address the problem
- Whether the study resolved the problem
- Why the results were obtained

- How they compare with other studies
- What the problem looks like now

Create a “Detailed” Outline by Adding Details to the Concept Outline

Once a basic outline is created, it can be filled in with details to create a detailed outline. Each of the bullet points or headings can be elaborated with the full details that would be included in a first draft. Unlike a first draft text, however, the information can be included as bullet points, which, compared to continuous text, are easier to edit, restructure, or even substantially rewrite.

Carefully Choose the Target Journal

Choosing the target journal early – before starting the first draft – saves a great deal of time by avoiding the need to edit, reformat, or substantially rewrite the article to meet the journal’s requirements. For example, if the “final” draft is 5,000 words long but the journal only allows 3,000 words, substantial rewriting would be needed, not to mention additional cycles of review and revision, all of which will add to the time and cost to complete the project.

Start with Searches of JANE and PubMed

Selecting the right target journal deserves careful thought and an organised process (see Figure 4). Start by looking where similar articles are published with keyword searches on PubMed (5) and BioSemantics Research’s Journal/Author Name Estimator (JANE) (6). A PubMed search will identify related individual articles, while JANE will identify journals publishing related articles and will list them in order of relevance. Neither PubMed nor JANE is perfect, so after excluding irrelevant journals, combine the results of both searches to come up with a shortlist of the best options.

Consider the Journal’s Reputation

Next, consider the journal’s reputation. Ask experts and consider the impact factor, which is a measure of how often a journal’s articles are cited. Most authors will reflexively want to target the journal with the highest impact factor, but beware – the higher the impact factor, the greater the importance of novelty and the higher the rejection rate. Journals with higher impact factors also tend to take more time for peer review. Therefore, carefully – and honestly – assess the article’s novelty and potential influence. Consider also whether the objective is to simply publish in a peer-reviewed journal or to make a big impact.

Other Important Considerations and Making the Final Decision

Other things to consider include the number of words and figures/tables allowed, whether supplementary information is allowed, the journal’s scope, and, if important, whether open access is available. The final decision should be made by the full team, but remind them that choosing the wrong journal will only delay publication and increase the cost.

Subject: Results of a phase 3 randomised trial on the efficacy and safety of an antibody-based biologic for treating rheumatoid arthritis
Novelty & importance: moderate

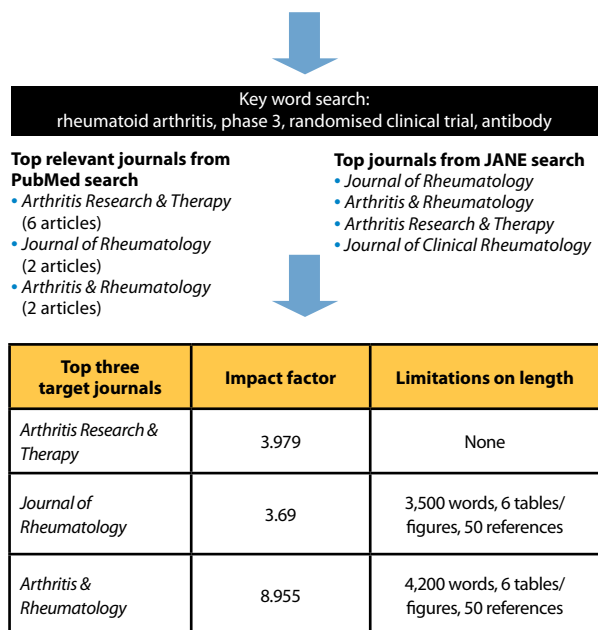


Figure 4: The journal selection process

Write the First Draft: Communicate with the Reader

With a detailed outline in place, creating a first draft is easy. Simply connect the different points into continuous text. Keep in mind that the goal of an article is to communicate, that is, to convince the reader of something. Communicating effectively requires writing that a reader can easily understand and process. This can be achieved by avoiding complex, technical-sounding language and aiming for a clear and concise – yet complete – text. This does not mean talking down to the reader or avoiding all technical language but rather using plain language whenever possible and avoiding certain grammatical constructions that lead to complicated sentences. Also, use abbreviations sparingly. This avoids frustrating readers by making them repeatedly look back for definitions. Instead, reserve abbreviations for complex or multi-word terms that appear several times. A summary of key points to clarify and simplify writing is provided in Table 1.

Ensure that All Necessary Information Is Included in the Article and Is in the Right Place

GPP states that the design and results of clinical studies should be reported in a complete, accurate, balanced, and transparent manner. Many guidelines are available

| Method | Explanation | Example |
|---|--|--|
| Eliminate nominalisations | Nominalisations are verbs turned into nouns. These almost always create complicated sentences. | Measurement of concentration was made by ELISA Improved: The concentration was measured by ELISA |
| Avoid phrases and sentences starting with 'it is' or 'there are' | These create complicated sentences | In patients treated with ibuprofen, <u>there was</u> a much earlier onset of pain relief Improved: In patients treated with ibuprofen, onset of pain relief was much earlier |
| Eliminate useless words | Useless words distract from the sentence's message | <u>It is well known that</u> fear of needles reduces vaccine uptake Improved: Fear of needles reduces vaccine uptake |
| Eliminate 'respectively' | Using 'respectively' tires readers by making them look backwards | The value was 1, 13, 27 and 54 in groups A, CD, A+CD and A-CD, <u>respectively</u> Improved: The value was 1 in group A, 13 in group CD, 27 in group A+CD and 54 in group A-CD |
| Use parallel structure | Parallel structure means using the same grammatical construction for items in a list | The time to treatment failure was 12.2 months in the group treated with drug X, <u>and in the placebo group it was 3.1 months</u> Improved: The time to treatment failure was 12.2 months in the drug X group and 3.1 months in the placebo group |
| Avoid multiple hedges | Hedges are ways to avoid saying anything definite. One is enough. | These results <u>suggest</u> the <u>possibility</u> that drug A <u>might</u> be more effective than drug B Improved: These results suggest that drug A is more effective than drug B |
| Keep your subject and verb close together and where the reader expects to find them | The reader may become confused if they have to hunt for the subject and verb | <u>A critical gene</u> [subject] that serves as a beacon and gives cells a much-needed sense of direction in the chaotic days of early development <u>has been identified</u> [verb] by Howard Hughes Medical Institute (HHMI) researchers Improved: HHMI researchers [subject] have identified [verb] a critical gene that gives cells a much needed sense of direction in the chaotic days of early development |

Table 1: Methods for simplifying writing

to help authors accomplish this. Key guidelines include CONSORT for randomised controlled trials, TREND for non-randomised trials, STROBE for observational studies, and CARE for case reports (see Table 2). A comprehensive and searchable database of guidelines for reporting clinical studies can be found on the EQUATOR Network website (7).

Reporting guidelines typically include checklists of the items that need to be included in each section of an article. Also included are detailed explanations for how to complete each item. Thus, reporting guidelines are excellent resources for planning and producing publications. Authors should be aware that most journals now require that the relevant reporting guideline is

followed and, in some cases, that the completed checklist is submitted along with the manuscript.

Write the Abstract Last

Take a close look at the journal's instructions for authors because the journal will not accept an abstract that is over their stated word limit. The instructions for authors may also have specific requirements for the structure and content of the abstract. In addition, use the CONSORT Extension for Abstracts as a checklist to make sure that the abstract is complete (8). If you are not reporting a randomised controlled trial, simply ignore any irrelevant items in the checklist.

As most readers will see only the abstract, a reader must be able to understand it without needing to read the main text. To write a

| Publication type | Reporting guideline | Website |
|--|---------------------|---|
| Randomised controlled trials | CONSORT | www.consort-statement.org |
| Non-randomised trials | TREND (or CONSORT*) | www.cdc.gov/trendstatement |
| Observational studies | STROBE | www.strobe-statement.org/index.php?id=strobe-home |
| Case reports | CARE | www.care-statement.org |
| Qualitative studies | COREQ | www.intqhc.oxfordjournals.org/content/19/6/349.long |
| Diagnostic/prognostic studies | STARD, TRIPOD | www.equator-network.org/reporting-guidelines/stard www.tripod-statement.org/tripod/tripod-checklists |
| Systematic reviews and meta-analyses | PRISMA | www.prisma-statement.org |
| Meta-analyses of observational studies | MOOSE | www.statswrite.eu/pdf/MOOSE%20Statement.pdf |

*CONSORT can be adapted to non-randomised trials by excluding any non-relevant items

Table 2: Types of clinical publications and their associated reporting guidelines

stand-alone abstract, begin with the main study objective. State the objective clearly in one sentence, removing all extraneous words. Next, state the conclusions in one sentence. Be sure that the conclusions directly reflect the main study objective. Next, add only the results that support the conclusions and then only the methods that support the included results. Add one sentence of background to complete the abstract. If any words are left, additional interesting results (and supporting methods) can be added.

Review, Revise, and Quality Control

The writer needs to work with the authors and other team members during the planned review cycles to prepare subsequent drafts and, eventually, the final draft. To avoid complications and confusion, stick to the process that was established during the kick-off meeting. Also, avoid moving forward with subsequent drafts until all participants have provided the necessary input. If essential contributors are not providing timely comments, it may be necessary to remind them that they need to participate to be listed as a by-line author.

As a final step before requesting author approval of the final version of the article, perform quality control to make sure it is free of errors. The quality control should include, at a minimum, checks of the following:

- Spelling, grammar, and punctuation
- Consistency of data/numbers between source information (eg clinical study reports), figures, tables, main text, and abstract
- References
- Formatting according to the instructions for authors
- Content according to the relevant reporting guideline (eg CONSORT)

Submitting the Article to the Journal

Write a Cover Letter that Convinces the Editor to Review the Article

Once the article is complete, prepare a cover letter to be submitted with the article. The cover letter is a chance to catch the editor's attention and convince them that the article should be published in their journal. It should briefly explain the purpose of the letter, summarise the purpose and findings of the article, and include a statement on the article's relevance to the journal and a short thank-you (see Figure 5). Refer to the instructions for authors to see if any additional information is needed. Be careful not to let the cover letter get too long: to avoid overwhelming the editor, it should not be longer than one page. Also, do not put any pressure on the editor to review or accept the article.

Plan Enough Time to Submit the Article

Plan a full day to submit the article. Although this might seem like a lot of time, it is often necessary because online submission systems can be tedious and time-consuming. Start by collecting the article and cover letter, the figures (prepared in the appropriate format and resolution), conflict of interest forms, and detailed contact information for all

authors. Some online submission systems ask for unexpected details that can take time to collect, such as highest degrees for all authors, copyright permission and transfer forms, detailed authorship contribution statements, lists of reviewers to recommend or exclude, and permission letters from people to be acknowledged. To avoid surprises, explore the online submission system in advance.

Dealing with the Editor's Decision: Revising and Resubmitting

After receiving the article, if all goes well, the editor will send it out for review. Many articles, however, are rejected without review. If this happens, do not waste time contacting the editorial office to ask them to reconsider. Instead, prepare to send it to a new, perhaps more carefully selected, target journal.

Most articles that make it into peer review will not be accepted immediately but will instead come back with many comments and questions. Usually, the editor will indicate that the article will be reconsidered if the comments and questions are addressed, but in some cases the editor will reject the article with no chance for resubmission after a full review.

In either case, consider the comments carefully. Put aside any negative emotions, and think about the comments from the reviewer's point of view. If the reviewer misunderstood something, it probably means that that part of the article was not clear enough. Consider also that the comments are of great value: they are expert opinion, and they are an opportunity to improve the article. For an article that has been

Dear Editor,

I would like to submit our manuscript "1-year follow-up of safety of drug X in patients with ankylosing spondylitis" for publication as a research article in *Joint Research and Therapy*. [Introduction]

The manuscript describes the results of a prospective, multi-centre, open-label observational study on the safety of drug X in patients with ankylosing spondylitis. This 1-year systematic safety survey provides important, detailed information about adverse events, predictors for adverse events and reasons for discontinuation in daily clinical practice. [Short summary]

We feel that this is important information and directly relevant to the readership of *Joint Research and Therapy*, particularly in the context of drug safety in the rheumatic diseases. [Statement of relevance]

Thank you for considering our manuscript for publication. We look forward to your response. [Thank-you]

Sincerely,

Professor John Johnson
Department of Rheumatology

Central Wyoming College of Medicine

Figure 5: Example cover letter

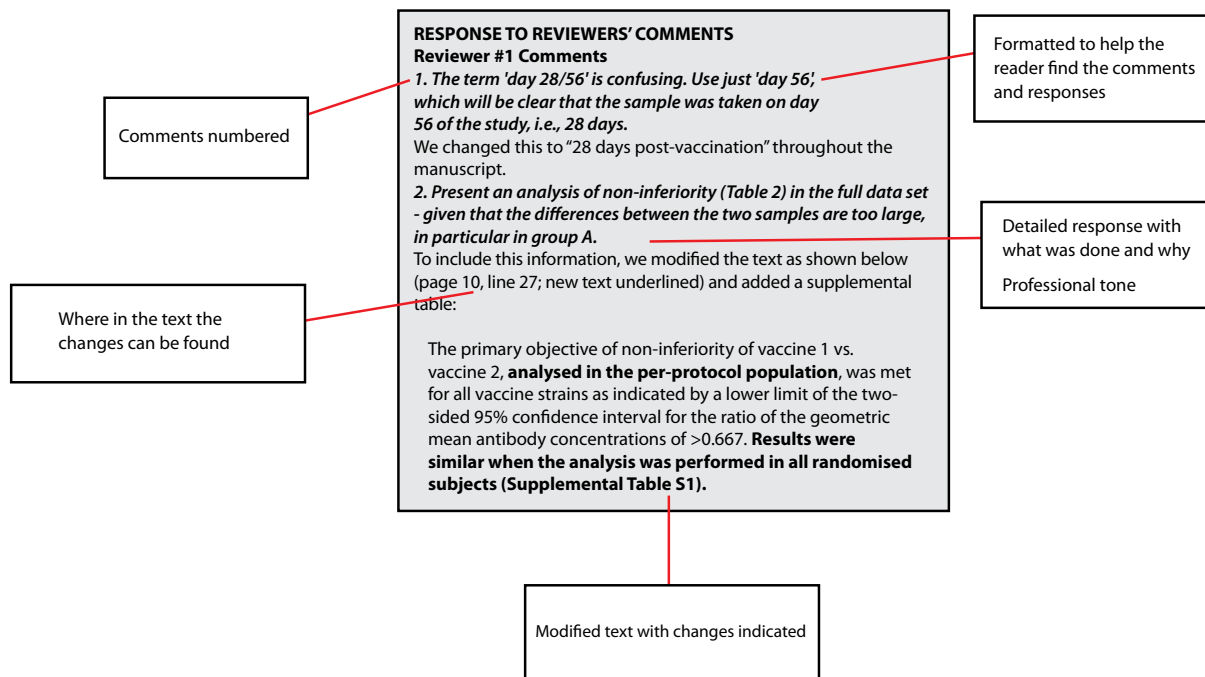


Figure 6: Excerpt from an example response document

rejected, revising it according to the comments can greatly improve its chances of being accepted by a new journal.

If the editor has offered you the opportunity to resubmit the article following revision, they will ask for point-by-point responses to the reviewers' comments. When responding, maintain a professional tone and provide the reviewers with any information that can help answer their question or address their comment. If two reviewers contradict each other, try to find a way to satisfy them both. If necessary, seek guidance from the editor. If it is impossible to do something requested by a reviewer, explain why. Finally, a well-formatted response document, such as the one shown in Figure 6, will be much appreciated by the editor and reviewers and will increase the likelihood that the article is accepted for publication.

Conclusion

Publication in a peer-reviewed journal is now required for all clinical studies, except for the few studies that do not provide meaningful data. This ensures a robust base of evidence to inform clinical decisions. To be effective, an article needs to communicate, which means making a link with the reader and convincing them of something. Keys to success include establishing and following an organised process for producing the article, selecting the right journal, following relevant guidelines, and making life easy for the reader, editor, and reviewers.

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Medical Publication Managers: Are Your Publications Future-Proof and Audit-Proof?



Medical publication managers are faced with the challenge of getting the results of clinical research out to targeted health professionals in an effective, efficient and compliant manner. This article describes tools, techniques and technology to help achieve this.

By Professor Karen L Woolley and Dr Mark J Woolley at Envision Pharma Group

“What you do today can improve all your tomorrows”
Ralph Marston

High-performing publication managers in the pharmaceutical industry consistently facilitate the delivery of compelling, credible, and compliant publications. How?

Firstly, they are leaders, not laggards. To help future-proof their publications in an environment that is continually evolving, they embrace innovation. They know they need to adapt their publication plans and practices or risk being left behind.

