Medical Communications

SECTION EDITOR

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Editorial

Most medical writers cut their teeth on manuscripts, and these documents are often mistakenly believed to be 'easy' to write. However, the truth is that with all documents, they are easy to write badly but require skill and knowledge to write well. A quick scan of any journal will quickly (and depressingly!) reveal the sheer number of poor quality manuscripts in circulation.

Producing a high quality manuscript from a clinical study report can be even more challenging. Not only do writers have to deal with the report itself, which may be of "less than ideal" quality, but they then have to tease out the vital messages from what may be a tangle embedded in the report, and also juggle the team – all of whom may be pursuing their own agenda for the manuscript.

In this issue, Michael Riley gives us his top tips for navigating these tricky waters. With many years of experience honing the skills needed to produce clear, accurate and ethically sound manuscripts, Mike is ideally placed to lay out the pitfalls and suggest how to avoid them when writing manuscripts from clinical study reports. His article has something for everyone, even if you have been writing manuscripts for years.

It only leaves me to wish you the best wishes for the season – a happy and healthy 2017, and in the words of Irving Berlin "may your days be merry and bright, and may all your Christmases be white".

Bestest.

Lisa

How to write a clear, complete and accurate clinical study paper: A medical writer's tips, and the importance of reporting guidelines

According to the ethical principles in the Declaration of Helsinki, researchers "are accountable for the completeness and accuracy of their reports",[1] while the Good Publication Practice 3 guidelines (GPP3) state that "professional medical writers have a responsibility to ensure that findings are presented clearly, accurately, and without any intent of misleading readers".[2] However, criticism has been levelled for incomplete reporting of results and methods, such as selective reporting of positive outcomes and inadequate reporting of adverse events (AEs), which may misinform the reader about the benefits and risks of particular treatments.[3] These issues may have various underlying reasons, including lack of awareness and use of reporting guidelines (such as the Consolidated Standards of Reporting Trials [CONSORT] guidelines for randomised trials), and inadequate knowledge of how to write a clinical research paper. In a recent study, papers produced with vs. without medical writing support were more likely to completely report at least 50% of CONSORT items (39.1% vs. 21.1%) and were more likely to be written in acceptable English (81.1% vs. 47.9%).[4] However, these data also suggest that considerable further improvements could often be made to manuscripts even when authors are assisted by a medical writer. This article aims to raise awareness of and encourage routine use of reporting guidelines, in order to improve clarity, completeness, accuracy and transparency in clinical research papers, and provides tips and links to further reading that may assist medical writers in creating clear, complete and accurate study papers.

Reporting guidelines and the EQUATOR Network

The EQUATOR Network (Enhancing the QUAlity and Transparency Of health Research) was set up in 2006 as an international 'umbrella' organisation of researchers and publication professionals, with the mission "to achieve accurate, complete, and transparent reporting of all health research studies to support research reproducibility and usefulness".[5] One of the EQUATOR Network's main aims is to actively encourage the use of reporting guidelines. A comprehensive list of over 320 reporting guidelines is available on the EQUATOR Network website; some are provided by study type (e.g. the CONSORT guidelines for randomised trials, the STROBE guidelines for observational studies in epidemiology), others are specific to particular medical conditions (e.g. response definitions for chronic myeloid leukaemia are proposed by the European LeukemiaNet).[5] Reporting guidelines by study design, such as CONSORT, comprised a checklist and a statement, both of which should be read. The statements may explain and clarify what is meant by each item on the checklist and why each item is important.

Some journals stipulate in their 'instructions for authors' that reporting guidelines should be followed, and may request submission of a checklist showing which items have been reported in the paper. Even if not asked for by the journal, reporting guidelines should routinely be used to improve completeness, accuracy and transparency when writing a research paper.

In addition to reporting guidelines, professional medical writers should be familiar with other important guidelines and regulations related to reporting of results, study conduct, and authors' and medical writers' roles and responsibilities (such as GPP3, ICMJE, the Declaration of Helsinki, and EMWA guidelines).

