



## A guideline for manuscript flow. Part 2 – The methods

New medical writers and medical writing students are often unsure how to start writing a manuscript and need help organising their thoughts.

How to link the sections and information within them is what I call 'manuscript flow'. This article is the second in a series on the flow of information in a manuscript. The first article, published in the March 2013 issue,<sup>1</sup> discussed how to organise the introduction. Here, I explain how to organise the methods.

As described in my previous article 'What are the most common reasons for a manuscript to be rejected (and how can they be avoided)?',<sup>2</sup> the methods is the part of a manuscript most likely to be the cause of rejection. This is mostly because the methods frequently do not provide enough detail to allow others to interpret the true significance of the results. Inadequate methods can be – or at least may be viewed as – a sign of problems in the study design.

Manuscript content guidelines (e.g. CONSORT) and ICMJE recommendations have been developed to help authors prepare articles whose methods are complete.<sup>3</sup> The journal's instructions for authors may also have detailed requirements for the methods section. Writing a clear, well-organised methods section that satisfies all of these instructions can be a challenge.

Described below and summarised in Figure 1 is a general structure that fulfils the requirements of complete reporting of methods. This is only one possible way to organise the methods, but it is one I have arrived at after writing manuscripts for more than 10 years and it seems to work. The structure is in no way rigid – you may find that a different flow works better for you – but this is a good place to start.

The examples I give are for clinical studies because they are what I and most medical manuscript writers work on. A similar flow can be used for all other kinds of articles or studies, although obviously some of the information will be irrelevant and specific guidelines will need to be followed for each article type.

*Start with the overall study design and key details*

I like to start the methods with a section called 'Study design'. This section gives the reader an overview of the kind of study performed, along with details of when and where it was performed. Begin this section with a sentence describing the overall design of the study, and give the clinical trial registration number if there is one. Follow it with a sentence describing the dates and location of the study. Finally, provide the study objectives, with an indication of the primary and secondary outcome measures. For example,

*This was a phase II randomized, double-blinded, multicenter study in adults with severe Crohn's disease (ClinicalTrials.gov NCT00109473). The study was performed between May 12 and August 12, 2011 at 6 centers in Austria. The primary objective was to demonstrate whether 30 µg xamimumab is superior to 20 µg xamimumab for the treatment of severe Crohn's disease as measured by the CDAI. The secondary objective was to compare the safety of 30 µg and 20 µg xamimumab.*

### Ethics

Next, describe the ethical considerations, including approval by ethics committees, ethical guidelines that were followed, and a statement about informed consent. This can be described in a separate section or combined with the study design section. For example,

*The study was approved by the local ethics committee of each institution and was conducted in compliance with the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, South Africa, Edinburgh, Washington and Tokyo), the International Conference for Harmonization Guideline for Good Clinical Practice (January 1997), and all international and national laws and regulations. All subjects gave written informed consent before being included in the studies.*

### Patients (or Subjects)

Once you have given the above generalities, describe how the patients or study subjects were selected. First make it clear who was considered eligible

and then follow with the reasons for exclusion. This should be done in a single paragraph. For example,

*Adults 18–50 years of age were eligible if they had a history of moderate to severe seasonal allergic rhinitis during at least the 2 previous years, a positive skin prick test (wheal diameter  $\geq 3$  mm) to any seasonal pollen, and a pollen-specific immunoglobulin IgE level  $>0.7$  kU/L. Subjects were excluded if they were taking systemic corticoids; had severe seasonal asthma requiring long-acting beta agonists or inhaled steroids; or had a vital capacity  $<80\%$  and a FEV<sub>1</sub>  $<70\%$  of the predicted value. Women could not be pregnant or lactating.*

This section would be structured in the same way for an observational study. If the article was a systematic review or meta-analysis, this section can be replaced with a description of how the articles were selected, and if the study was in cells, animals, or tissues, this section should describe what these are, how they were handled, and how or from whom they were obtained.

#### *Study conduct*

Study conduct should form the middle part of the methods because the study design and population need to be described first. For an interventional study, start by explaining what was done to the patients or subjects. This includes how they were split up or randomised into groups, what the subjects were treated with, how the treatment was administered, and what assessments were made. For example,

*Patients were randomized 1:1 to receive a single subcutaneous injection of 30  $\mu$ g zipitone (Anonymous Drug Company, Felix, NC) or an equivalent volume of 0.9% NaCl (placebo). Subjects were randomized to treatments using an interactive web response system, with randomization lists generated by SAS version 9.2 (SAS Institute, Cary, NC). Treatments were provided in identical, numbered glass vials so that both subjects and investigators were blinded to the treatment type.*