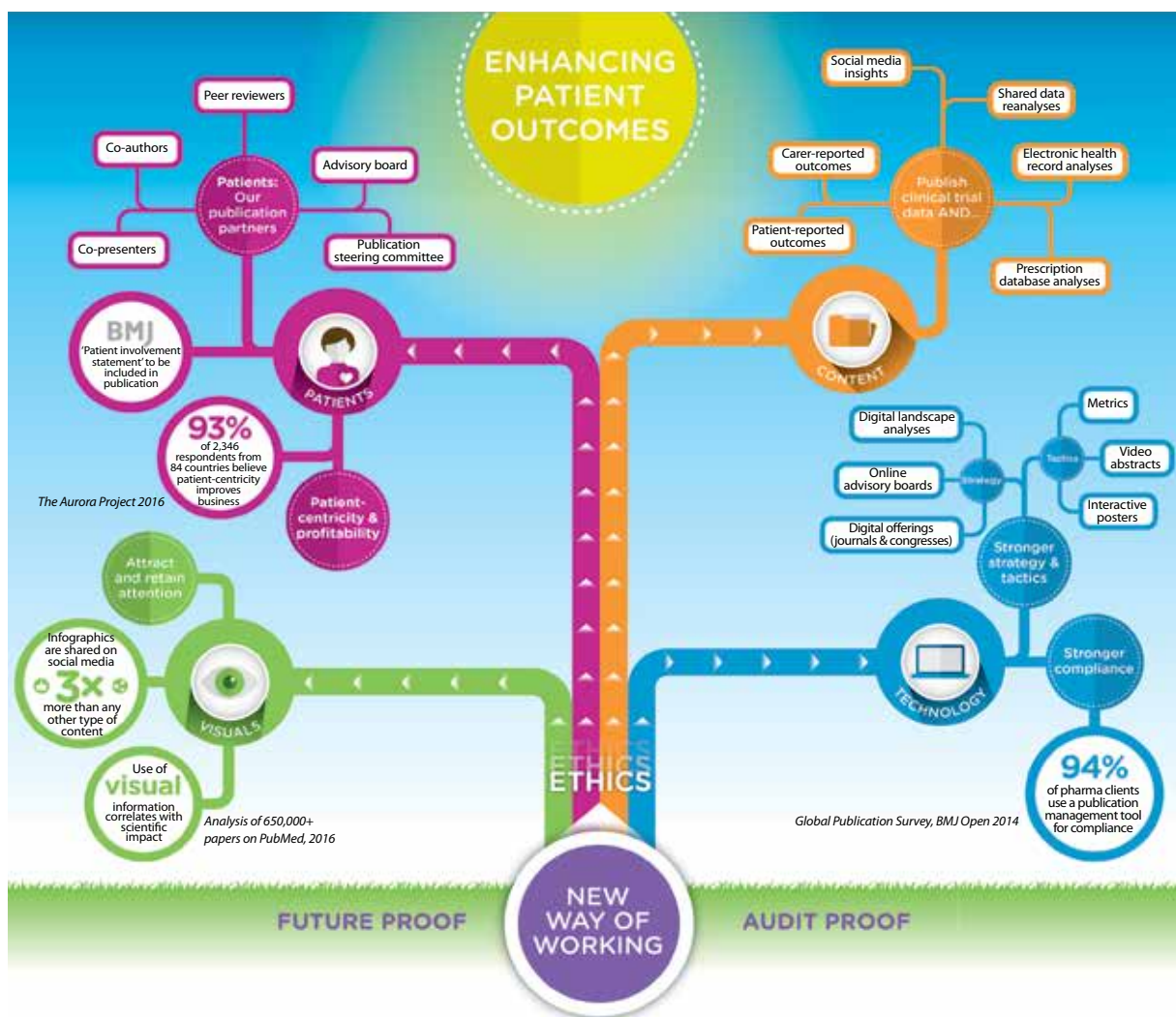


Figure 1: Four trends publication managers can leverage to future-proof and audit-proof their publications. All publications should be developed ethically, with the ultimate goal of enhancing patient outcomes

Secondly, they are audit-ready, not audit-averse. To help audit-proof their publications, particularly when transparency is critical to building trust, they embrace technology. They know they can leverage technology to transparently track and document compliance – globally, efficiently, and effectively.

The purpose of this article is to help publication managers become high-performing publication managers. To help managers future-proof their publications, we identify four trends affecting the publication environment and provide practical guidance on how to leverage these trends to deliver compelling and credible publications. To help managers audit-proof their publications, we share real world insights on how to use publication management software to transparently track and deliver compliant publications.

How to Future-Proof your Publications

“The best way to predict the future is to create it”

Peter Drucker

Publication managers can help future-proof their publications by identifying and responding to important trends in the publication environment. There are many changes affecting publications, but we will focus on four major trends (see Figure 1).

Patients as Publication Partners

Clearly, patients are not new; they are the *raison d'être* for publishing medical research. What is new is the increasing recognition that patients, as well as carers and the public, can be publication partners (see Figure 1). This is a change that publication managers can and should embrace, and champion among their internal and external stakeholders.

Patients can be authors, presenters, and peer-reviewers. Patients can offer ‘end user’, first-hand, expert insights through appointments to Advisory Boards (eg providing insights on unmet needs and research protocols) and Publication Steering Committees (eg providing insights on how, when, and where to present and publish research results). Notably, more journals are embracing patient-centric publications, and publication managers can use

publication management software (eg Datavision®) to help authors – be they patients or healthcare professionals – to select journals and congresses that strive to include patients as partners. We are currently conducting research on how well journals and congresses are performing on this metric, based on predetermined criteria established by patient advocates.

High-performing publication managers recognise the importance of patient engagement, but also understand the need to respect patient diversity – not all patients want to be publication partners, not all patients want to immerse themselves in the peer-reviewed literature. However, to deny or ignore those who do robs medical research of the insights necessary to truly enhance patient outcomes. Assumptions about patients and publications are being challenged by research, including studies that we have conducted on patient acknowledgements in publications, on consumer preferences for sharing research results, and how the public around the world engages with the peer-reviewed literature via social media (1-3).

This research has established that publication managers are well-positioned to be change agents in the drive to engage patients as publication partners. Publication managers can bring patients, researchers, and sponsors together to develop publication plans and outputs that meet the educational needs of patients. Further, in our interactions with inspiring and pioneering patients and advocacy organisations around the world (eg the International Alliance of Patients’ Organizations, the Patient Innovation Platform, the Advocacy Service for Rare and Intractable Diseases, Genetic Alliance Australia) there has been genuine interest, if not optimistic impatience, about the role that patients should have in publication planning and delivery.

In practical terms, we acknowledge that concerns may be raised about the costs and compliance issues of engaging patients as publication partners, particularly for industry-sponsored publications. It would be naïve to assert that publication managers should not consider such costs, even if they believe patient engagement is the right thing to do. We are not aware of any empirical research on the return on investment of engaging patients as publication partners. We note, however, that results from the Aurora Project survey (conducted in March 2016; N = 2,346 respondents from 84 countries) showed that



Patients can be authors, presenters, and peer-reviewers. Patients can offer ‘end user’, first-hand, expert insights through appointments to Advisory Boards (eg providing insights on unmet needs and research protocols) and Publication Steering Committees (eg providing insights on how, when, and where to present and publish research results)



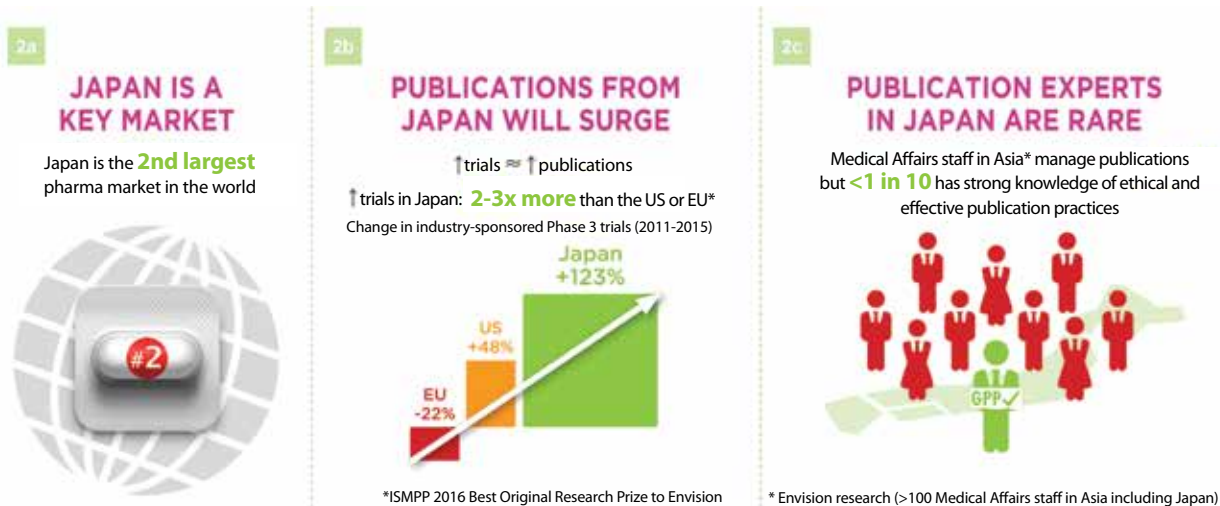


Figure 2: Publication managers need to ensure their publications are audit-ready, globally. This is especially true in countries like Japan, which a) is a key market, b) is increasing its industry-sponsored clinical trial activity, and c) has limited staff with expert knowledge and experience of GPP

93% of respondents believed that patient-centricity improves business outcomes, including enhancing patient outcomes and trust (4). Engaging patients as publication partners could help drive these positive outcomes and justify the incremental investments made to do so.

In terms of compliance, changing publication practices will, and arguably should, raise questions about the right way to proceed. Minimal guidance is provided in the *Good Publication Practice* (GPP) 3 guidelines (5). Publication managers can, however, refer to general and publication-specific recommendations from other sources, including:

- *The Consensus Framework for Ethical Collaboration between Patients' Organisations, Healthcare Professionals and the Pharmaceutical Industry* (6)
- *The Guidance for Reporting Involvement of Patients and Public* (GRIPP) checklist (7); GRIPP 2 is under development
- Journal guidance on involving patients in publications (eg recommendations from *The British Medical Journal* (BMJ)) (8)

Content beyond Clinical Trial Data

With the regulatory requirements for clinical trials, the core of many publication plans consists of clinical trial publications. However, given the time, cost, and complexity of clinical trials, as well as their imperfect reflection of the real world, these publications do not address all unmet needs. Additional sources of content can provide credible, yet quicker and cheaper answers to real world questions and complement findings from clinical trials.

Publication managers can work with internal and external stakeholders to identify unmet needs that can be legitimately addressed by generating and sharing content outside clinical trials (see Figure 1). For example, we have worked with clients and our own research teams to analyse, present, and publish content from patient- and carer-reported outcomes,

administrative claims and prescription databases, shared data re-analyses, and social media insights (3, 9-11).

Visuals

Scientists have long recognised the value of graphics as an educational tool, but have been slower than other professionals to fully appreciate the value of infographics and other visual storytelling tools. Although the traditional conservatism of science may have hindered the rapid uptake of these tools, the visual trend is now gaining ground (see Figure 1).

Industry associations (eg the International Federation of Pharmaceutical Manufacturers & Associations, European Federation of Pharmaceutical Industries and Associations, Pharmaceutical Research and Manufacturers of America), medical journals (eg *The BMJ*), and regulators (eg the EMA, FDA) are publishing their own infographics, providing strong signals to scientists that creativity and credibility can coexist. Increasing research on visual communication tools and the emerging science of viziometrics are also providing empirical evidence on the use and value of visuals in research publications (12-15).

Unless authors fully engage their readers, they cannot educate them. High-performing publication managers can help authors access the resources needed to develop engaging, creative, and credible visuals. These visuals focus on the needs and preferences of the relevant target audience. In our world of information overload, visually appealing graphics can help attract and retain reader attention. Not surprisingly, medical journals have started to encourage authors to submit infographic-style abstracts. Publication managers are well-positioned to guide authors on how to develop infographics that may enhance efficient and effective comprehension and retention of complex ideas.

Technology

Technological advances offer high-performing publication

| Audit risk | Datavision feature | Compliance solution |
|--|--|--|
| Noncompliance with company policies and procedures and publication guidelines (eg ICMJE, GPP3) | Authorship agreements can be tracked, documented, and archived per company requirements | Able to ensure authors understand the need to comply with the company's requirements before the project begins; able to access and use agreements to reinforce the need for compliance during the project |
| Lack of author access to data | Study-related documents can be stored and shared; authors can have direct access during the project | Able to show that authors are able to access the information they need to fulfil their authorship responsibilities |
| Guest authorship | Author input can be tracked, documented, and archived | Authorship eligibility can be proven based on documented compliance with internationally recognised criteria |
| Ghostwriting | Author and writer input, as well as all drafts, can be tracked, documented, and archived | Early, continual and appropriate author input, as well as legitimate contributions from the writer can be proven based on a review of input from each on successive versions of the document |
| Non-disclosed conflict of interest | Disclosure forms can be distributed, collected, tracked, and archived | The risk of inconsistent, outdated, or incomplete disclosures can be reduced. Automation can reduce the administrative burden, providing more time for reviewing disclosure content |
| Non-acknowledgement of contributions | Input and support by non-author contributors can be tracked. Acknowledgement agreements can be distributed, collected, tracked, and archived | The risk of incomplete, inappropriate, or unauthorised acknowledgement can be reduced |
| Not following reporting standards (eg CONSORT) | Datavision checklists help ensure documents can be checked against reporting standards before submission | The risk of not including information deemed critical by reporting experts can be reduced |
| Unjustified publication | Needs assessments can be tracked, documented, and archived. Datavision also allows the entire plan to be visualised | The rationale for each publication can be verified efficiently and effectively. The risk of duplicate publications can be minimised (ie duplicates can be readily detected from a visual overview of the plan) |
| Unjustified choice of conference or journal | The Datavision Journal and Conference database lists legitimate journals and metrics. Authors' choices can be documented and archived | Rationale for authors' choices can be retrieved and metrics used to support those choices can be identified. Comprehensive and regularly updated lists can help minimise the risk of selecting predator journals and conferences |

Table 1: Examples of Datavision features that can help publication managers become audit-ready

managers new ways to enhance publication planning, delivery, and compliance (see Figure 1). Digital platforms and social media analytics can help publication planners develop and evaluate strategies that address real world issues. Publication managers and their stakeholders do not have to wait for years to determine the impact of a publication – technology now allows them to quantify who engaged with their publications, when, where, and how this engagement took place, and how positive (or negative) these reactions were to the published research.

Technology can also help publication planners enhance the speed, novelty, and geographic reach of their publication tactics. We have worked with clients and authors in Europe, North America, and the Asia-Pacific region to deliver timely, durable, and high-quality digital publications (eg video abstracts and interactive posters) that can be accessed simply and freely, in English or local languages. Technology can also be used to help authors identify journals and congresses that have embraced these innovative digital delivery methods. For example, publication management software, such as Datavision, which is used as both a project management and compliance tool (see Table 1), has a Journal and Congress database that managers can use to

efficiently check which, of the more than 27,000 journals and congresses listed, offer digital options. Given the evolving publication environment and rapid advances in technology, developers of publication management software should consult regularly with their end user community and dedicate the resources required to ensure software updates meet the needs of this community.

How to Audit-Proof your Publications

“Remember that even if you haven't been audited in the past, it doesn't mean you won't be in the future. And it only takes one audit to ruin your day”

Kathy Burlison

To help build trust in industry-sponsored publications, publication managers should ensure compliance with company policies and procedures. Compliance should be transparent and global. This may be ‘easier said than done’, but auditors want to know what was done and will ask for the documentation to prove it. That is why high-performing publication managers want to be audit-ready. They know that compliance and audit readiness can be influenced by both people and technology.



Increasing number of Datavision clients

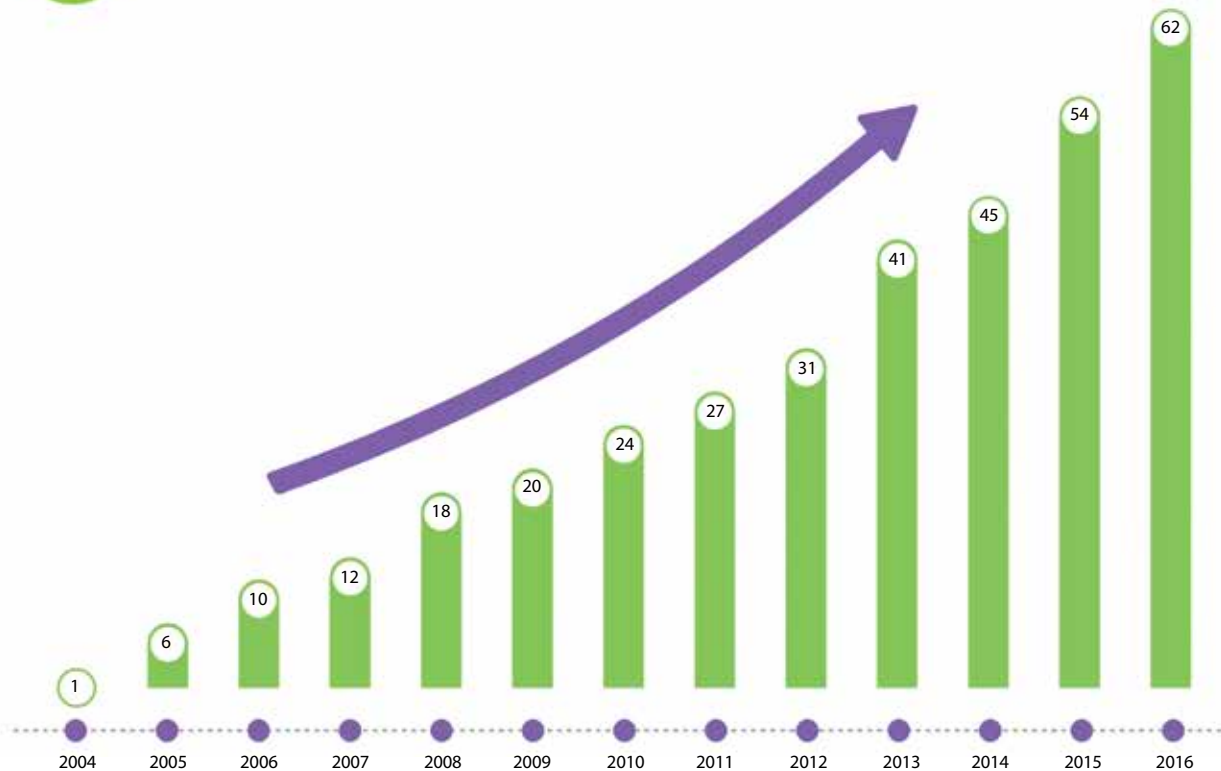


Figure 3: The use of publication management software (eg Datavision), as both a publication management and compliance tool, is continually increasing in terms of its global reach (eg Japan is now one of the top 10 countries using Datavision) and client base (eg Datavision is licensed by more than 30 of the world's top 50 biopharmaceutical companies and used by more than 150 medical communication companies; there are more than 115,000 registered Datavision users worldwide)

In terms of people, we and others have shown that people's knowledge can influence compliance (11,16). For example, publication professionals who have proven their knowledge (ie have passed an exam at an independent, secure, testing facility) to become certified medical publication professionals are more likely to have broader and more current knowledge than those without this credential (11). Professionals with stronger knowledge are also more likely to comply with ethical publication practices (16). Importantly, audit readiness must be global. High-performing

publication managers provide the resources necessary to manage audit risks, particularly in major markets. For example, Japan is a key market and is experiencing a surge in industry-sponsored clinical trials (see Figure 2). Compared with other key markets, however, Japan and the wider Asia-Pacific region have relatively few experienced and certified publication professionals. Medical Affairs staff typically have responsibility for publications and, although their knowledge of GPP and other publication-specific guidelines is increasing, strong

“ Medical Affairs staff typically have responsibility for publications and, although their knowledge of GPP and other publication-specific guidelines is increasing, strong support may be required to ensure audit readiness. The need for additional resources is likely to intensify as more internationally focused Japanese pharma companies take responsibility for global publication plans ”

support may be required to ensure audit readiness. The need for additional resources is likely to intensify as more internationally focused Japanese pharma companies take responsibility for global publication plans. Notably, in some organisations, the transfer of global publication planning from US teams to Japanese teams has already occurred.