Practical tips and resources for medical writers to produce clear, complete and accurate clinical study papers

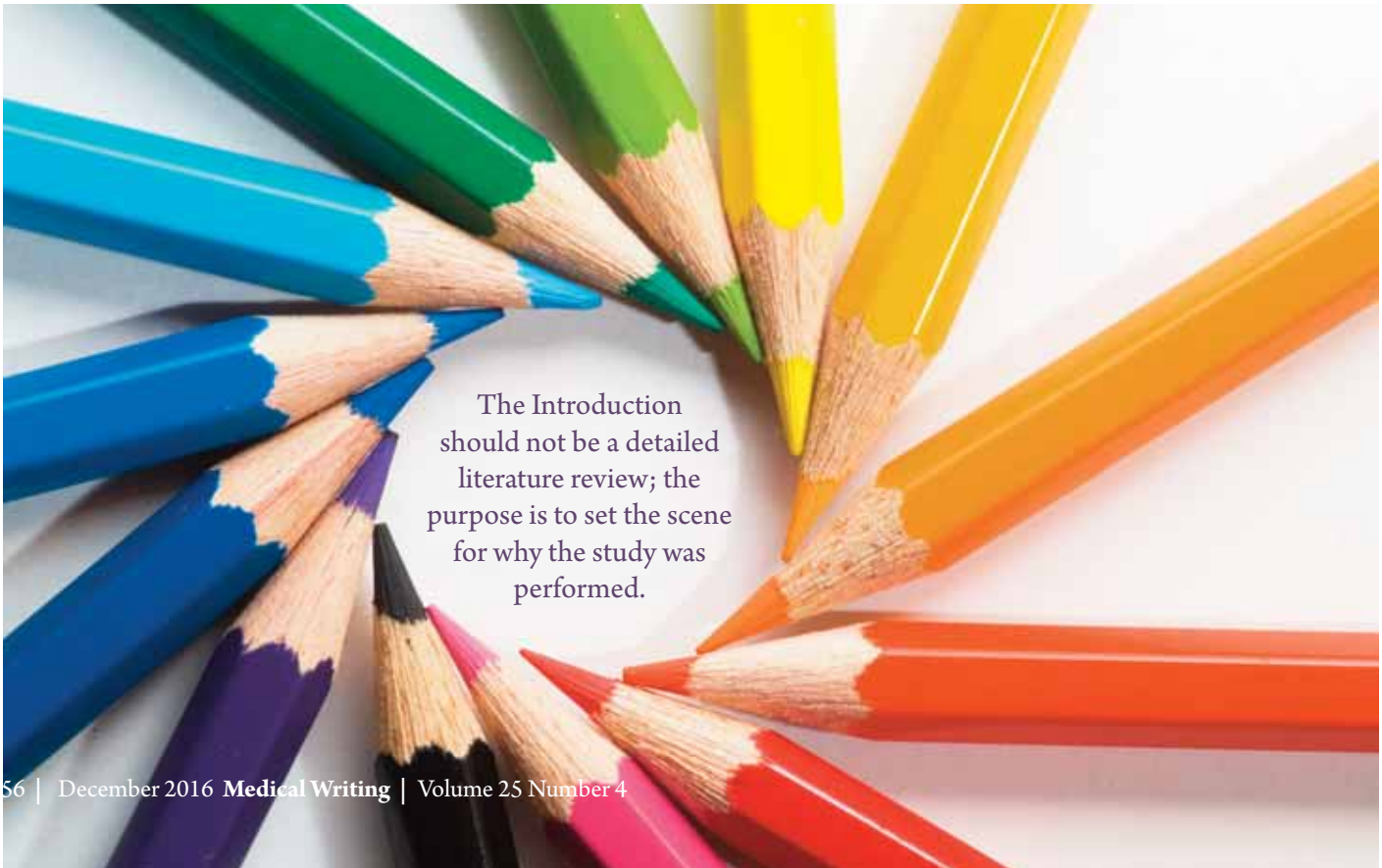
Besides reporting guidelines, other valuable tools are also available via the EQUATOR Network website. These tools include a scientific paper that is annotated with practical advice,[5,6] and an overview of the layout and key contents of a generic medical research paper alongside a list of reporting guidelines.[7] Based on my own experiences of medical writing, and on published papers about scientific writing style including the aforementioned annotated scientific paper,[6,8,9] a few basic medical writing procedure and style tips are shown in Box 1. Hereafter I provide additional practical tips from my own experiences and also from published papers and reporting guidelines.[4-12]

Clear, complete and accurate reporting: general tips

Before writing the paper, the first step should be to ensure that you identify the key data and messages that should be communicated. As your starting point when becoming familiar with the project, it may be appropriate for the study sponsor or an author (or you, the medical writer, in early discussions with the sponsor or author) to physically highlight the key data, messages and methods in the source document. The sources may be one or more of several documents, including a clinical study report (CSR) and associated tables, a congress presentation, or a file of tables generated post hoc that may have no explanatory document. The latter source can be particularly confusing without appropriate guidance. If the paper is based on a CSR, it may be clear which are the key data, methods, and messages, although these are still often worth discussing. For example, if mean and median values are reported for the primary endpoint in the CSR, you may need guidance about whether one or both should be included in the paper. Similarly, even if the primary objective was to study efficacy, should other important issues (e.g. cost-effectiveness) be discussed in relation to efficacy in the paper, even if they were not addressed in the study or in the CSR Discussion section? You may ask the sponsor or authors for key papers and, if necessary, to identify the key messages in these papers that should be included in the Introduction and/or Discussion.