You may wish or need to describe the treatments in detail in their own paragraph or section, especially if they have not been described before or are not commercially available. The following example could be a paragraph within the ‘Study conduct’ section or could be a section of its own entitled ‘Vaccines’:

*All vaccines were split virion and contained the A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/*

*67/2005 (H3N2), and B/Malaysia/2506/2004 strains. The investigational intradermal vaccines contained either 15  $\mu$ g or 21  $\mu$ g of HA per strain in 0.1 mL in a prefilled Toluva™ microinjection device. The high-dose vaccine contained 60  $\mu$ g of HA per strain in a ready-to-use 0.5-mL syringe. The standard-dose vaccine contained 15  $\mu$ g of HA per strain in a ready-to-use 0.5-mL syringe.*

Next, describe the assessments, measures, or assays. For each technical method, if it has been previously published, you only need to give a single sentence providing the citation, although if you think it important, a sentence or two summarising the method can be included. If not previously published, describe the method in full. In all cases, be sure to describe the limits of detection and sensitivity for the method as well as the source of any materials or equipment used. For example,

*Quality of life was assessed on day 28 using the HAQ (12).*

The following is a more detailed section that should be presented as a separate paragraph or section entitled, for example, ‘Immunogenicity’:

*Blood samples were collected before vaccination (day 0) and 28 days after vaccination. Hemagglutination inhibition (HI) titers were measured using a standard assay (12). The serum HI antibody titer was defined as the reciprocal of the highest serum dilution that completely inhibited hemagglutination. To calculate geometric mean titers, samples with HI not reaching 100% at the lowest serum dilution tested (1:10) were assigned a titer of 5. Seroconversion in a subject was defined by either a pre-vaccination HI titer  $<1:10$  and a day-28 titer  $\geq 1:40$  or by a pre-vaccination titer  $\geq 1:10$  and a minimum four-fold titer increase at day 28. Seroprotection was defined as a pre- or post-vaccination HI titer  $\geq 1:40$ .*

For clinical studies where safety was assessed, you may want to create a separate section called ‘Safety’ describing in detail the assessments of adverse events, severe adverse events, and scoring of solicited reactions (expected adverse events).

#### *Sample size*

For interventional studies, describing the sample size calculation is essential. This information puts the results of statistical tests in context. For example, the relevance of statistical tests will be unclear if too few subjects were included to detect



Figure 1: Summary of flow of the methods.

a meaningful difference. Even if a power calculation was not performed, an explanation of how the sample size was selected can help put the results in context. This information about sample size can be combined with the statistics section, but it can also be effective as an independent section, especially when it has an important bearing on the interpretation of the results. I like to include a section on sample size just before the section on statistics. For example,

*A total of 1600 subjects (800 subjects 18–60 years of age and 800 subjects >60 years of age) were estimated to be needed to provide 95% power to detect the primary objective, assuming a one-sided alpha level of 2.5%, a non-inferiority margin for the geometric mean titer ratio of 1.5, a standard deviation of log-transformed titers of 0.7, and 90% of subjects evaluable.*

#### Statistics

The statistics section should explain the software used, the statistical tests used, specific populations

or subgroups, and general statistical considerations, such as how statistical significance was defined and whether (and how) missing data were replaced or imputed. For example,

*Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC). Missing and incomplete data were not replaced and no imputation was performed. Safety was assessed in all subjects treated. Immunogenicity was assessed in all subjects who were randomized and treated, had a valid post-vaccination serology result, and completed the study according to protocol. Non-inferiority was assessed in subjects completing the study according to protocol and superiority was examined in all vaccinated subjects with a post-vaccination blood sample. For non-inferiority, the age-stratified confidence interval was calculated using an analysis of variance model of log-transformed titers, with age group (18–60 and >60 years) as the stratifying factor in the model. Non-inferiority was demonstrated if the lower limit of the age-stratified two-sided 95% confidence interval of the ratio of day 21 geometric mean titers was >0.667. The frequency of solicited reactions was compared between groups using Fisher's exact test. Differences were considered statistically significant if the p-value was less than 0.05.*

#### Conclusion

To avoid having your article rejected because of an inadequate methods section, you must include all information required by the appropriate content guidelines (e.g. CONSORT) and the journal's instructions for authors, and everything needed for readers to put the study in context and to allow the results to be interpreted. The flow described here can accomplish this and is one way of logically organising the information, although you should adapt it to the specific needs of your article.

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#### References

1. Leventhal PS. A guideline for manuscript flow. Part 1 – The introduction. *Med Writing* 2013;22(1):59–60.
2. Leventhal PS. What are the most common reasons for a manuscript to be rejected (and how can they be avoided)? *Med Writing* 2012;21(1):66–8.
3. Leventhal PS. Guidelines for manuscript writing: here to help. *Med Writing* 2012;21(2):164–8.