In terms of technology, one of the largest surveys of publication professionals (conducted in November 2015; N = 469 respondents from 23 countries) highlighted how publication management software is now being used not only as a planning tool, but also an audit tool (17). Of the agency respondents, 94% reported that their pharma clients used such software to assess compliance. Consistent with this finding is the global growth in the use of publication management software, such as Datavision (see Figure 3), which can help clients and agency staff be audit-ready (see Table 1) (18).

In summary, high-performing publication managers are catalysts for advancing the publication profession. They embrace new trends in a judicious and compliant manner. They know that in a rapidly evolving environment, they need to adapt their practices or risk being left behind. Because they are leaders, not laggards, they are proactively leveraging trends and technology. At all times, however, they base their actions on ethical principles and focus their actions on improving patient outcomes. Publication managers can become high-performing publication managers if they work with their stakeholders to ensure their publications are, indeed, future-proof and audit-proof.

Acknowledgements

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The Pharmacovigilance Medical Writer: Medical Writer, Project Manager, Regulatory Expert

Pharmacovigilance is a critical element of drug development and marketing. The evaluation and monitoring of patient safety and a drug’s benefit/risk is a highly regulated global task, which is required continuously throughout a drug’s lifecycle. The results of such analyses are reported to health authorities in periodic aggregate reports, and further PV documentation such as the RMP are increasingly required in regulations worldwide.

By Sven Schirp at Boehringer Ingelheim and Lisa Chamberlain James at Trilogy Writing & Consulting

The pharmacovigilance (PV) medical writer plays a crucial role – not only in the production of these documents, but also in their management. A skilled PV medical writer provides PV expertise; extensive knowledge of formal requirements and guidelines; document, format, and content expertise; and writing, communication, and project management skills. These skills ensure that the presentation of patient safety, the drug’s benefit/risk profile and the company’s risk management assessments to regulatory authorities are clear and consistent across the whole suite of PV documents, and that these documents are produced in a timely and efficient manner.

Introduction

Throughout clinical development and the post marketing phase, drug developers and marketing authorisation

holders (MAHs) invest heavily in monitoring and evaluating patient safety, and in managing the risks associated with drug exposure. The term “pharmacovigilance” encompasses the science and activities relating to the surveillance, detection, assessment, understanding, and prevention of adverse effects or any other drug related problem. Surveillance of safety data is a permanent activity, designed to ensure that potential safety signals are detected early and that the risks of exposing a patient to adverse drug effects are minimised.

Safety data are then analysed and the results provided to regulatory authorities (RAs) in periodic aggregate reports, most notably the Development Safety Update Report (DSUR) and the Periodic Benefit Risk Evaluation Report (PBRER or PSUR). The MAH has a legal obligation to assess and manage the risks

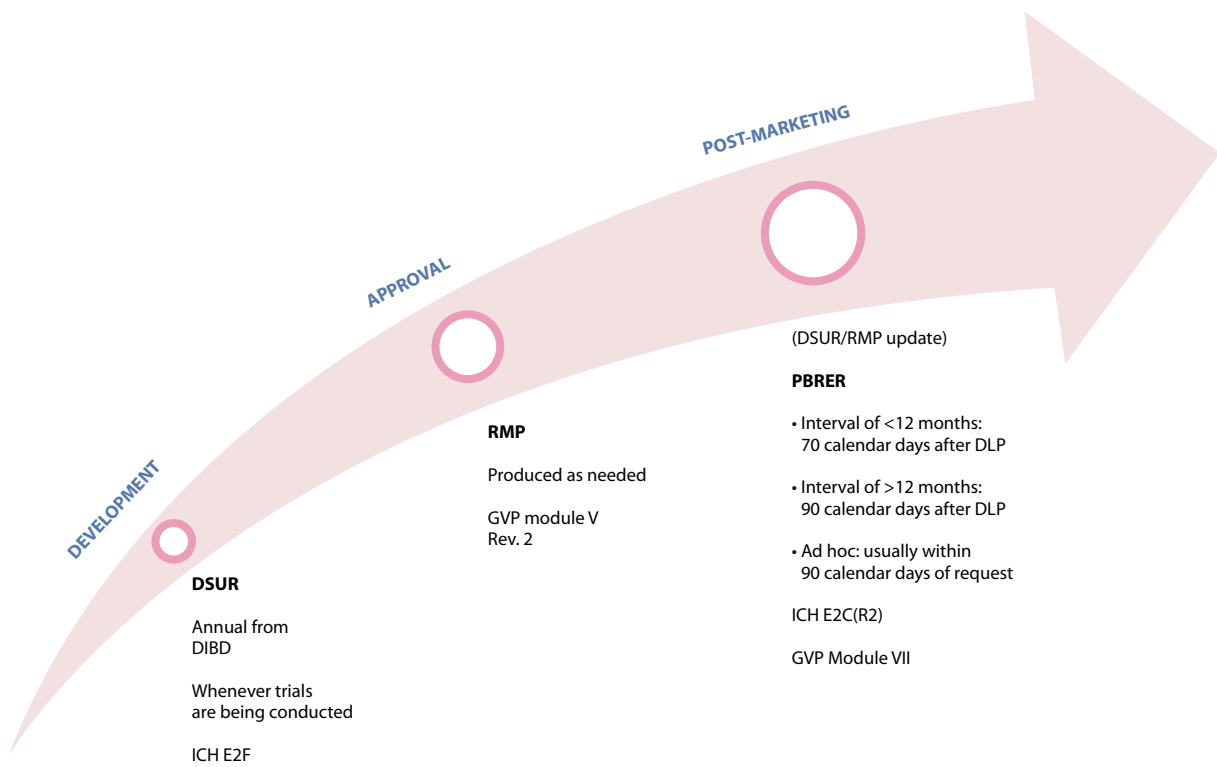


Figure 1: PV documents in the drug’s lifecycle

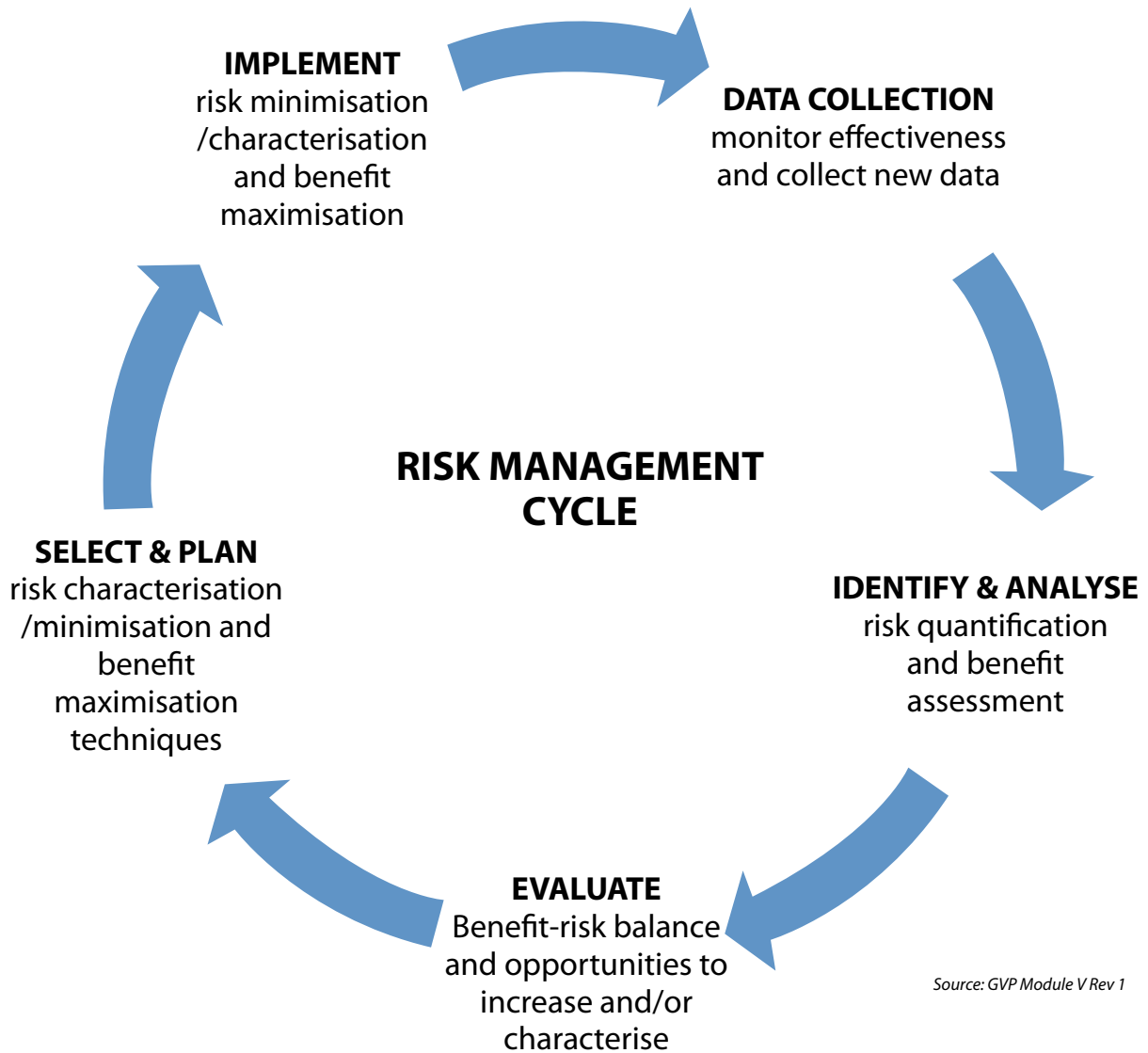


Figure 2: The risk management cycle

associated with their drug, and their risk management system and its associated risk minimisation activities are documented in the Risk Management Plan (RMP). Each of these documents is required at a different stage of a drug's lifecycle and fulfils different roles (see Figure 1).

Traditionally, PV documents have been authored by experts from the main contributing disciplines, eg PV, regulatory affairs, and medical affairs. However, implementation of the EU Guideline on Good Pharmacovigilance Practices (GVP) in 2012 introduced extensive changes, particularly to the format and scope of the PBRER and RMP, and to the way PV documents are assessed.

To meet the challenge of these changes, the PV medical writer works in collaboration with the traditional team of authors. The medical writer's role is crucial to ensure that the presentation of patient safety, the drug's benefit/risk profile, and the MAH's risk management assessment are clear to RAs, are consistent across the whole suite of PV documents, and that PV documents are produced in accordance with their strict deadlines.

The PV Medical Writer and the PV Document Lifecycle

DSURs

The requirement to submit PV documents to RAs starts with the first authorisation to conduct a clinical trial in any country worldwide. This date is defined as the development international birth date (DIBD) and marks the beginning of the reporting period of the first DSUR. The first data lock point (DLP) is 12 months thereafter and, as defined in ICH E2F along with their content and format, annual DSURs must then be submitted for as long as patients are exposed to the drug in interventional clinical trials. The DSUR must be submitted to RAs within 60 days after DLP.

The aim of the DSUR is to provide a periodic analysis of the safety of an investigational drug in clinical trials, to ensure patient safety during clinical development. There are several other requirements for reporting individual adverse events during trials, and so the DSUR is not the primary tool for

| EU | US* | Japan |
|--|---|---|
| Every 6 months for 2 years Annually for 2 years Every 3 years afterwards | Every 3 months for 3 years Annually afterwards | Every 6 months for 2 years Annually afterwards |

*The FDA accepts all three formats, the PADER/PAER, PSUR, and PBRER to fulfil the post-marketing periodic safety reporting requirements. Timings given here are for the PBRER.

Source: ICH E2C (R2), www.fda.gov and www.redlinepv.co.uk (accessed Dec 16)

Table 1: Reporting frequencies of PBRERs

reporting new important safety information to RAs. Instead, it summarises all relevant safety information that was collected during the reporting period. As for all PV documents, time can be a critical issue, and this is especially the case when working on DSURs for drugs well advanced in clinical development. The PV medical writer guides the team through the specific requirements of the DSUR and ensures that the document is concise and focuses on new and relevant safety information.

DSURs are produced during clinical development, and so the most critical point is the introduction of “important identified and important potential risks”. These are well defined subsets of the risks known to be, or are potentially, associated with the investigational drug, as described in the Investigator’s Brochure. An important risk is any risk that could have an impact on the benefit/risk profile of the drug or have implications for public health. Once defined in the DSUR, important identified and potential risks are carried forward beyond marketing approval and significantly drive the content of other PV documents (eg the RMP and the PBRER), and may require specific PV activities to prevent or minimise them. They must therefore be selected carefully and the PV medical writer’s role and experience is crucial to guide the team and alert them to the implications for future documents.

RMPs

In the EU and an increasing number of non EU countries, an RMP is required for any new marketing application. The content and format of the RMP is defined in GVP Module V. The document is well regulated in the EU and is well established globally. It is provided to RAs in Module 1 of the Common Technical Document (CTD) submission dossier and is one of the last documents to be completed before the Marketing Authorisation Application is submitted because it can only be finalised when the Summary of Product Characteristics is final. The aim of the RMP is to describe the safety profile of the drug, ie the important identified and important potential risks, plus any missing information (which is usually composed of potential risks for sub populations that were not sufficiently investigated in clinical trials).

In addition, the RMP must describe measures to prevent or minimise these risks and methods to assess the effectiveness of the interventions. It describes any post authorisation obligations and evaluates whether the efficacy shown in clinical studies is also seen in everyday medical practice, and whether there is a need for post authorisation efficacy trials. To write the RMP, the PV medical writer must have a sound knowledge of

the relevant guidelines and ensure that all contributions from other authors comply with GVP requirements. In addition, they must ensure that information contained in other submission documents (eg CTD clinical summaries) is in line with the data presented in the RMP.

The PV medical writer also uses his/her expertise and knowledge of the guidance and requirements to plan the most appropriate document format and the level of detail for data presentation, leading discussions on the risks and their categorisation as safety concerns, and on the strategic planning of related submission documents.

Risk management is a permanent activity that is ongoing for as long as patients are exposed to a drug. In this sense, the RMP is an exceptional document because it can be revised at any time in the drug’s lifecycle. Starting with version 1 (submitted with the initial marketing application), the RMP is assessed by RAs and might then be updated and revised multiple times until the drug is approved. In the post-marketing phase, the RMP is frequently updated whenever new safety information becomes available and in response to specific PV activities (see Figure 2).

RMP management is also an ongoing activity, involving updating the RMP and implementing or responding to comments from regulatory assessors. Depending on the level of project activity (eg submissions for new indications, line extensions), multiple versions of the RMP can be under assessment simultaneously by various global RAs. PV medical writers have a central role in maintaining oversight of the RMPs created for parallel submissions, managing complicated version control. The content of the RMPs can also vary between different regions according to local requirements. These are often complex issues, and good team interaction and internal processes are crucial.

PBRERs/PSURs

In the ICH regions, creating post marketing PSURs is a prerequisite of marketing approval. This can be the PBRER in the EU (GVP module VII) and most Eastern European countries, the Periodic Adverse Drug Experience Report (PADER) in the US, or the Annual Safety Report (ASR) in Canada. The PBRER is accepted by most countries, even those that provide specific local report templates, and its content and format are specified in ICH E2C (R2).

The reporting requirement and period of the PBRER starts with the International Birthdate ie, the marketing approval date. In the EU, the reporting frequency for each drug is published online in the EU reference date list. After

marketing approval, this frequency varies by region and drug lifecycle point (see Table 1).

The aim of the PBRER is to present a comprehensive and critical analysis of the benefit/risk profile of the drug, taking into account new or emerging information, in the context of cumulative information. This is to assure RAs that the evolving risk profile of the drug is adequately monitored. The PBRER focuses on summarising important relevant safety information from the reporting period, putting it into context with the cumulative experience. It is neither a tool to provide relevant information for the first time nor a “data dump” of extensive data from individual case reports. In the EU, PBRERs covering up to 12 months of data are due 70 days after the DLP and reports covering more than 12 months are due 90 days after the DLP.

The PBRER is assessed by the RA and feedback is provided to the MAH in the form of assessment reports. In these reports, an authority may request more detail on existing issues, or for new safety topics to be addressed in the next PBRER. PV medical writers have to guide teams through the relevant topics, advise on the level of detail, and manage the report timeline. Especially when writing for drugs on a six month periodicity, good time and project management skills are essential, considering that the assessment report for the last PBRER can be expected when the team is already writing the next report. The DSUR, PBRER, and RMP are designed to be modular documents, meaning that sections should be common to all three documents. Therefore, PV medical writers also have to ensure that the content of the PBRER is consistent with the information provided in the parallel DSUR and the potential RMP update.

Management of global PBRER periodicities and frequencies poses an enormous challenge to MAHs worldwide. DLPs and periodicities cannot be harmonised globally, eg China and Brazil accept the PBRER, but have their own DLPs, the Eurasian regions have different periodicities to the EU, and the US and Canada require annual reports. The PBRER can be a very large document, and requires input from many different stakeholders. An experienced and skilled PV medical writer can work with a dedicated medical writing group to establish a global report strategy for each drug so that as few PBRERs are written as absolutely necessary, while complying with global regulatory requirements.

Although the PBRER, DSUR and RMP are ICH formats and are widely accepted for submission to most health authorities, local formats like the PADER and the Investigational New Drug Annual Report in the US, or the ASR in Canada are often still submitted in lieu of these reports. Particularly when the PBRER EU periodicity is over one year, some MAHs prefer to write PADERS as annual reports and then submit the PBRER, eg every three years.