It may also be appropriate to remind or inform the sponsor and authors of the existence of particular reporting guidelines or of specific items before and during the writing process.

Be proactive about completeness, accuracy and transparency, both when presenting data and methodological details from the study and also when discussing other studies in the Introduction and Discussion. For example, when discussing other studies, key factors that may



affect the data, such as study design, should be stated; and if an author adds or changes data in the paper, don't presume it is correct – check the source files. Contact the sponsor or authors if you see an important issue and, if you can, suggest possible solutions. For example, if an author includes the absolute numbers of subjects who experienced AEs in the text without the percentages but the treatment groups were unequally sized, should the percentages be included in the text?

Clear, complete and accurate reporting: Tips by paper section

An often neglected item in reporting guidelines such as CONSORT is that the study design should be included in the title, i.e. 'randomised' in the case of CONSORT.[10]

The Abstract should have sufficient detail to accurately reflect the benefits and harms, methodological details and conclusions that are described in the paper and, as with the rest of the paper, should follow applicable reporting guidelines. For example, CONSORT has issued reporting guidelines specifically for randomised trials reported in congress and journal abstracts.[11]

The Introduction should not be a detailed literature review; the purpose is to set the scene for why the study was performed. It should be as concise as possible (about 350 words in 3 or 4 paragraphs) and, as with all sections of the paper, it should flow logically. Introductions often start with a brief summary of relevant information about the disease, followed by other relevant information about the therapy area and study drug (often about previous trials the study drug has been through), in order to then highlight the gap in the literature addressed by the study. The Introduction should then finish with the overall objective of the study.

The subsections of the Methods are sometimes stipulated in the 'instructions for authors' sections of journal websites. The Methods should be complete, transparent and accurate enough that the reader knows what was done and could actually repeat the study. There should be a method for each result and vice versa. Typically, the Methods will begin with a description of the study design, subjects, settings and locations (e.g. "a multicentre, randomised, double-blind, parallel-group, placebo-controlled trial of drug X in adults with disease Y in hospital outpatient clinics in Germany, Spain, and the US") and a statement that the study was conducted ethically (usually mentioning the Declaration of Helsinki). If available, the study identifier (for registries such as www.clinicaltrials.gov and www.clinicaltrialsregister.eu) should also be included somewhere in the paper (often early in the Methods), potentially allowing the reader to check whether a study is truly prospective and whether all the objectives and outcomes have been reported in the paper. Some studies, such as observational clinical research, may be exempt from registration on www.clinicaltrials.gov. Subsequently, the Methods include the inclusion and exclusion criteria for the subjects, the objectives of the study (primary, secondary, exploratory, etc.), and more detailed information (e.g. doses, schedule) about the interventions and outcomes (variables), and statistical methods. For randomised trials, disclosure of how randomisation and blinding were achieved, and the sample size calculation, are often inadequately reported.[4,10] Similarly, changes to investigated endpoints, relative to the original study protocol, should be disclosed. Post hoc analyses should be clearly identified in the Methods and elsewhere in the paper. If technical information has already been published in detail, then it may be appropriate to refer to the publication and not give full details, as long as they are available in the referenced publication. For commercially available materials and methods (e.g. biomarker test kits, computer software), report the name of the company, city, state and country.

Journals will often have word limits for papers, which may seem detrimental to complete reporting. However, they often allow the use of sections that may be termed "Online Supplementary Materials". Thus methodological information and results that are relevant, although not of the upmost importance, can be reported here and referred to in the Methods or Results sections of the paper.

Most of the text in the Results section will usually describe the figures and tables, highlighting and summarising the key data and patterns, thus making it easier for the reader to understand the figures and tables and vice versa. The text should not merely repeat all the data that are in the figures and tables, and interpretation of what is shown by the data should be left for the Discussion. The Results often begin with a subsection about the subjects' characteristics at baseline, which should allow the reader to determine how well balanced the treatment groups were and also how similar the subjects were relative to those that may be in the readers' clinical practices. Similarly, include a flowchart, such as a CONSORT diagram, at the beginning of the Results so that the reader can compare how many subjects (absolute numbers and percentages) discontinued and why. Reasons for discontinuations are not always reported in papers, but they should be as they are informative; treatments that are more efficacious than placebo tend to have less discontinuation related to lack of efficacy (which supports efficacy analyses of the study), although discontinuations due to AEs are more likely with active treatment and could mask the lack of discontinuations related to lack of efficacy if reasons for discontinuation are not provided.