Conclusion

Since the introduction of GVP, PV has become more complex and further regulated. This has led to an increasing demand for medical writers who are familiar with PV documents

and have the skill set necessary to deal with multi disciplinary teams, complicated data, and challenging deadlines.

It is of utmost importance that the presentation of patient safety, the drug’s benefit/risk profile, and the MAH’s risk management assessments to RAs is compliant with requirements, clear and consistent across the whole suite of PV documents, and that these documents are produced in a timely and efficient manner. Involving an experienced PV medical writer in a product team ensures this, and enables the PV and medical experts to focus on their core task – patient safety.

Guidelines and Templates

GVP Modules

Visit: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

DSUR – ICH E2F

Visit: www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html

PBRER – ICH E2C (R2)

Visit: www.ich.org/products/guidelines/efficacy/efficacy-single/article/periodic-benefit-risk-evaluation-report.html

RMP

Visit: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp

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Tips and Tricks for Medical Writers: How to Produce High-Quality Regulatory Documents

This article will provide useful advice for authors of all types of medical and scientific regulatory documentation. It can be used as a training tool for new staff and a repository of helpful reminders for more skilled writers. It is a collection of rules and suggestions built up over nearly two decades of medical writing experience and of training and mentoring new medical writers.

By Helen Baldwin
at Scinopsis

Authors are often frustrated that reviewers of their documents do not focus on the key messages and clinical interpretation of the data, but instead make numerous corrections of minor issues such as formatting, abbreviations and punctuation. What the authors do not realise is that the reviewers cannot see the wood for the trees. It is a bit like the fact that my brain could not concentrate on writing this article until I had tidied my desk and emptied my email inbox! If our documents are messy, reviewers do not have time to look at what matters because they are too busy correcting the minor irritations. I guarantee that if you follow the advice provided in this article the quality of your documents will significantly improve and your reviewers will be free to concentrate on the content of your message instead of its packaging.

Document Structure and Formatting

A well-structured and well-formatted document should be pleasing to the eye and should help the reader navigate through its numerous chapters. In regulatory writing, we do not have much choice about structure as the chapter numbers are often predefined. Nevertheless, we have the possibility of inserting additional subheadings which can be invaluable for organising complex information. We can also use bulleted lists, bold, italics, paragraphs, tables and diagrams to break up the text and improve readability. In my opinion, no document should contain a full page of text with none of the above.

The simplest way to get your formatting right in Word is to attach a template with pre-set styles. Many companies also have customised tool bars to facilitate the use of styles and standardise certain repetitive tasks such as inserting references and tables. Never copy and paste formatting from another document unless it has identical Word styles. If in doubt, always use 'paste special' or the 'keep text only' paste option to avoid copying formatting.

Page headers and footers are important as they define the identity of the document, eg date, version number, study number etc. Do not forget to update these for each draft and

Medical Writing Tips

- Chapter numbers should never be typed manually. Create automatic chapter numbers using Word styles (Heading 1, Heading 2 etc.) and insert an automatic table of contents (References tab)
- Check consistency of the use of capitals in chapter headings.
- Use the 'navigation pane' (View tab) to view the document chapter headings. If any additional text appears, you probably need to correct the styles
- Always insert table and figure titles using 'insert caption' (References tab). This allows you to produce a table of contents and to insert cross-references (References tab)
- Use 'cross-reference' (References tab) for all references to chapters, tables, and figures. Check that the hyperlinks function correctly
- 'Refresh' your document regularly (CTRL+A then F9) to ensure that all automatic numbers are correct. Avoid use of page breaks or adding carriage returns to position text on a new page. It is better to use 'keep with next' (Layout tab, paragraphs, line and page breaks) to ensure that chapter headings stay with text, and that tables stay with their captions and footers
- Make sure that bulleted lists are consistent throughout with respect to symbols, indentation, and choice of punctuation at the end of each line (. , ; or blank)
- Use non-breaking hyphens (CTRL+Alt+Hyphen) to avoid hyphenated words splitting across lines and non-breaking spaces (CTRL+Alt+Space) between numbers and their units to avoid ending a line with a number

in all sections of the document. For more advice, please refer to the medical writing tips above. Table 1 consists of Word shortcuts that are useful for medical writers.

Harmonisation

It is essential to decide what terms to use, and then to stick to them throughout the whole document. Readers do not like to have to keep switching between words that look different but are really saying the same thing. So define your terms from the beginning and then be consistent. It is also important to reach an agreement with the statistician to ensure harmonisation between the statistical tables and your text. Below are some of the most important concepts and terms that should be consistent.

British versus American Spelling

Many scientific words are spelt differently on the two sides

of the Atlantic (see Table 2). It is important to choose one 'language' or the other. The choice may depend on the instructions for authors, company style guide, or whether you are writing for Europe or the US.

Medical writing tip: Set your spellchecker to the correct language and be careful when you copy and paste text from other sources in case the language changes.

'Subjects' versus 'Patients'

Some companies describe participants as 'subjects' in Phase 1 studies (because they are usually healthy as opposed to having the disease to be treated) and as 'patients' in Phase 2-4 studies. Other companies use a single term for all study types, so check this before you start.

Medical writing tip: You can use CTRL+F to search for both words to check you have used one term consistently. However, do not automatically replace one with the other as this can lead to mistakes, eg 'subjective' becomes 'patientive'.

Investigational Product Names

Harmonise the product names and avoid switching between generic names, trade names and internal product numbers.

Treatment Group Names

Think about these carefully as you will have to repeat them many times throughout your document. Decide whether the dose and route of administration need to appear in the group name or not. Generally, these are only needed if they are

“ A well-structured and well-formatted document should be pleasing to the eye and help the reader navigate through its numerous chapters. In regulatory writing, we do not have much choice about structure as the chapter numbers are often predefined ”

different between groups. Say, for example, you are writing a clinical study report about a study with three treatment groups:

- Drug A 5mg orally once daily for seven days
- Drug B 10mg orally once daily for seven days
- Placebo orally once daily for seven days

'Orally once daily for seven days' is identical for each group so it could be deleted from the group names. However, the dose is needed as it varies.

Visit Names

A visit could be called 'Day 30', 'Week 4', 'Month 1', 'End of

| Action | Shortcut |
|--|-------------------|
| Capitals, no capitals or first letter capitals | SHIFT+F3 |
| Repeat last action | F4 |
| Update fields (refresh) | F9 |
| Cut | CTRL+X |
| Copy | CTRL+C |
| Paste | CTRL+V |
| Paste special | CTRL+ALT+V |
| Copy format (paintbrush) | CTRL+SHIFT+C |
| Paste format (paintbrush) | CTRL+SHIFT+V |
| Select all | CTRL+A |
| Bold | CTRL+B |
| Italic | CTRL+I |
| Underline | CTRL+U |
| Centre text | CTRL+E |
| Left align text | CTRL+L |
| Right align text | CTRL+R |
| Undo | CTRL+Z |
| Re-do | CTRL+Y |
| Non-breaking space | CTRL+SHIFT+Space |
| Non-breaking hyphen | CTRL+SHIFT+Hyphen |

Table 1: Useful Word shortcuts

| British | American |
|---|--|
| Words spelled with 'ae' aetiology, anaemia, anaesthesia, glycaemic, gynaecology, haematology, haemophilia, ischaemia, orthopaedic, paediatric | Words spelled with 'e' etiology, anemia, anesthesia, glycemic, gynecology, hematology, hemophilia, ischemia, orthopedic, pediatric |
| Words spelled with 'oe' diarrhoea, foetus, gonorrhoea, oestrogen | Words spelled with 'e' diarrhea, fetus, gonorrhea, estrogen |
| Words spelled with 'our' behaviour, colour, favourable, rigour, tumour | Words spelled with 'or' behavior, color, favorable, rigor, tumor |
| Words ending in 're' centre, goitre, litre, millimetre | Words ending in 'er' center, goiter, liter, millimeter |
| Words ending in 'ise' or 'yse' analyse, dialyse, emphasise, paralyse, randomise, realise, specialise, standardise | Words ending in 'ize' or 'yze' analyze, dialyze, emphasize, paralyze, randomize, realize, specialize, standardize |
| Other words aluminium, grey, sulphur | Other words aluminum, gray, sulfur |

Table 2: British versus American spelling

Wash-Out Period' etc. Choose one name for each visit and stick to it. This is particularly important for clinical study protocols and avoids confusion for the investigators later. Whenever possible, choose meaningful names, eg 'Month 6' provides more information than 'Visit 6'.

Study Names

In certain documents, for example summaries of the common technical document, you may have to refer to several studies many times. Simply using the study numbers may not be helpful as people outside your company will not know what they refer to. The full study titles are probably too long to use. So define short, relevant names in agreement with the project team and use them consistently.

Medical Writing Style: The Importance of Being Clear and Concise

I am a pharmacologist, not a linguist, and I would not pretend to know everything about grammar or writing style. However, I do have many years of experience of reviewing text written by junior medical writers, and there are a few key points that I try to teach new writers as I believe they significantly enhance readability. I would like to share some of this advice here:

| Long | Short |
|------------------------|-------------|
| A greater number of | More |
| A higher proportion of | More |
| The majority of | Most |
| Most of the | Most |
| Higher compared with | Higher than |
| With the exception of | Except |
| In order to | To |

Table 3: Long phrases and how to shorten them

Use Short, Single Topic Sentences

Let your reader breathe. If you need to take a breath while reading your sentence, it should probably be split into two or three sentences.

Avoid Repetition

It is often advisable to change the word order in a sentence in order to avoid repetition.

- Example: Group A had a mean systolic blood pressure of 13.3mm Hg on Day 1 and Group B had a mean systolic blood pressure of 15.6mm Hg on Day 1
- Improved version: *The mean systolic blood pressure on Day 1 was 13.3mm Hg in Group A and 15.6mm Hg in Group B*

I only advise using 'respectively' for studies with three or more groups. It requires a little more mental gymnastics to understand.

Put the Most Important Information at the Beginning of the Sentence

- Example: During the 13-week treatment period, 3.6% of subjects in the Drug A group and 2.3% of subjects in the placebo group reported headaches

The sentence is about headaches, so it needs to be mentioned first. That way, anyone who is not interested in headaches does not have to read it.



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Hopefully, if you follow this advice, you will find that reviewers focus on the content and clinical interpretation instead of what may sometimes seem like petty details such as punctuation at the end of your bulleted lists ””

- Improved version: Headaches were reported by 3.6% of subjects in the Drug A group and 2.3% of subjects in the placebo group during the 13-week treatment period

Use ‘Parallel’ Sentences

Keep the order of sentences the same wherever possible. Once again, this avoids the reader having to perform mental gymnastics.

- Example: Osteoporosis was reported for 10% of women and 2% of men. The data showed that 5% of men versus 15% of women suffered from headaches
- Improved version: Osteoporosis was reported for 10% of women and 2% of men. Headaches were reported for 15% of women and 5% of men

Do Not Try to Sound Clever by Using Fancy Words

In English literature, using different words to say the same thing is encouraged as it makes the text more interesting. However, you should not need a thesaurus to read a scientific document. When writing scientific texts, just use the same wording to say the same things throughout your document and that way the reader will be sure to understand the data.

Do Not Waste Words

Many writers seem to believe they appear more intelligent if they use as many words as possible. However, your job is to make the reader feel that he/she is intelligent because they understand your text easily! The best way to do this is to write clear, succinct text without superfluous words. Table 3 lists a few examples of common longer phrases, which can easily be shortened.

It drives me crazy when I read a phrase such as: ‘A *higher proportion of* patients in Group A had adverse events *compared with those* in Group B’. We can simply say: ‘*More* patients in Group A had adverse events *than* in Group B’. Can you imagine how strange we would sound if we said ‘My sister is older *compared with* me and she has a *greater number of* friends’?

Abbreviations

The generally accepted convention is that abbreviations should be defined at first use and then used consistently throughout a document. However, the abstract or synopsis is usually treated as a standalone document. So, define abbreviations at first use in the synopsis and then again in the body of the text. Regulatory documents should contain an abbreviations list, whereas most manuscripts do not (check instructions for authors). Make sure this list contains all the

abbreviations you have used and, equally importantly, none you have not used.

You may be tempted not to sort out abbreviations in your first draft. However, be aware that reviewers are often irritated by this. So you should insert an explanatory comment at the start of the document.

Medical writing tip: The quickest and safest method for frequently used abbreviations is to use them throughout the first draft of your document. Then, when you are nearly ready to finalise your draft, use CTRL+F to search for the first appearance and define it there. Also, use CTRL+F to search for the full term throughout the document in case you have forgotten to use the abbreviation somewhere.

Conclusion

I hope this list of ideas for how to improve the quality of your documents will be helpful for new medical writers, as well as being a useful reminder for more experienced writers. Hopefully, if you follow this advice, you will find that reviewers focus on the content and clinical interpretation instead of what may sometimes seem like petty details such as punctuation at the end of your bulleted lists. Medical writing can sometimes be frustrating, but it can also be extremely rewarding, especially when you get to the end of a long, difficult project and your boss or your client says: “Well done, you’ve done a really great job”!

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Improving Statistical Reporting in Medical Research Journals

An excellent way to improve your professional reputation is to learn how to interpret and report statistics. Statistical reporting guidelines are now available, and the learning curve for applying them is not steep. You don't need to know how to answer statistical questions, only how to ask the right question at the right time. The reporting problems described here are among the most common and illustrate how easily some of them can be recognised.

By Tom Lang at Tom Lang Communications and Training International

"The medical literature is plagued by poor reporting of research studies hindering its utilisation in clinical practice and further research. This is unethical, wasteful of scarce resources and even potentially harmful"

Douglas Altman & Alison Hirsch, 2012 (1)

The Problem of Poor Statistical Reporting

Since the first *P* value was reported in the mid 1930s, hundreds of studies have found that large numbers of articles in the clinical literature contain statistical or methodological errors (2-9). Furthermore, most of these errors are serious enough that they threaten the validity of the authors' conclusions (5,10). The problem is especially serious because most of these studies are of the world's leading peer-reviewed medical journals.

Many of these errors are in basic, not advanced, statistical methods (10). In fact, authors are far more likely to use only elementary statistical methods, if they use any at all (11-13). Thus, the problem of poor reporting is long-standing, widespread, potentially serious, concerns mostly basic statistics, and yet is largely unsuspected by most readers of the biomedical literature (14). Nevertheless, the first comprehensive guide to reporting statistics in medicine and the first complete set of statistical reporting guidelines suitable for a journal's instructions for authors were developed recently and not by statisticians or physicians (14,15).

In this chapter, I describe some of the most common statistical reporting errors in medical journals. There are many more where these came from.

Problems with Reporting Descriptive Statistics

Errors in Basic Math

Authors make lots of **counting** and **mathematical errors**. In an unpublished study by the Department of Medical Editing Services at the Cleveland Clinic, 21 of 32 consecutive manuscripts received for editing had errors in basic math. This problem of carelessness with numbers has been noted for almost 60 years (16).

Choices in Measures of Centre and Dispersion

Distributions of data are often described with a "measure of centre," such as the **mean, median, and mode**, and with a "measure of dispersion," or spread of the data, such as the **standard deviation, range, or interquartile range**. From habit, many researchers report distributions as means and standard deviations. However, standard deviations, and to a lesser extent, means, are meaningful only for more-or-less normally distributed data, and most biological data are not normally distributed. Thus, other descriptive statistics are often indicated.

Percentages

In small samples, a few values can be a large percentage of the total, which can be misleading: "33% of the rats lived, 33% died, and the last one got away." For this reason, **percentages** should not be used for small samples, say, less than 25, and the numerator and denominator on which a percentage is based should *always* be readily available to the reader.

Problems with Reporting Measures of Relationships

Tests versus Measures of Association

Association describes relationships between categorical (usually nominal) variables. Most often, association is assessed with a **test of association** and is declared to be simply present or absent by whether the *P* value is statistically significant or not. In contrast, **measures of association** indicate the strength of the relationship. For example, the phi coefficient ranges from +1 (a perfect positive association) to -1 (a perfect negative association), where values farther away from zero indicate a stronger direct or inverse association, respectively.

Correlation

Correlation coefficients describe relationships between continuous variables. These coefficients also range from +1 (a perfect positive correlation) to -1 (a perfect negative correlation). Some authors insist that coefficients between 0 and +0.3 (or -0.3) indicate a weak correlation, those between +0.3 and +0.6 indicate a moderate correlation, and those between +0.6 and 1 indicate a strong correlation. In fact,

| Measure of risk for death by prostate cancer | Value |
|---|---------------|
| • Absolute risk with watchful waiting | 15% |
| • Absolute risk with prostate resection | 7% |
| • Absolute risk reduction with resection | 8% |
| Risk ratio for watchful waiting (versus resection) | 2.14 |
| Relative risk reduction with resection | 53% |
| Odds with watchful waiting | 0.18 |
| Odds with resection | 0.08 |
| Odds ratio with watchful waiting | 2.25 |
| 5-year hazard rate with resection | 0.4% |
| Number of patients needed to treat with prostatectomy to prevent 1 more death | 12.5 |
| • Natural frequency, watchful waiting | 15 of 100 men |
| • Natural frequency, resection | 7 of 100 men |

Table 1: Risk of death from prostate cancer treated with watchful waiting or prostate resection. These nine measures of risk are common and accurate indications of the probability of death from prostate cancer. They all have their uses, but each gives a different impression of the risk involved. For example, compare the absolute risk reduction for resection with the relative risk reduction. The absolute risk, absolute risk reduction, and natural frequencies are probably the easiest for most people to understand (in this example, 14 of 200 men treated with resection died, and 30 of 200 men with watchful waiting died)

there are no meaningful arbitrary cut points for degrees of correlation. Coefficients have to be interpreted in light of the medicine. The concentration of a drug in an IV infusion should be highly correlated with serum concentration; even a coefficient of 0.85 may be unacceptably low.

Choice of Measures of Risk

Risk can be reported in several ways, some of which can be misleading and some of which are more easily understood than others (see Table 1). The absolute risk should always be reported, because the other measures of risk can be derived from it.

Problems with Reporting Hypothesis Tests

Hypothesis tests are statistical procedures used to determine the probability that chance is a plausible explanation for a relationship indicated by the data, such whether the mean values of three groups differ or whether two variables are correlated. If this probability is low (typically <0.05), chance is discarded as an explanation, and the relationship is considered to be real.

Violations of Assumptions

All hypothesis tests are based on assumptions about the data that, if violated, should reduce confidence in the results. One commonly violated assumption is that data are “independent”, such as coming from separate patients, when they are actually paired, in which they come from the same patient. An unpaired test does not account for changes in the post-test scores of individual patients, for example, whereas a paired test does.

Another commonly violated assumption is that data are linearly related, in which case they can be analysed with linear regression analysis. However, linearity should be verified,

often with an “analysis of residuals,” which is a graph of the differences between the actual and predicted values of each data point. Small differences close to zero all along the X-axis indicate that the data are linear; other patterns do not.

Low Statistical Power

A statistical power calculation computes the number of subjects who need to be studied to have a given probability of finding a given difference, if such a difference exists in the population studied. The “given probability” is the statistical power coefficient. A coefficient of 80% or 90% is typical. The difference of interest is usually the “minimum clinically important difference.” If statistical power is inadequate – that is, if the sample is too small – a nonsignificant *P* value does not necessarily mean that the groups are similar: “absence of proof is not proof of absence.” In such cases, the study results are not negative, they are inconclusive.

Misinterpreting *P* Values

Probably the most common statistical error in the literature is assuming that a statistically significant *P* value indicates a biologically important difference. A *P* value is a measure of chance as an explanation for a difference; it has no clinical meaning. The actual difference – the “effect size” – should be interpreted in the context of the study, and it may be important whether the *P* value is significant or not.

Not Reporting Confidence Intervals

A **confidence interval** is a measure of precision for an estimate. The difference between groups, say, is actually an estimate and thus should be accompanied by a confidence interval. A 95% confidence interval identifies the range of values in which we would expect the difference between groups (the estimate or effect size) to fall in 95 of 100 similar studies.

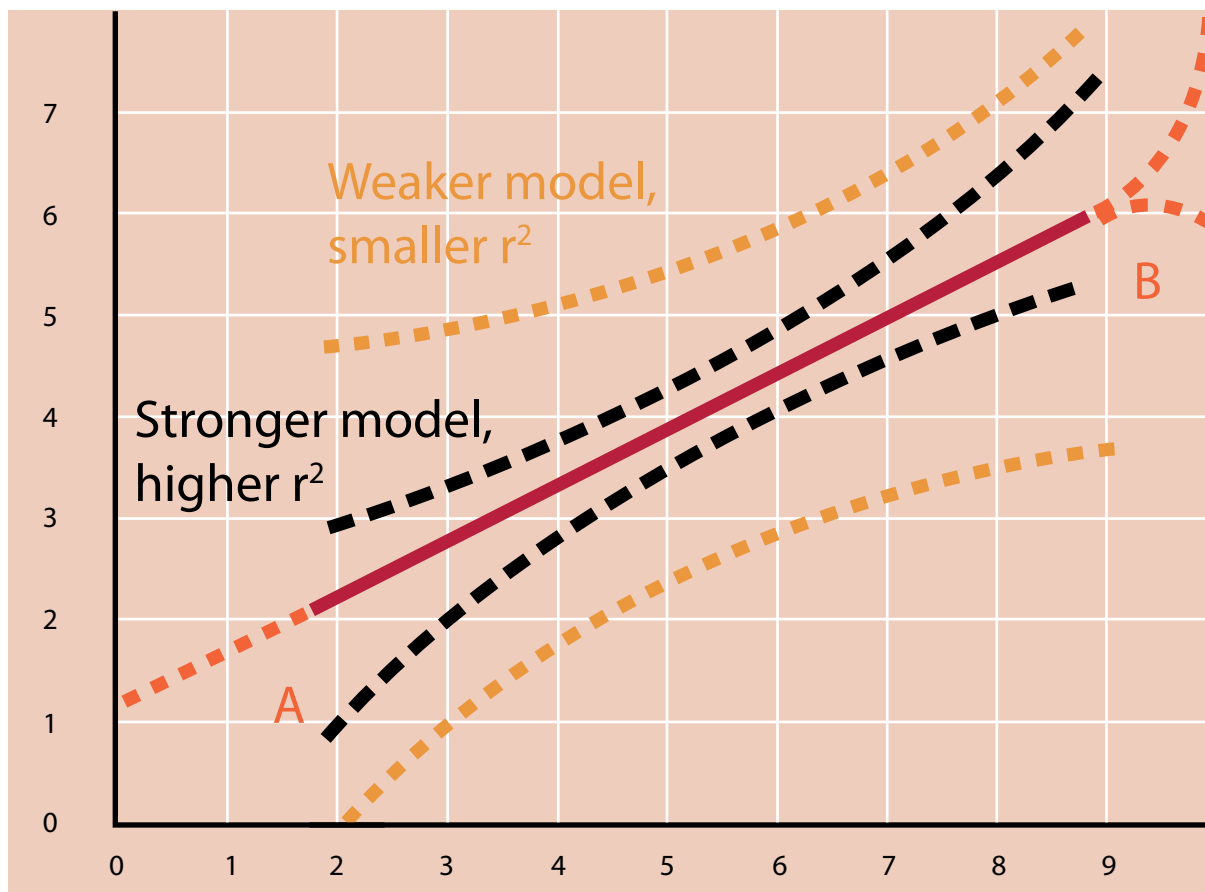


Figure 1: A simple linear regression model: $Y=1+0.6X$, where 1 is the Y-axis intercept point, 0.6 is the regression coefficient or beta weight, and X is the value of the predictive variable. Here, for each 1-unit increase in X, Y will increase by 0.6 units, which is the slope of the regression line (the solid line in the figure), calculated as the “rise over the run,” or 5/8 (0.6) in this case. The wider pair of dotted lines is the confidence band for the slope of the regression line when the model does not fit the data as well as a model with the narrower confidence band. Thus, the coefficient of correlation, r^2 , is smaller (closer to zero) for the wider confidence band and larger (farther away from zero) for the narrower band. The bands flare at the ends because typically there are fewer data points on the ends of the distribution of values of X. Less data means a weaker estimate and hence, a wider confidence interval for those values of X. Two other mistakes are A) extending the regression line beyond certain threshold values. For example, birth weight can never be zero, so the line should not be extended to the Y-axis. B) Assuming that the regression line will stay linear for values of X beyond the data collected. There are no guarantees that the line will continue to have the same slope or shape in areas for which data have not been collected

“The drug lowered systolic blood pressure by a mean of 18 mm Hg (95% CI = 2 to 34 mm Hg; $P = 0.02$)”

In this one study, the drug resulted in a mean 18-mm Hg drop in blood pressure, and the drop was statistically significant. The confidence interval, however, is “heterogeneous”: it contains both clinically important values at the high end and unimportant values at the low end. That is, in 95 of 100 similar studies, we might or might not get a clinically important reduction in blood pressure. So, rather than claim that the study result is positive on the basis of a single P value, we have to acknowledge that it is inconclusive. When the interval is “homogeneous,” or includes only clinically important or only unimportant values, we can make a more definitive conclusion.

Confidence intervals, with their associated estimates, keep the attention focused on the medicine and away from P values when interpreting results. Many journals now prefer confidence intervals instead of P values for this reason.

Problems with Reporting Regression Analyses

Regression analyses are a class of statistical tests used to predict an unknown value of one variable from the known values of one or more predictor variables. Simple regression models (either linear or logistic) have a single predictive variable; multiple regression models have two or more. Linear regression models (simple or multiple) predict a continuous value (eg, triglyceride concentration); logistic regression models predict a binomial value (eg, survival or death).

Not Reporting the Model's Goodness of Fit

In any regression analysis, we need to know how well the model predicts the variable of interest. One measure of this "goodness-of-fit" to the data is **the coefficient of determination, r^2** , for simple regression models, and **the coefficient of multiple determination, R^2** , for multiple regression models. These coefficients range from zero to 1, with higher values indicating better predictive abilities (see Figure 1). Other measures exist.

Not Reporting the Model-Building Process

The model-building process consists of selecting candidate variables even remotely related to the endpoint, often those with a *P* value of 0.1 or 0.2 for their relationship with the predicted variable. Candidate variables are then screened for **colinearity and interaction**. Colinear variables add the same information to the model, so only one is used. Interacting variables produce a result greater than that of their separate results (eg, the combination of sub-lethal doses of alcohol and barbiturates can cause death.) This interaction must be accounted for by adding an "interaction term" to the model.

Candidate variables remaining after screening are then combined using any of several variable-selection methods, such as forward, backward, stepwise, and best-subset techniques.

Not Validating the Final Model

Validating the model means to test how well it predicts, usually on a different set of data. One of several methods is the split-half technique, where the model is developed on a portion of the data and then tested in the remaining data to see how well it predicts.

Conclusions

Evidence-based medicine is *literature*-based medicine. By applying statistical and methodological reporting guidelines, medical writers and editors can assure that research designs and activities are appropriately documented, greatly improving the quality of manuscripts and the literature and, hence, the evidence on which medical care is based.

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Clinical Trial Disclosure and Transparency: Ongoing Developments on the Need to Disclose Clinical Data

Public demand and regulatory changes have brought pressure for greatly improved transparency of information about medicines, clinical trials, and drug development in general. This article reviews the regulations demanding clinical trial disclosure as well as its implications on sponsors and marketing authority holders. It focuses in particular on the disclosure requirements of two leading regions in this field: the EU and the US.

By Kathy B Thomas

'Clinical Trial Disclosure', with its efforts to increase transparency of information on clinical trials, is an established topic for all involved in clinical drug development. Stakeholders come from across the pharmaceutical industry, academic institutions and hospitals performing clinical trials, as well as from groups representing patients, health professionals and prescribers, and groups with political-, industry-, economics-, or legislative-motivated interests that are relevant to drug development, approval, and marketing.

The regions of the world particularly active with regard to transparency laws on 'Clinical Trial Disclosure' are the European Union (EU), including countries of the European Economic Area (EEA), and the United States of America (US). Additional national disclosure obligations also apply in some 40 countries world-wide.

Current Disclosure Obligations and Requirements

EU/EEA and US

Key issues regarding disclosure are defined by Regulation (EU) No 536/2014, which was issued on 16 April 2014 and will come into force in 2018 (1). In the interim, the applicable laws are the Clinical Trials Directive 2001/20/EC and the Paediatric Regulation (EC) 1901/2006 (Articles 41, 45, 46 in particular) (2). The two main instruments in clinical trial

disclosure efforts are the separate legal EU/EEA and US provisions described in Table 1.

Regulation (EU) 536/2014 harmonises the assessment and supervision processes for clinical trials throughout the EU via the EU portal and database. It addresses the publication of clinical data, including the registration of all interventional studies and posting of trial result summaries for both *approved* and *not yet approved* medicinal products (1,3). However, it does not apply to non-interventional studies or those with medical devices, unless the devices are part of a trial involving a medicinal product. European regulators have established a clear distinction between 'clinical trials' ('interventional clinical studies') and 'clinical studies' (1). Accordingly, the term 'clinical study' represents a broader concept, whereby a 'clinical trial' is defined as a specific type of clinical study.

Implementation of Regulation (EU) 536/2014 is under the responsibility of the EMA, that also manages the EU portal and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database (www.clinicaltrialsregister.eu).

EudraCT database can only be used for studies performed in the EU/EEA (ie those studies that have a Eudra number) or for those associated with regulatory applications in this region, such as those conducted *outside* of the EU/EEA in

“ Regulation (EU) 536/2014 addresses the publication of clinical data, including the registration of all interventional studies and posting of trial result summaries for both *approved* and *not yet approved* medicinal products ”

| The EU/EEA (Regulation (EU) 536/2014) (1,3) | The US (FDAAA 801, expanded by Final Rule) (6,7) |
|--|---|
| <p>Register and disclose all <i>interventional</i> clinical trials with EudraCT number</p> <p>Trial registration is performed by the EMA upon receiving the official request for authorisation of a clinical trial on a medicinal product for human use</p> <p>Applies to trials ongoing or started:</p> <ul style="list-style-type: none"> • After May 2004 in adults • After May 2006 in children | <p>Register all <i>applicable clinical trials</i> ongoing or started after September 2007 in the US or as part of a US regulatory application</p> <p>Trial registration is performed by the sponsor within 21 days after <i>enrolment</i> of the first trial participant</p> |
| <p>Applies to trials in:</p> <ul style="list-style-type: none"> • Children: Trial category 1, 2, 3^(4,8) • Adults: Trial category 1, 2, 3^(4,5) | <p>Applies to trials in:</p> <ul style="list-style-type: none"> • Children: Phases 2, 3, 4 • Adults: Phases 2, 3, 4 |
| <p>Disclose summary results for:</p> <p>Any tested medicinal product, regardless of the regulatory approval status</p> | <p>Disclose summary results for:</p> <p>Any tested medicinal product, regardless of the regulatory approval status</p> |
| <p>Timelines for disclosure of summary results (1,3,18):</p> <ul style="list-style-type: none"> • Trials in children within 6 months of last patient last visit (LPLV) (for primary endpoint)⁽¹⁾ • Trials in adults within 12 months of LPLV (for primary endpoint)⁽¹⁾ | <p>Timelines for disclosure of summary results (6-8):</p> <ul style="list-style-type: none"> • For all <i>applicable clinical trials</i> within 12 months of LPLV (for primary endpoint)^(1,2) |
| <p>Additional documents to disclose:</p> <ul style="list-style-type: none"> • Layperson language summary⁽¹⁾ • Study Protocol (<i>each</i> version and modification)⁽¹⁾ • Investigational medicinal product dossier (Section S and E)^(3,7) • Investigator's brochure⁽³⁾ • Subject information sheet⁽³⁾ • Clinical trial report (redacted)⁽³⁾ | <p>Additional documents to disclose:</p> <ul style="list-style-type: none"> • Full study protocol including <i>all</i> amendments⁽⁶⁾ • Statistical analysis plan including <i>all</i> amendments⁽⁶⁾ |

Table 1: Clinical Trial Disclosure: A summary of the main requirements in the EU/EEA and the US

| |
|---|
| <p>In addition to the EU/EEA and the US, other national obligations for disclosure exist in at least 40 countries. National requirements do not necessarily harmonise in their regulations (details of necessary information, its format, or timelines). Some expect registration of a clinical study protocol only, while others also require posting of results after a specific time of clinical study completion.</p> <p>[1] Completion date of an applicable clinical trial is defined as the date that the final subject was examined, or received an intervention for the purposes of final collection of data for the primary outcome or endpoint – whether or not the study was completed according to the protocol or was stopped prematurely</p> <p>[2] Delayed posting of results with certification is possible. A conditional delayed posting is possible for two additional years (three years in total), after the completion of the <i>primary outcome</i> or endpoint. The conditions for delay of results posting may include commercial product development for initial FDA marketing approval or clearance, or approval for a new use (6-8)</p> <p>[3] Timing of publication of these documents varies, depending on the trial category (3)</p> <p>[4] For definitions, see Table 2</p> <p>[5] Currently, data on Phase 1 trials in adults (that are not part of a PIP) are not made public, although this may change. At the time of writing, it was not clear whether the documents submitted to the EMA for only some or all category 1 trials in healthy adults will be made public</p> <p>[6] Post study protocol and statistical analysis plan (with <i>all</i> amendments for both documents), at or before the time of trial results information submission (8)</p> <p>[7] Structure the IMPD sections (section Q, S, E) as modules that can be easily separated and sent for public posting at required timelines</p> <p>[8] A paediatric trial is a trial that includes at least one participant less than 18 years of age</p> |
|---|

so-called 'third countries'. The EudraCT database contains details on 29,165 clinical trials as of November 2016.

Another topic of intense interest in the EU is the EMA Policy 0070, which stipulates a step-wise and proactive release to the public of 'clinical reports', and later of the clinical trial participant-level data for all studies submitted as part of a centralised marketing authorisation application in the EU. Policy 0070 has been in effect since 1 January 2015 and applies to medicinal products that were approved, *but* also to those applications that were rejected or withdrawn (4,5).

In the US, disclosure of clinical study information is legislated under the FDA Amendments Act of 2007, Section 801 (also known as FDAAA 801), that expanded in September 2016 by the final rulemaking (Final Rule), as well as the complementary

commitments announced by the National Institutes of Health (NIH) Policy to share individual trial participant-level data (6-9). The extended FDAAA 801 law and the NIH Policy comes into effect on 18 January 2017.

The US law on disclosure is administered by the FDA, managed by the US National Library of Medicine (a service of the NIH) and uses the database ClinicalTrials.gov (www.clinicaltrials.gov). The main purpose of this database is to accommodate applicable clinical studies performed in the US or as part of an FDA regulatory drug application. Nevertheless, the database is open to all clinical studies irrespective of country of origin, sponsor or clinical phase. As of November 2016, the database contained registration details on 230,427 trials with locations in 193 countries. Most are from non-US only study sites (46%), 37% are situated only in the US, and 6% have both non-US and US locations.

| Document/item | Content/definition/comment | Citation |
|--|--|----------|
| Regulation (EU) 536/2014 | Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC | 1 |
| Appendix, on disclosure rules, to the 'Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014' | This document sets out rules and criteria for the application of Regulation (EU) 536/2014 | 3 |
| Low-intervention clinical trial ^[1] | A clinical trial which fulfils <i>all</i> of the following conditions: (a) the investigational medicinal products (IMPs), excluding placebos, are authorised (b) according to the protocol of the clinical trial, (i) the IMPs are used in accordance with the terms of the marketing authorisation; or (ii) the use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned | 3 |
| Category 1 trial ^[1] | Pharmaceutical development clinical trials include: • Phase 1 clinical trials in healthy volunteers or patients; test whether a treatment is safe for people • Phase 0 trials – studies in healthy volunteers or patients; explore pharmacokinetics or pharmacodynamics • Bioequivalence and bioavailability trials • Similarity trials for biosimilar products • Equivalence trials | 3 |
| Category 2 trial ^[1] | Therapeutic exploratory and confirmatory studies include: • Phase 2 and 3 trials • Not only trials by the marketing authorisation holder (MAH), but also those by other researchers looking at safety and efficacy in new indications, pharmaceutical forms and routes of administration, or patient populations and not covered by the definition of category 3 | 3 |
| Category 3 trial ^[1] | Therapeutic use clinical trials include: • Phase 4 • Low-intervention clinical trials | 3 |

Table 2: Clinical Trial Disclosure in the EU/EEA: Supporting documents and definitions based on Regulation (EU) 536/2014

[1] Definition that applies for the purposes of the Regulation (EU) 536/2014

Overall, the current regulations in both EU/EEA and the US require the registration of new clinical trials and posting of summary results for all completed studies, regardless of the approval status of the medicinal products. In addition, the EU/EEA also requires the release of clinical reports and patient-level data for trials of approved, rejected, or withdrawn medicinal products. These are described more fully below and are also summarised in Tables 1, 2 and 3.