After describing the baseline characteristics and flow of subjects, it is often logical to then describe the results of the primary analysis, followed by the secondary and exploratory analyses. All analyses should be based on the intention-to-treat principle, otherwise findings can be skewed by discontinuations; in randomised trials, all randomised subjects should be included in the analyses, even if they didn't receive the intervention. Results can be shown for the per-protocol population, which excludes subjects who discontinued, but only as a secondary endpoint. Disappointing results should not be left out. Similarly, there should be accurate, complete and transparent reporting of the potential harms of treatment, e.g. it may be appropriate to only include AEs that occurred in >5% of subjects, although it may be necessary to report some AEs reported by a smaller proportion of subjects, such as serious events, in the paper. Also, think about what types of figures are needed to accurately and clearly show the data and whether you can improve the clarity of figures and tables, e.g. by making rows in a table stand out from each other with alternate shading or indentations to the text.

The Discussion section explains the meaning of the findings, and usually starts with a brief recap and interpretation of the main results in 1 or 2 paragraphs and includes a brief conclusion. Thereafter, the paragraphs should flow logically, perhaps in the following order: compare the findings to those from previous studies, further consider the clinical and scientific implications of the findings of the study (including discussion of negative or unexpected results, and their possible causes), discuss the strengths, limitations and generalisability of the study, and summarize the conclusions again in a final brief paragraph. If relevant, a discussion of possible or planned additional research can be included, perhaps demonstrating that one or more limitations will be remedied.

In relation to strengths and limitations, some issues that could or should be in the Discussion, and perhaps elsewhere in the paper, include discussion of study design and potential sources of bias. For instance, was the comparator group appropriate (if there is a current established

therapy, this should be included as a comparator group), was a surrogate outcome used and what evidence supports its use (see Govani and Higgins[12] for inappropriate use of a surrogate outcome with lethal consequences), was the sample size appropriate, how was missing data addressed? It may also be appropriate to define (perhaps in the Methods or Discussion) what is meant by a "clinically relevant" difference in the study, particularly as this may differ from small but statistically significant changes. Generalisability of the study outcomes to public health practices, which may have different subject characteristics than the subjects in the study, should also be discussed. Issues such as these are discussed in detail by Govani and Higgins.[12]

Finally, medical writing is not ghost writing. Medical writers usually do not fulfil all the criteria for authorship. However, for completeness and transparency, always be acknowledged on the paper for the work that you've done, usually in an appropriately worded sentence in the Acknowledgements section, e.g. 'Michael Riley at Trilogy Writing & Consulting Ltd, Cambridge, UK, provided medical writing services on behalf of XYZ Ltd'.

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Box 1. A few basic procedural and writing style tips for clinical study papers

- It's often appropriate to write a basic outline with a few sentences, tables and figures (maybe placeholders), and to check that the study sponsor, author and/or a senior colleague is happy with it before writing the first draft.
- Try to overcome writer's block by:
  - Writing the easier sections or parts of the easier sections first, i.e. often in the order of Methods, Results, Introduction, Discussion.
  - Not labouring over choice of words (an author may rewrite text that you spent hours beautifully constructing anyway!), e.g. leave sentences and paragraphs unfinished or not worded perfectly, as you can complete them later in this draft or they may not need further revision, maybe after seeking advice from a colleague.
- Scientific papers are often written with personal "we did" and "our study" statements, particularly in the Methods and Discussions sections, whereas authors of clinical study papers often prefer less or no use of personal pronouns, e.g. instead of "We randomly allocated patients to …" consider stating "Patients were randomised to …".
- Subheadings in the Methods and Results sections will often aid readability.
- Use transition words (e.g. "however", "although", "while", "whereas", "conversely", "in addition") at the beginning of sentences and midway through sentences, particularly in the Introduction and Discussion, in order to allow trains of thought to connect and flow.
- When discussing the study and other studies in the Introduction and Discussion, it is often appropriate to use words such as "suggest" rather than "demonstrate" to avoid overstating the implications of the findings.
- In the Discussion, when discussing several strengths or limitations, flow and readability may be aided by starting sentences with "First, …", "Second …" etc., and "Finally".
- Avoid using multiple terms when one will suffice, particularly if it could confuse the reader, e.g. "patients", "subjects", "participants", or "individuals" – some authors use "healthy volunteer" and "patient", although it is worth remembering that patients are also volunteers!
- For clarity and readability, keep the paper succinct, possibly replacing data in the text with tables and figures or by rewriting or deleting text; however, keep essential data and information in the paper so that the study is reported completely.
- While readability may be enhanced by using various sentence lengths, try to avoid exceptionally long sentences (>40 words may be too long, particularly without appropriate punctuation with commas, brackets and semicolons).