Requirements in Other Countries

Publication of clinical trial information is also mandatory in over 40 other countries worldwide. Unfortunately, there is no freely available list or electronic database with the national requirements for clinical trial disclosure. Painstaking research on national websites is necessary to identify what is needed. While some only expect registration of a clinical study protocol, others also demand disclosure of results by a specified time after study completion. The national requirements differ in their content, format, or timelines and thereby present a challenge for sponsors of multinational trials.

In the current maze of regulatory demands on this topic, a summary of clinical disclosure requirements in other countries or world regions would be a very welcome and useful tool. The WHO might be in a position to take the stewardship of such a centralised information repository, which would nicely complement the available clinical trial search possibilities that are already available on the WHO website (10).

Requirements by Other Advocates of Transparency and Disclosure

Declaration of Helsinki 2013

The legally binding regulations for clinical data disclosure in the EU and the US are in agreement with the latest version of the Declaration of Helsinki 2013. The Declaration stipulates the ethical obligation and duty of researchers, authors, trial sponsors, journal editors and publishers to register their clinical trials before the start of patient recruitment, and to follow up with publication and public dissemination of results (11). Since most study protocols contain the statement that the “study will be performed in



agreement with the Declaration of Helsinki”, trial registration and disclosure are also an ethical requirement. In some countries, ethics committees and institutional review boards demand proof of registration of the clinical trial in a public database.

ICMJE

In 2004, the International Committee of Medical Journal Editors (ICMJE) stipulated that registration of studies in a publicly accessible database is a condition for publication of trial results. Since then, many peer-review journals have adopted this principle (12,13). In February 2016, the ICMJE proposed even bolder orders: that data generated in interventional clinical studies be responsibly shared with external investigators (14). The suggested data sharing would require authors to make de-identified individual patient data (IPD) underlying the results presented in the article – including tables, figures, appendices or supplementary material – available no later than six months after publication. The scientific community’s response to this

proposal has been mixed; the ICMJE have published more than 300 comments that they have received on their website and plan to adopt data sharing after considering this feedback (15).

Pharmaceutical Trade Associations

Trade associations Pharmaceutical Research and Manufacturers of America (PhRMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA) prepared a common document titled ‘Joint principles for responsible clinical trial data sharing’ that was implemented on 1 January 2014. This document emphasises the commitment of the pharma member companies of PhRMA and EFPIA to disclosing clinical trial data (16).

Registration of New Clinical Trials

EU and US

Laws on the registration of clinical studies aim to ensure that information about those performed with human

“ In 2004, the International Committee of Medical Journal Editors (ICMJE) stipulated that registration of studies in a publicly accessible database is a condition for publication of trial results. Since then, many peer-review journals have adopted this principle ”



For an interventional clinical trial in adults completed *before* 21 July 2014, disclosure of results can be made using the synopsis of an ICH E3-compliant clinical study report (CSR) or a pre-specified dataset of summary results ('full dataset'), or both. For all trials that have concluded *on or after* 21 July 2014, the full dataset must be posted in the EudraCT database

subjects is available or registered in the public domain. This allows patients and relatives as well as treating doctors to inform themselves about the availability and suitability of a study; it also allows full public scrutiny and prevents selective dissemination of results that can distort the medical evidence. It enables doctors, prescription guideline writers, payers and formulary decision-makers to recommend and provide the right drugs for the right patients.

Legally binding trial registration of a trial requires submission of a dataset comprising substantial detail on each study, including the indication, all primary and secondary outcomes, the estimated number of participants and time of outcomes completion. Updates of information are required. Registration of clinical trials in a public database is managed in various ways (see Table 1. In the EU, after sending an application for authorisation to perform a study to the EMA, selected information fields about the trial are released to the public sector of the EudraCT database automatically by EMA representatives.

In the US, the responsibility to register a trial resides with the sponsor; a proof of compliance must be supplied to the FDA by completing Form FDA 3674 (Certification of Compliance). Regular updates of the registration database entries are obligatory at least annually, even if no changes are necessary; status changes in participant recruitment must be updated within 30 days.

Posting of Summary Results

EU/EEA

Under EU law, posting of results in the EudraCT public database has been mandatory for all clinical trials since 21 July 2014. Particularly stringent rules regarding the timing of the submission and the format of results apply to trials involving children (in which at least one participant is under 18 years of age). Even the unintended inclusion of a trial participant under 18 years of age turns the study into one covered by paediatric rules.

For an interventional clinical trial in adults completed *before* 21 July 2014, disclosure of results can be made using the synopsis of an ICH E3-compliant clinical study report (CSR)

or a pre-specified dataset of summary results ('full dataset'), or both. For all trials that have concluded *on or after* 21 July 2014, the full dataset must be posted in the EudraCT database. The usual timeline for releasing results of trials in adults is within 12 months from the primary endpoint completion date, but all paediatric trials must have their outcomes posted within six months from the primary endpoint completion date. The timelines and modalities for publishing results in the EudraCT database are explained in a document provided by the EMA (see Table 1) (17).

Other regulatory documents associated with a trial (clinical summary, layperson's summary, clinical protocol and the CSR) are also required to be posted publicly. Data must be available in an easily searchable format, with related data and documents connected by the EU trial number. Hyperlinks should be used to link together the summary, the layperson's summary, the protocol and the CSR of one trial, as well as referring to data from others who used the same investigational medicinal product (18). The timelines for posting the various documents depend on the category of trials (see Table 2) (3).

US

According to the FDAAA 801 expanded by the Final Rule, as of 18 January 2017, the release of results will be mandatory within 12 months after final data collection of the pre-specified primary outcome measure (primary endpoint completion date) for all applicable trials, irrespective of the approval status for the medicinal product. Other regulatory documents associated with a clinical trial – such as study protocol, statistical analysis plan and all their amendments – are also required for public posting, at the time of the results information reporting at the latest (see Table 1) (7,8).

Disclosure of Clinical Data and Trial Participants-Level Data

EMA Policy 0070

In the EU, another important pioneering transparency effort of clinical data has been accomplished by EMA Policy 0070. This policy deals with the proactive release of clinical data and applies to documents on medicinal products that were submitted as part of the procedure for

| Document/item | Content/definition/comment | Citation |
|--|---|----------|
| EMA policy on publication of clinical data for medicinal products for human use | Developed by the EMA in accordance with Article 80 of Regulation (EC) No 726/2004 | 5 |
| External guidance on the implementation of the EMA policy on the publication of clinical data for medicinal products for human use | Topics covered: <ul style="list-style-type: none"> • External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA Policy 0070 • External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with the policy • External guidance on the identification and redaction of CCI in clinical reports submitted to the EMA for the purpose of publication in accordance with the policy • Annexes: redaction, anonymisation, templates for documents (letters) submitted, redaction proposal version process flowchart, workflow for the submission of clinical reports for publication, sample of justification table for CCI redactions, redaction consultation process flowchart, in and out of scope of Phase 1 of Policy 0070 | 4 |
| Clinical data | <ul style="list-style-type: none"> • Clinical reports and IPD | 4 |
| Clinical reports | <ul style="list-style-type: none"> • Clinical overviews (submitted in module 2.5), clinical summaries (submitted in module 2.7) and the CSRs (submitted in module 5) • The following appendices to the CSRs: 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form), and 16.1.9 (documentation of statistical methods) | 4 |
| Individual patient data | <ul style="list-style-type: none"> • Individual data separately recorded for each participant in a clinical study | 4 |
| Protected personal data | <ul style="list-style-type: none"> • 'Personal data' shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity | 4 |
| Commercially confidential information | <ul style="list-style-type: none"> • Any information contained in the clinical reports submitted to the EMA by the applicant/MAH that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant/MAH | 4 |
| Terms of Use | <ul style="list-style-type: none"> • Governs the access and use of clinical data that are made available to users | 5 |

Table 3: Clinical Trial Disclosure EU/EEA: Supporting documents and definitions based on EMA Policy 0070

the EU centralised marketing authorisation application – regardless of whether the application was approved, rejected, or withdrawn (4,5). As such, Policy 0070 tries to establish an opportunity for secondary research on studies and the claims made for tested medicinal products.

Policy 0070 separates clinical data into clinical reports and IPD. The term 'clinical reports' includes several key regulatory documents that are submitted as part of the centralised marketing authorisation procedure. IPD means individual data, separately recorded for each participant in a clinical trial (ie trial participant-level data), as listed in Table 3.

The EMA is implementing Policy 0070 in two phases:

- Phase 1: concerns the proactive publication of anonymised clinical reports submitted to the EMA starting from 1 January 2015
- Phase 2: focuses on the publication of de-identified IPD. The EMA will execute this phase at a later date that has not yet been specified

The proactive nature of the disclosure implies that sponsors will be required to submit two sets of regulatory documents

when preparing their centralised marketing authorisation application in the EU:

- Full information set: for regulatory reviewers involved in the scientific evaluation process that will contain all of the information
- Redacted/de-identified information set: for documents intended for public release after the decision on the application has been made. The latter should be a copy of the clinical reports submitted in the context of the scientific evaluation procedure, but stripped of elements so that the trial participants can no longer be identified and commercially confidential information (CCI) not interpreted

Items that qualify for anonymisation, redaction or de-identification are described by the EMA. All items that are redacted, anonymised or de-identified by the sponsor have to be justified using the suggested templates and relevant consultation methods, and agreed upon by the Agency (4,5).

The EMA has defined a process for public release of clinical reports such that these are available on-screen for any user with a simple registration process, and for downloading by recognised users. Both situations are governed by a dedicated 'Terms of Use' agreement, which clarifies that the user of



To ensure consistency across all documents associated with a particular study, sponsors must establish an overall company policy that summarises their intentions in the current data disclosure landscape, and adjust their internal workflow and standard operating procedures accordingly ”

the data shall not, in any case, attempt to re-identify trial participants or other individuals (4,5).

In October 2016, the EMA announced that a new clinical data database for Policy 0070 had gone 'live' (19). The initial release of information on just two drugs comprises 260,000 pages of information in over 100 clinical reports. Data for other drugs will be added progressively. Once the backlog has been dealt with, the Agency aims to publish clinical reports 60 days after a decision on an application has been taken, or within 150 days of receiving the withdrawal letter. According to current forecasts, they expect to offer access to approximately 4,500 reports per year (see Table 3).

EMA Policy 0070 was processed in parallel to Regulation (EU) 536/2014, and represents the Agency's commitment to continuously extend their approach to transparency. Nevertheless, it is important to recognise that the Policy has a wider implication than the disclosure requirements of Regulation (EU) 536/2014. Policy 0070 also applies to the publication of clinical trials that are conducted outside the EU but are submitted to the EMA for marketing authorisation in the EU.

NIH Initiatives for Sharing Trial Participants-Level Data

At the same time as the American release of the FDAAA 801 Final Rule, the NIH has issued a complementary policy that applies to all NIH-funded trials – including those that are not subject to the FDAAA 801 and the expansion by the Final Rule. According to this policy, in addition to publicly posting the summary of clinical trials, sharing of trial participants-level data is also planned. The NIH has evaluated various models for making this feasible and useful to researchers (20).

Company and Consortium Initiatives for Clinical Data Sharing

In parallel to the EMA's Policy 0070, several international pharma companies and consortiums have organised voluntary sharing of de-identified clinical trial participant-level data in a controlled way (21). The conditions under which sponsor participants agree to share this data include a research proposal, a statistical analysis plan,

and a commitment to publish the findings of the secondary research. The requestors' proposals are reviewed by an independent panel that decides whether to grant permission to release those results (21). Through these efforts, any individual or organisation can request access to de-identified trial participant-level data and other supporting documents from studies. Members of the PhRMA and EFPIA have also committed to sharing this data according to their company's own policy on clinical trial disclosure (16).

Implications of Disclosure

To ensure consistency across all documents associated with a particular study, sponsors must establish an overall company policy that summarises their intentions in the current data disclosure landscape, and adjust their internal workflow and standard operating procedures accordingly. Further requirements for regulatory documents and new tasks for existing ones will increase demands on document preparation, processing, supervision and quality control. All of these tasks must be considered when planning drug development projects regarding timelines, costs, and staff (22,23).

At the operative level, specific requirements apply to the release of information. Although these often differ only slightly from the usual reporting practices of a trial, they should be planned by the study and data managers. Thus, for example, results disclosure in the EudraCT database needs a presentation of the randomised trial participants by country and by pre-specified age categories.

For the safety section, the number of subjects impacted by non-serious and serious adverse events must be presented separately. For the actual non-serious adverse events, a threshold can be applied (up to 5% of participants affected in any treatment arm), whereas for serious adverse events all must be shown. For each serious adverse event, the following information is required: the number of participants affected; the number of occurrences; relatedness to treatment; and all fatalities and fatalities regarding treatment. Some sponsors use a customised file for uploading the information on adverse events (eg XML).

To cope with the requirements of clinical trial disclosure, a number of excellent tools have been developed, some of which are freely available through the internet. These help in preparing documents that are transparency-compliant and disclosure-ready and include:

- A study protocol template for Phase 2 and 3 trials (24)
- An annotated and commented user manual intended to improve the reporting of interventional trials in CSRs (25)
- Recommendations on preparing layperson summaries (3,26)

Publications of trial results in journals should be fully consistent with respective protocols, study reports, and entries on company websites, in public registries or databases. In the global world of the internet, discrepancies can easily be identified between published papers and information available in the public arena (27).

Indeed, for some time now, many medical journals have required the clinical trial registration number from a public database – or the full version of the final study protocol – to verify details of submitted study manuscripts against the information from the public domain. This particularly applies to the declared endpoints of studies. Ideally, all pre-specified primary and secondary outcomes of a trial would be included in the publication, or else a clear declaration of ‘why not’ should be provided. This could be done, for example, by referring to the study registration entry in a recognised public database and thus prevent unacceptable incidents of undisclosed endpoints or ‘outcome switching’ (28).

The recent calls for disclosure of study protocols and raw data from trial participants show how seriously the matter of transparency is being taken by journal editors, medical and scientific communities, the pharma industry, private and public funders, regulators, politicians and patient groups (23,29). Innovations regarding the clinical data disclosure are intended to help fulfil scientific discovery and improve health, while elevating the entire biomedical research enterprise to a new level of transparency and accountability (20). Responsible and wise use of the vast amount of available data should maximise the benefits and minimise the risks for all involved – in particular, the trial participants – and, in the long term, help patients in need (15,21).

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3. Visit: www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195084.pdf
4. Visit: [www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016-03/WC500202621.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf)
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6. Visit: www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82
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Medical Writing for Submission to Asia-Pacific Regulatory Authorities

The need for quality medical writing services is growing in Asia. While some Asian countries follow the ICH guidelines, sometimes with additional local requirements, others have their own specific regulations. Medical writers are being called upon to help guide teams in navigating the different regulations during document preparation. This article reviews the current landscape for key regulatory documents for submission to major health authorities in Asia, and describes how seasoned writers with local knowledge can contribute to successful submission.

By Julia Cooper, Rui Yang, Henny Wati, Ryoichi Hirayama, Becky Lu, Sylvia Kang, Christine Siew, Marissa Laureta and Supamas Chansida at PAREXEL

The pharmaceutical market in Asia-Pacific is expanding. Japan is the largest pharmaceutical market in the region, at \$116 billion, and China is rapidly catching up (\$99 billion, and 18.7% compound annual growth rate projected for 2015-2017). The growth of other Asia-Pacific countries is also projected at 9-13% over the same period. There is increasing demand for studies to launch new medicinal products in the Asia-Pacific region, especially in China and Japan where regulatory changes are speeding up the drug review and approval process. Consequently, the need for medical writing support for the regulatory documents that make up the marketing approval application is growing in parallel.

While the documentation required by some Asian regulatory authorities is largely harmonised with ICH, there are also some local variations or additional requirements. For economic and practical reasons, most multinational companies do not have a medical writing function in each country within Asia. Instead, they may establish medical writing functions in one or two hub locations in the region. Medical writers in these teams may therefore need to be familiar with the regulations for marketing applications across multiple countries in Asia.

The clinical regulatory documents most frequently prepared by medical writers in Asia are:

- Protocol and informed consent form (ICF)
- Development safety update report (DSUR)
- Clinical study report (CSR)
- Clinical sections of the marketing application dossier
- Periodic safety update report (PSUR)
- Risk management plan (RMP)

There are many considerations and requirements, some different from ICH, which medical writers must keep in mind when preparing these types of documents for key regulatory authorities in the Asia-Pacific region.

China Food and Drug Administration

The Chinese pharmaceutical market is dynamic and increasingly complex. In the past two years, the Center for Drug Evaluation (CDE) affiliated to China Food and Drug Administration (CFDA) has released more than one guideline or draft guideline seeking public opinion almost every month. Recent changes include the prioritisation of approval of certain drug classes in order to accelerate approval times. Priority drugs include new drugs not yet marketed in China or overseas, products undergoing simultaneous marketing application in the US or Europe, products showing clinically significant superiority for certain diseases (HIV, viral hepatitis, tuberculosis, oncology, rare diseases), and products intended for paediatric use (1).

Medical writers are increasingly involved in writing protocols for studies run in China. The protocol, together with the ICF, generally follows the content outlined in the ICH E6 guideline.

A pre-approval safety update report such as the DSUR is not mandatory unless requested by the sponsor or CFDA. However, this may soon change because the draft *Administrative Provisions for Drug Registration (Revision)* includes a requirement for an annual report during clinical studies, which will periodically summarise data relating to drug manufacturing and safety and efficacy data for preclinical and clinical studies, and will evaluate the actions taken or to be taken (2).

A CSR guideline was issued by the CFDA in 2005 defining three types of CSR structure (3): for Phase I tolerability studies, Phase I pharmacokinetic studies and Phase II/III studies. The elements of the CFDA CSR guideline are very similar to ICH E3, but it does have some unique requirements regarding CSR appendices that are not covered by the ICH guideline, including individual by-site summaries, and a statistical analysis report. Some

| Protocol | |
|------------------------|--|
| China | ICH E6 compliant |
| Japan | ICH E6 compliant Must also include: • No. of Japanese subjects to be enrolled • Definition of adult as 20 years in inclusion criteria • Summary of investigational product labelling • Statement of compliance with Japanese GCP • Planned study period • Study organisation appendix listing Japanese clinical sites and vendors |
| Korea | ICH E6 compliant |
| Taiwan | ICH E6 compliant |
| Malaysia | ICH E6 compliant |
| The Philippines | ICH E6 compliant |
| Thailand | ICH E6 compliant |

| ICF | |
|------------------------|---|
| China | Generally complies with ICH E6. No age threshold specified for signature by adolescents or children. Adolescents/children should sign the ICF as long as they can understand it. A legal guardian must sign in addition |
| Japan | Follows ICH E6 but more detailed information is required, eg: • General explanation of a clinical trial • Data on adverse drug reactions (ADRs) from previous studies, package inserts of similar products and investigator brochure • Explanation of inclusion and exclusion criteria ICF should be 'visually-friendly': • Table, charts and pictures are often used • Font and font size are carefully considered |
| Korea | ICF follows ICH E6. MOH ICF (Form 34), applies to studies that require human-derived material storage or other usage except for clinical trial purposes (15) |
| Taiwan | ICF follows ICH E6, and requires customisation for several local requirements – eg specific terms that cannot be changed, local sponsor identification and injury liability |
| Malaysia | ICF follows ICH E6. Country-specific customisation is required and a standard checklist is provided by the central EC |
| The Philippines | ICF follows ICH E6, and requires customisation for several local requirements (templates provided) |
| Thailand | ICF follows ICH E6, and requires customisation for several local requirements |

companies strictly follow the CFDA guideline for CSRs. In practice, the CFDA also accepts the CSR body in the ICH E3 format, if the CSR appendices are supplemented by the additional documents required to comply with the CFDA guideline. Data in Chinese patients are required to obtain marketing approval from the CFDA. These data may be obtained from a stand-alone China study or by including Chinese sites within a multi-country study. A recent CFDA draft guideline clarifies that for a multinational clinical trial, comparisons between Asian versus non-Asian, and Chinese versus non-Chinese data must be included in the CSR (4). A skilled medical writer will be able to help the team determine how best to present these data.

The format of the CFDA marketing application dossier is changing. The following new guideline was issued in May 2016, and is already being followed although it is still in draft stage: *Requirement on Registration Dossier under the New Categorization for Chemical Drug Registration (Tentative)* (5). This regulation requires inclusion of

additional documents not previously specified, such as a data management plan and data management report. The draft guideline also refers to *The Guideline of the Structure and Content of Summary Documents for Chemical Drug – Summary of Clinical Studies* (6), the content of which is similar to Module 2.5 of ICH M4, Common Technical Document (CTD). For Chinese marketing applications for drugs already marketed outside of China (category 5), the CTD modules including the comparisons of Chinese to non-Chinese data may be submitted instead of the CFDA dossier format, if supplemented by Module 1 (administrative and summary section) from the CFDA guideline. If the company does not have a global CTD to use as the starting point, the clinical summary guidance may be followed but the actual structure of the documents may need to be determined depending on the data to be presented (6).

PSURs are required for marketed drugs, and these follow ICH E2C. At present there is no requirement for an RMP in China.

| DSUR | |
|------------------------|--|
| China | No requirement for DSUR yet. CFDA requires annual reporting safety information during clinical development stage; no guidance available |
| Japan | DSUR required for pre-approval products. ICH E2F compliant. A cover letter in Japanese including executive summary and listing of SAE cases from Japan are needed in the specific format (7) |
| Korea | DSUR not mandatory, but MFDS accepts DSUR if submitted |
| Taiwan | DSUR not mandatory, but should be submitted if available |
| Malaysia | DSUR not mandatory, but submission is encouraged |
| The Philippines | DSUR required for pre-approval products. ICH E2F compliant |
| Thailand | Annual safety report is required. There is a local format, however DSUR is accepted |

| CSR | |
|------------------------|---|
| China | CFDA guideline for CSR format (3). CSR in ICH E3 format is accepted if CFDA-specific appendices are included: <ul style="list-style-type: none"> • Individual by-site summary for multicentre clinical trials • Statistical report • Approval letters from ECs, also for all protocol amendments • Study site qualifications • Principal investigators' qualifications • Certification of analysis and pre-production record (including placebo) • Package insert for comparator and investigational product (if marketed) • Chromatograms for samples from all subjects (pharmacokinetic and bioequivalence studies) |
| Japan | ICH E3 compliant. Separate comparison of Japan versus non-Japan data is required (can be a separate report in Module 5.3.7) (8) |
| Korea | ICH E3 compliant |
| Taiwan | ICH E3 compliant plus Taiwan data summary |
| Malaysia | ICH E3 compliant |
| The Philippines | Submission of CSR not mandatory |
| Thailand | Submission of CSR not mandatory |

The recent CFDA requirement for sponsors to conduct self-inspection activities places an increasing focus on data quality, and by implication, the quality of the marketing application dossier. Overall, there is a general trend towards aligning quality with international standards, as illustrated by a recent CFDA decision to accept regulatory and technical guidance from ICH, EMA, FDA and WHO, to facilitate dual registration of new drugs. An experienced medical writer can assist not just in the writing of the documents required in the pre- and post-approval phases, but increasingly in providing guidance to the responsible teams to align the strategy with both local and international standards.

At present, the marketing application in China may be one of the last in a multinational company's global development plan, in part due to the long investigational new drug (IND) and new drug application (NDA) approval times. The prioritisation of applications for specific drug classes, as well as plans to increase the numbers of CFDA reviewers will serve to shorten approval times in the long term. For now, however, medical writers can contribute to global submissions by anticipating presentation formats, resource and timelines for the additional data displays required by

CFDA. A medical writer with local knowledge can also help the team ensure their approach is up to date, as the regulations continue to evolve.

Although the eCTD is expected to be implemented at some point, the clinical dossier is currently required as a paper submission, and timelines must be planned accordingly. In addition, the study report and submission documents may be prepared in English if a global team will be involved in the review, then translated into simplified Chinese for CFDA submission. Writers with excellent verbal and written English skills, in addition to Chinese, will be able to ensure this process runs smoothly.

Pharmaceuticals and Medical Devices Agency (PMDA) – Japan

Japan has a Good Clinical Practice (GCP) guideline that follows the ICH GCP requirements, with some Japan-specific additions. These include emphasis of the role of the head of the hospital/institution, in addition to those of the investigators. To conduct a clinical study, an approval letter from the head of the investigational site based on Ethics Committee (EC) approval is required.

| CTD | |
|------------------------|---|
| China | Structure outlined in CFDA guideline (5). ICH M4 CTD plus module 1 of CFDA dossier accepted for drug already marketed ex-China (category 5 per new categorisation). The guideline on Summary of Clinical Studies (6) is similar to CTD Module 2.5 |
| Japan | ICH M4 CTD, with additional assessments of Japanese data (9): <ul style="list-style-type: none"> • Module 2.5: comparison of Japanese and non-Japanese data • Module 2.7.2-2.7.4: separate assessment of Japanese subject data • Module 2.7.4: Listing of SAE and death cases by study, identifying Japanese vs non-Japanese • Module 2.7.6: more detailed presentation of disposition of subjects, primary and secondary efficacy analysis, safety analysis and subject narratives in Japanese for pivotal studies (SAEs and deaths) |
| Korea | ICH M4 CTD modules accepted but additional Korea-specific documents are required, according to MFDS format (13). Bridging data from Korean patients is usually required; MFDS published a guideline for bridging data report (12) |
| Taiwan | ICH CTD is followed. A BSE report may be submitted to request waiver of the bridging study requirement (17). If a waiver is not approved, the study will need to be conducted and the study report submitted to support the marketing application |
| Malaysia | ACTD and ACTR guidelines are followed |
| The Philippines | ACTD and ACTR guidelines are followed |
| Thailand | Either ACTD or ICH M4 CTD is required, depending on the type of application |

Protocols are accepted by PMDA in English although a Japanese language version is needed for the site personnel. An appendix of the study organisation, including by-site listing of clinical sites, with address and name of investigator, and list of study-related vendors, should be submitted together with the protocol.

The ICF generally complies with ICH E6, but general background about clinical trials must be included, as well as more detailed information on the study procedures and inclusion/exclusion criteria. In addition, use of visual components is considered to be important, such as tables, pictures or certain font types.

DSUR submission is mandatory for clinical trials using pre-approval (not marketed) study drug (7). Submission of the global DSUR in English is accepted if accompanied by Japan-specific cover letters including an executive summary in Japanese and separate assessments of Japanese cases in a specified format (Form 1, Form 2).

The CSR is accepted in English in ICH E3 format. Separate assessments of data in Japanese subjects are required (8).

The marketing application dossier follows ICH M4 CTD format. Module 1 is prepared in Japanese and includes the local regulatory requirements. Module 2 is also prepared in Japanese, but Modules 3, 4, and 5, may be submitted

in English. The Japanese CTD requires a separate assessment of Japan data in the clinical modules (Modules 2.5 and 2.7), inclusion of a listing of Serious Adverse Events (SAE) and death cases in Module 2.7.4, and safety narratives in Japanese for pivotal studies in Module 2.7.6 (9).

A Post-Marketing Safety Periodic Report is required. It includes the post-marketing safety survey reports, and the PSUR is appended. A PSUR in Periodic Benefit Risk Evaluation Report (PBRER) format is accepted in English for global studies. For local studies, a PMDA-compliant PSUR format in Japanese should be used (10).

The RMP is required for new drugs and for biosimilars/follow-on biologics for applications submitted on or after 1 April 2013, and follows ICH E2E.

In Japan, writing in local language is very important, as many documents must be submitted in Japanese, or require a Japanese cover letter. This typically includes a summary of the document and will specifically highlight the separate assessment of Japanese subjects. Overseas sponsors need to be aware of the additional requirements for Japan. Similar to China, the medical writer can help the team by helping to plan timelines and resource for the separate analysis of Japanese data and the additional documents, and by using their expertise to help determine the best presentation of the data.

“ In Japan, writing in local language is very important, as many documents must be submitted in Japanese, or require a Japanese cover letter. This typically includes a summary of the document and will specifically highlight the separate assessment of Japanese subjects ”

| PSUR | |
|------------------------|---|
| China | PSUR guidelines are mainly based on ICH E2C. Major differences are: <ul style="list-style-type: none"> • Must be submitted in Chinese or with Chinese translation, except for line listings and summary tabulations • Any differences between China and other countries, such as drug indications, formulations and dosages, and any safety information, need to be addressed and explained • Required annually in new drug monitoring period (3-5 years); thereafter every 5 years |
| Japan | Post-Marketing Safety Periodic Report is required every 6 months for the first 2 years, then annually until re-examination (drug re-examination system: part of the PMS to examine safety and efficacy data collected during a certain period of time) (10). The report includes post-marketing survey reports: overview and analysis of the survey, ADRs reported, individual case report of ADRs, actions taken for safety reasons including any changes to the drug labelling, the package insert, and an analysis of safety. The PSUR is attached to the Post-Marketing Safety Periodic Report. PBRER format is accepted in English for global studies. For local studies, a PMDA-compliant PSUR format in Japanese should be used. For non-marketed products, a 6-month periodic report of serious ADRs is to be submitted, including all serious ADRs reported in and outside Japan |
| Korea | Periodic PMS report is required every 6 months for the first 2 years, then annually until the end of the surveillance period. The report must summarise the results of use-result surveillance and special surveillance studies, local and foreign safety data, and sales data (14) |
| Taiwan | PBRER format plus local appendices (package insert, domestic sales information and analysis of domestic ADRs). Required every 6 months for the first 2 years, then annually for next 3 years |
| Malaysia | PBRER format, required every 6 months for the first 2 years, then annually for next 3 years |
| The Philippines | PBRER format. For drugs under regular registration: every 6 months for the first 3 years, annually for the next 2 years, thereafter every 2 years |
| Thailand | Not required unless requested by Thai FDA |

Ministry of Food and Drug Safety (MFDS) – Korea

ICH guidelines are generally accepted by MFDS for the protocol, investigator brochure, CSR, CTD, periodic safety report, etc. However, there are some local requirements, listed below:

- In addition to the ICF, Ministry of Health (MOH) ICF (Form #34), is applicable for clinical studies that require storage of human-derived material or its usage apart from the purpose of the clinical trial (11)
- The DSUR is not mandatory but is accepted if submitted
- The CSR follows ICH E3. In addition, bridging data from Korean patients is usually required to obtain marketing approval, obtained from a stand-alone Korea study, or by including Korean sites within a global study. The bridging data report must be included in the marketing authorisation application. MFDS has published a guideline for the required content and format (12)
- The marketing application dossier is accepted in ICH M4 (CTD) format, but additional Korea-specific documents are required, according to MFDS guidelines (13). The local requirements mostly concern the chemistry, manufacturing and controls sections in Module 3. Submission in eCTD format is mandatory
- A periodic post-marketing surveillance (PMS) report must be submitted every six months for the first two years, then annually until the end of the surveillance period. The report must summarise the results of use-result surveillance and special surveillance studies, local and foreign safety data, and sales data (14)
- The RMP has been implemented since 2015 and must be submitted as part of the marketing authorisation application for new or orphan drugs. Local regulation and guidelines apply to the RMP format (15)

The Korean regulatory environment is continuously evolving and medical writers need to keep up to date with the

frequent changes in regulations. As of October 2016, a new regulation on safety of pharmaceuticals has been announced (16). The impact is under assessment; however, it does include updates on requirements for clinical trials.

Taiwan Food and Drug Administration (TFDA)

The regulatory infrastructure is well developed in Taiwan. Although Taiwan follows most of the global standards, the medical writer needs to understand the specific local requirements relating to clinical documents.

ICH guidelines are followed for most documents, eg protocol, investigator brochure, CSR, and other global standards, eg US FDA guidance, are accepted. There are additional local requirements for certain documents:

- The ICF generally complies with ICH E6, although certain specific terms or template text must be used
- The DSUR is not mandatory. However, according to GCP, the sponsor should submit all safety updates and periodic reports to the regulatory authorities, and the ICH E2F format is accepted
- ICH E3 is followed for the CSR, supplemented with a summary of the data in Taiwanese patients. The Taiwan data should generally be compared to non-Taiwan or global population
- The marketing application dossier follows ICH M4 CTD. If there are sufficient data to demonstrate ethnic insensitivity, a bridging study evaluation (BSE) report may be submitted to request waiver of the bridging study requirement (17). If a waiver is not approved, the bridging study will need to be conducted, and the bridging study report submitted to support the marketing application
- A PSUR in PBRER format is required every six months for the first two years, then annually for next three years

| RMP | |
|------------------------|--|
| China | RMP not required at present |
| Japan | ICH E2E compliant. RMP is required for new drugs and biosimilars/follow-on biologics for applications submitted on or after 1 April 2013. The RMP should be submitted together with a cover letter containing a Japanese summary of RMP in a specific format |
| Korea | RMP required as part of marketing authorisation application for new drug or orphan drug. Local regulation and guidelines apply (15) |
| Taiwan | Specific RMP guideline. Product-specific templates apply depending on product risk, eg for TNF-alpha product |
| Malaysia | RMP required for new drug/biologics applications, or for significant change to existing registered product |
| The Philippines | RMP guideline is in development and will be implemented once available |
| Thailand | Not mandatory |

- There is a TFDA specific guideline for RMPs. In addition, depending on the risk of the product, use of product-specific templates, eg for tumour necrosis factor (TNF)-alpha products, may be required

Malaysia MOH

The Malaysia regulatory environment is well structured and a guideline is available for submission of clinical trials in Malaysia (18).

In general, Malaysia has adopted the ICH and EMA guidelines.

- The ICF follows ICH E6 but country-specific customisation is required and a standard checklist is provided by the central EC
- The DSUR is not mandatory; however, its submission is encouraged
- The CSR is mandatory and follows ICH E3
- The marketing authorisation application follows the *ASEAN Common Technical Dossier/Requirement (ACTD/ACTR)* guidelines. The structure is similar to ICH M4, however there are four parts instead of five modules. A Clinical Overview and Clinical Summary are required
- A PSUR in PBRER format is required every six months for the first two years, then annually for next three years
- The RMP will normally be required for an application involving new drug products or new biologics or for any significant change to an existing registered product, as specified in the guidelines

Philippines Food and Drug Administration (PFDA)

The regulatory environment in the Philippines is changing in line with global standards. The PFDA follows global guidelines such as ICH guidelines, and a Bureau Circular has been published on the process of evaluating clinical trials (19).

- There are country-specific requirements for the ICF, and local templates are provided
- A DSUR is required, and should comply with ICH E2F
- Submission of the CSR is not mandatory but it is best practice to submit it when available
- The marketing authorisation application follows the ACTD/ACTR guidelines
- A PSUR is required in PBRER format. For drugs under regular registration, the PBRER is required every six months for the first three years, annually for next two years, thereafter every two years
- A RMP guideline is in development and will be implemented once available

Thailand Food and Drug Administration (Thai FDA)

The regulatory environment is evolving in Thailand. Guidance for clinical trial applications was announced and implemented in August 2015, with further guidance implemented in October 2016 (20). A new guidance implementing electronic submission for pharmaceutical product registrations for New Chemical Entity, New Biologicals and Human Vaccines came into effect in January 2016. Nevertheless, ICH guidelines and other



The regulatory environment is evolving in Thailand. Guidance for clinical trial applications was announced and implemented in August 2015, with further guidance implemented in October 2016



“ ICH guidelines are widely adopted in Asia-Pacific, and there is increasing alignment with other global standards. However, each country generally has its own local requirements in addition ”

global standards, eg US FDA guidance, are recognised by the Thailand FDA. Most of the core documents such as protocol and investigator brochure follow the global standards and structure.

- The ICF must comply with ICH E6, however several country- and site-specific requirements apply
- The CSR is not a mandatory document, although an end-of-study safety report is required within six months of end of study
- There is a local format for the annual safety report; however a DSUR in ICH E2F format will also be accepted
- For the marketing authorisation application, a dossier in either ICH M4 CTD or ACTD format may be required, depending on the type of application
- The RMP is not mandatory

Conclusion

ICH guidelines are widely adopted in Asia-Pacific, and there is increasing alignment with other global standards. However, each country generally has its own local requirements in addition. Furthermore, the regulatory environment is evolving in some parts of Asia-Pacific, and it is important to keep up to date with local requirements to avoid delays in the submission approval process.

The quality of the data presentation is important, in addition to regulatory compliance. Separate analysis of local patient data is required for some countries, and the writer's skills are needed to understand how best to present and discuss this data. Bi- or even trilingual written and verbal communication skills can also be essential. The value of the medical writer is achieving increasing recognition in Asia, and experienced writers with the ability to contribute local regulatory and writing knowledge are in demand to assure the success of local submissions as well as the overall global submission strategy.

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17. Visit: www2.cde.org.tw/FAQ/NDA/sublink/%E8%A1%9B%E7%BD%B2%E8%97%A5%E5%AD%97%E7%AC%AC0980303366%E8%99%9F.pdf
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Managing or Outsourcing your Medical Writing

As medical writing has advanced as a functional competency, a variety of business models have been developed (in-house writing, full-service outsourcing, functional service provider models, use of sole proprietors/freelancers, etc) to enable pharmaceutical companies to deliver high-quality document work on time and on budget. The talents and skill sets that make for great medical writers are not always the same talents and skill sets required to partner effectively between companies, to measure and ensure quality, and to drive efficiency across a portfolio of work. This article focuses on best practices and winning strategies for managing or outsourcing medical writing deliverables within this complex business environment. Suggestions on how to kick-off effective working relationships, measure and optimise performance, and how to innovate through partnership are discussed.

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Randstad Life Sciences

Introduction

The expectations within the pharmaceutical industry for excellence in regulatory document work have never been higher. The diversity of regulations and document types globally continues to expand, while the expectations around document quality and transparency and the downward pressures on cost and speed are immense. As a result, the profession of medical writing has advanced tremendously in the past 20 years.

As the profession has evolved, so too have the employment opportunities for medical writers. Medical writers are employed within pharma companies, by large and small CROs, by third-party companies that specialise in medical writing services, for themselves as sole proprietors, and just about everywhere else in between. As a result, there are a number of different “engagement” models for how and where document work gets done – providing great opportunity and flexibility in how documents are developed but creating potential obstacles in the forms of complexity and the need to successfully manage business-to-business relationships. Balancing these opportunities and challenges can be achieved through the implementation of best practices for successful partnerships between Sponsors (usually pharma or biotech companies) and Service Providers (CROs, freelancer/sole proprietors, medical writing companies, etc).

Types of Service Providers

Due to the diversity of Service Providers, a number of different partnership arrangements are available to Sponsors, each with their own set of advantages. Matching the correct medical writing Service Provider to the right set of document work is becoming increasingly challenging. But finding a good fit for the size of the Sponsor and the volume and complexity of the document work to be done can be very valuable in terms of

delivery, timeliness, cost, and even enhancing the quality of the work itself. Table 1 displays some of the more common partnership arrangements and compares important aspects for each model.

In general, the selection of medical writing models is dependent on a variety of factors. For programmes with a limited scope or those that require an individual niche expertise (either document type or therapeutic area), freelancers can be an excellent choice. But due to their limited capacity as individuals, freelancers may not be the right choice for more complex or expansive projects. Full-service CROs can be very convenient for the delivery of study-related documents for a particular outsourced trial or programme. Functional service providers (FSPs) represent an area of innovation in medical writing partnerships, creating opportunities for efficiency and optimisation across larger document plans and programmes. However, an FSP model requires substantial initial training investment from both the Sponsor and the FSP itself. This initial training investment is aimed at producing writers who are not only well-versed in the Sponsor’s document style but also have a deep understanding of the Sponsor’s drug programmes.

Starting and Maintaining a Relationship

A medical writing partnership requires an initial investment to define not only the document plan but also the scope of the relationship. This process should include a detailed discussion of the interactions between the two companies, project planning, process expectations, and implementation of quality standards.

Interactions between the Two Companies

Interaction guidelines can be quite simple for freelancers/sole proprietors, but can be quite complex for FSPs, which may benefit from the creation of a governance body consisting

| | Model | Cost | Expertise/familiarity | Investment/convenience |
|-----------------------------------|---|--|---|--|
| Freelance/ sole proprietor | <p>A single professional medical writer contracting with a Sponsor, usually on a document-by-document basis</p> <p>Document scope is basically unlimited within the experience of the individual writer</p> | <p>Varies: generally higher than CRO or FSP for highly experienced writers</p> <p>Can be lower for less experienced writers</p> | <p>Expertise varies: can often be extremely high, must be carefully vetted</p> <p>Familiarity with a particular Sponsor must be built over time</p> | <p>Investment: can usually contract on a document-by-document basis, can be a lower upfront cost commitment required</p> <p>Convenience: often very straightforward to start a contract.</p> <p>However, if a particular freelance writer becomes critical to a document plan, the Sponsor must be careful to schedule ahead – freelancers only get paid when they are writing, and will often have multiple clients</p> |
| Full service CRO | <p>A CRO that is executing a study provides the supporting document work for that study</p> <p>Can include protocols, informed consent forms, clinical study reports (CSRs), investigator’s brochures (IBs), even regulatory filings</p> | <p>Usually lower than freelance or FSP on a document-by-document basis</p> <p>Can be bundled into study costs, which can be a cost advantage</p> <p>Writers generally need to maintain stricter budgets for their writing time – as a result, the initial cost may be lower, but change controls orders can increase costs</p> | <p>CROs tend to maintain broad document expertise within their organisations, but may have less expertise in non-study related document types</p> <p>Familiarity with a sponsor is often lower than other models, because the writers are generally sourced to multiple clients</p> | <p>Investment: usually contracted on a study-by-study or programme-by-programme basis, so forecasting work, timelines and costs can be straightforward</p> <p>Convenience: writers often have strong internal relationships with other members of the study team, when they are internal to the CRO (statistics, clinical, medical monitor, etc) – this can be a huge advantage</p> <p>Writers may be less flexible in terms of working within standard sponsor processes and norms, usually less ‘customisation’ is available in the document team approach</p> |
| FSP | <p>A medical writing company (or department within a CRO) that dedicates a team of medical writers to a particular Sponsor</p> <p>Usually involves extensive training for a team of writers in the Sponsor’s processes and systems</p> <p>Document scope is usually very broad, both study- and programme-level documents</p> | <p>Costs are generally lower than freelance, but higher than full-service CRO arrangements</p> <p>Volume-based price discounts are negotiable</p> <p>Multiple costing models (time and materials/hourly, deliverable based) are available</p> | <p>FSPs usually maintain departments with broad and deep expertise from both a document type and therapeutic area perspective</p> <p>Familiarity with the Sponsor is a key advantage of this model – medical writers are dedicated over time to the Sponsor and establish familiarity and expertise within their processes, systems and norms</p> | <p>Investment: substantial. FSPs generally expect a commitment of a certain threshold of document volume and built-in fixed pricing</p> <p>Convenience: lower for individual documents or smaller projects, due to the larger up front investment</p> <p>High for larger programmes, due to the familiarity with the Sponsor that builds over time</p> |

Table 1: Medical writing partnership models

of members from both companies. A formal escalation pathway should be created for possible issues that may arise, with an emphasis on keeping issues management as “local” as possible – not every issue that might arise should require the involvement of senior management. The establishment of Key Performance Indicators (KPIs) for the relationship (even if they include no more than the start and target end date for a single document) is an important early step.

Project Planning

For one-off projects, planning is usually straightforward. However, in cases where several documents are involved, project planning requires close communication to ensure projects can

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At the start of a partnership, the Sponsor and Service Provider must establish which company’s standard operating procedures for medical writing documents will be followed. Beyond that, discussion and agreement on more detailed roles and responsibilities are essential as well

be adequately staffed so that they are completed on time and budget. For models where specific documents are not specified at the contract stage, it is essential that a defined process of forecasting and staffing documents is in place well before they start; this “look-ahead” time should be agreed to by both parties (3 months, 6 months, etc). Some documents, such as responses to regulatory requests, may be difficult to forecast. However, there should be a clearly defined mechanism on how these drop-in requests will be communicated and how they will be resourced.

For larger partnerships, a worthy goal is “strategic sourcing”: the concept that the Service Provider knows the Sponsor’s business well enough to make intelligent resourcing decisions from a therapeutic area and document type perspective, optimally matching the right writer to the right team. For this to occur, the Sponsor needs to provide a transparent view into their upcoming work and overall development priorities, and the Service Provider needs to invest in the time to analyse and intelligently staff against the plan/priorities. This is an opportunity for the Service Provider to enhance the Sponsor’s staffing plans, rather than simply meet a staffing need from a capacity standpoint. Critical questions for project planning and staff resourcing are presented in Table 2.

Process Expectations

At the start of a partnership, the Sponsor and Service Provider must establish which company’s standard operating procedures for medical writing documents will be followed. Beyond that, discussion and agreement on more detailed roles and responsibilities are essential as well. Who is responsible for scheduling and running document kick-off meetings, are

documents drafted by scientific experts within the Sponsor company or drafted by the writer, who maintains the timeline, etc. Some Sponsors may not include contract medical writers in team meetings or critical strategic discussions. However, a medical writer is best utilised when they are fully integrated into the project team and truly understand the rationale behind the document. Documenting these roles and responsibilities in a shared guide or a Responsible/Accountable/Consulted/Informed Matrix is a best practice.

Implementation of Quality Standards

At the document level, an essential part of mapping out the scope of a project is defining quality control (QC) measures (QC review, formatting, copy-editing, etc) and planning their implementation. It should be clear what guidelines are being followed, which partner is providing these services, and at what point during the process they will occur. For new relationships, the Sponsor may want to consider providing additional quality assurance checks, even if the Service Provider is performing the bulk of the QC work, to ensure that expectations and standards are equivalent across each company.

At the partnership level, quality standards should be defined as well. Communication about the relationship should be happening at the project level (through lessons-learned meetings), and also at the management/governance level. Regular assessment of predefined KPIs should occur to confirm that the relationship is functioning as intended, and hopefully, is improving over time. Communication should be occurring in both directions, not just the Sponsor evaluating the Service Provider. The Sponsor should ensure that the

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| <p>Project Forecasting</p> <ul style="list-style-type: none"> • Has the Sponsor mapped out the anticipated documents for each drug programme based on the current development phase? • How will the Sponsor communicate the relative priority of projects, especially in cases where short-term resourcing conflicts arise? • How will planned and ongoing projects be tracked and communicated between the Sponsor and the Service Provider? • How far in advance should each project be resourced? • How will ‘drop-in’ projects, eg, regulatory requests, be resourced? • How will changes in anticipated timelines be communicated? <p>Staff Resourcing</p> <ul style="list-style-type: none"> • Are there sufficient resources to staff the forecasted project(s)? • How will the Service Provider manage shorter-term peaks and valleys in workload? • Does the assigned writer have experience in the relevant therapeutic area and document type? If not, will they be overseen by someone who does? • Will the writer be trained on Sponsor-specific guidances, templates, etc by the Sponsor or the Service Provider (eg, the train-the-trainer model)? • When do training activities need to occur so that the writer will be fully trained before the document starts? • How will writer unavailability (sickness, paid time off, resignation, termination, etc) and changes to timelines be communicated and managed? |
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Table 2: Critical questions for project forecasting and staff resourcing

| Metric | Definition | Value |
|---|--|--|
| Types of documents completed | Measure documents completed per type (CSR, IB, briefing document, etc) | Allows for the calculation of documents completed per writer, or per writer type (Junior Writer, Senior Writer, etc). Measurement of writer productivity Also allows for calculation of overall departmental productivity and an understanding of the overall portfolio of work that a department is producing |
| Calendar cycle times | Cycle times per draft, per review, per QC round – how long are these activities taking? | Allows for more accurate forecasting, and measures of on-time delivery |
| Document cycle times | Number of drafts, overall hours per document for writing and QC | Important for Service Providers to understand how to invoice, calculate utilisation and realisation for budgetary purposes, support resourcing estimates, and identify where potential efficiencies can be gained Important for Sponsors to understand the root causes of additional drafts and overall time spent on writing and QC – is the Service Provider creating drafts and finalising documents within a reasonable timeframe? If not, is that because of issues with the Service Provider or difficulties getting required information from the Sponsor? |
| Timing of data locks and TLF delivery | Measure dates and number of re-locks and tables, listing, figures (TLF) re-issues | These events are generally on the critical path for writing activities, and disruption in these events – or the need to re-run data programmes – is a common obstacle to on-time and on-budget document work |
| Time spent on re-work | Measure writing and QC time that is required to re-work text or tables within a document, due to an error or change in strategy | Re-work is problematic for the Sponsor, but can be crippling for the Service Provider – particularly when writing resources are tight and or pricing is deliverable-based |
| Number of major QC findings or 'unlocks' | Measure instances where updates are required after document approvals; can include amendments, errata | Often related to a failure of the quality checks within a particular document. Should be categorised by document type to monitor for trends Simply collecting the number of QC findings for a particular document generally tends to be an overly granular measure and can be difficult to correlate directly to the quality of the writing; may also be QC reviewer dependent |
| Quality checklists | Pre-specified quality checklists that can be measured for compliance | Checklists/checkpoints can be put in place for individual drafts, final documents, etc. In general, a quality measure of the completeness of a document at a particular stage. May be less useful as a KPI per se, but can be valuable to drive consistency and compliance |
| Satisfaction surveys | Surveys of writing team members of the quality and experience of completing a particular document | Surveys are a subjective measure, but can be a useful assessment of quality. Should be conducted in 'both directions' – the Sponsor writing team members evaluating the quality of the writing, and the Service Provider evaluating the experience working with members within the Sponsor writing team Surveys can also be conducted at the relationship level on a quarterly or yearly basis to assess aspects like collaboration, communication, etc |
| Budget | Planned versus actuals for both the Sponsor and the Service Provider | Provides a measure of the financial health of the relationship for both partners |
| Planned versus unplanned documents | Record for each document when the assignment was made, and when the document was started | It is recommended that the Sponsor and Service Provider agree to a standard time for advanced notice before starting a document. This KPI is a metric of how many of the documents completed within a partnership met that standard advance notice In some larger relationships, the percentage of 'drop-in' work can be as high as 30-50% – this has a significant effect on the capacity of a Service Provider to conduct thoughtful resourcing on a project-by project basis |
| Percent to forecast | What percentage of the documents completed matched the initial forecast of the projected work for a quarter or a year? | Assesses the Sponsor's accuracy in forecasting work as well as the Service Provider's ability to deliver to plan. Even if the forecast of the overall document 'volume' is accurate, are the documents that are projected to start the same documents that are being completed? Is there a high degree of drop-out and/or replacement? |
| Turnover and resource changes | Measure of the instances where the Service Provider either had a writer leave the partnership, or had to replace/reassign a projected writer due to an assignment conflict | For FSP relationships that depend on a dedicated set of writers, this can be an important measure of the return on a training investment from the Sponsor perspective. It can also serve as a measure of the general health of the relationship – if the Service Provider is losing a high number of staff, is it related to the working conditions within the partnership? |

Table 3: KPIs for a medical writing partnership



KPIs should be measured ‘in both directions’ – for a successful partnership, it is important not only for the sponsor to evaluate the performance of the service provider, but also for the sponsor to assess its own performance in meeting the needs and expectations of the service provider



clarity of expectations, the work environment for the writers, and the financial health of the relationship are working successfully for the Service Provider as well.

Key Performance Indicators

Pharmaceutical document work has been particularly difficult to quantitatively assess, as more traditional editing standards (words per page, pages per document, number of typesetting errors, etc) are poor quantitative stand-ins for the important qualitative measures of a regulatory document:

- Was the document written in a manner that was fit for purpose?
- Did it meet regulatory standards?
- Did it appropriately advance the development programme on time and on budget?

However, it is important to continue to develop and implement quantitative measures of medical writing because measuring performance is the key first step in understanding and improving performance.

Within a Sponsor-Service Provider partnership, it is recommended that KPIs be agreed to at the beginning of the relationship, and that they be monitored, discussed, and evaluated on an ongoing basis. KPIs for medical writing can be categorised at the document, departmental, and relationship level, ranging from simple measurements of dates and cycle times to more advanced measures of document quality. Examples of proposed KPIs for a medical writing partnership are provided in Table 3.

It is recommended that KPIs be measured “in both directions” – for a successful partnership, it is important not only for the Sponsor to evaluate the performance of the Service Provider, but for the Sponsor to also evaluate its own performance in meeting the needs and expectations of the Service Provider. Furthermore, it is recommended that KPIs be transparently reviewed by a governance team of the Sponsor and the Service Provider together, working from the same shared data set. Ensuring that each partner is working with the same set of facts is critical to working openly on challenges and making informed decisions with respect to process improvement or innovation efforts.

The reliable collection of a set of KPIs gives medical writing managers the ability to assess and improve performance and

affords Service Providers the opportunity to ensure their own financial solvency and quantify the value of their contributions. Furthermore, it empowers both to effectively communicate the critical contribution of medical writing partnerships to the development of new medications.

Conclusion

Successful medical writing partnerships are based on great medical writing talent, proactive planning, and mutual respect for the value that each partner can provide. Matching the right Service Provider with the right document plan is a key first step, but no matter what the model, setting clear expectations for the partnership is critical. In the current global development environment, establishing strong and lasting working relationships with thoughtful investment in cooperative success is a competitive advantage for both Sponsors and Service Providers.

About the authors



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