



The joy of writing a paper

Why am I doing this?

Tell us, did you enjoy writing your first scientific paper? Or, if you are an enthusiastic newcomer to science, are you looking forward to it? Science is writing. You have probably spent weeks on writing your protocol. Furthermore, it may have taken days to put your standard operating procedures, clinical record forms and analysis plan on paper. Eventually, you may have reserved the next few months to write up your paper. How can one enjoy writing a paper, meant to be read by unknown colleagues somewhere else on the globe? Who are your customers? They could be clinicians, trying to keep up to date, or biomedical scientists searching for the best work in their field of interest.

What is the best approach to writing a manuscript on a biomedical scientific study? Well, the most solid approach, obviously, is to read a textbook on scientific writing. Both of us have Mimi Zeiger on our shelves [1]. But did we actually read the book? We may say we followed a more modern medical concept: an "evidence-based" approach using two simple facts: a) our papers that have been accepted for publication must have had some sense in them; and b) our rejected papers could probably benefit from some improvements. The key reader is the reviewer. In fact, we are primarily writing for our reviewers. The customer-reader comes second. So how should we comply with the expectations of reviewers and editors?

The present paper is meant to give you some guidance by providing a checklist with bullets. This does not pretend to be complete, but rather is an encouragement to spend a bit more time on thinking about writing. It is our experience that this saves a lot of time. Our list is applicable for clinical as well as basic research papers. However, you may skip issues that do not relate to your study.

What do I need to consider in advance?

Several issues need to be taken into account after deciding to write a paper. The best summary is given by the International Committee of Medical Journal Editors (ICMJE) [2]. The first principle is: the paper should present novel data. Duplicate publication of data is a suicidal boobytrap and must be avoided at all times [3].

Consider the following:

The data

- Are these novel or confirmative?
- What are the strengths and weaknesses of the data?

The journal

- Is my paper suitable for a specialty journal or a general medical journal?
- Am I heading for a high impact factor journal [4]?
- Is this kind of paper well cited [5]?
- Do I need a fast acceptance?
- Does my institution or granting body require that my paper have open access?

The authors

- The decision about authorships should be based on substantial input in drafting the study, generating the data, writing the paper and/or the final responsibility for and approval of the paper [2].
- Avoid ghost- and gift-authorships.

Integrity

- Consider the rules of the journal when providing statements of interest for all authors. Conflicts of interest do have an impact [6].
- Be alert in avoiding any integrity problems such as plagiarism, twisted statistics, suppression of data, manipulation of figures, inadequate citations, etc. [7, 8].

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Split the thinking from the writing

When it comes to actually starting to write, there are a few tricks for making it all a bit easier. Some of you may have threshold fear, or may even have experienced a real "writer's block". For a novelist, this can be a real problem. But don't worry, for a scientist it can be solved.

If there is a single take-home message in this paper it is the following: split the thinking from the writing. There is nothing worse than to follow a line of thinking only to have to stop half-way through in order to check for supporting literature. Usually this opens too many options, often

leading to a halt in the writing process.

The way to get around this, for instance when building up an introduction section, is the following. (This can also be applied to the other sections of the paper.)

- First do the thinking, and then the writing.
- Start by building a flow chart of the main paragraphs of the introduction.
- Usually this is about 5–6 paragraphs: the general problem, the specific dilemma and its relevance, why it is still unresolved, your bright idea of how to solve it, and your hypothesis and aim (for details, read on).
- Give each paragraph a single label (to be used in your flow chart). An example on a study aimed to test an anti-viral drug in exacerbations of asthma is shown in figure 1.
- Add the major message of each paragraph to the flow chart.
- Finally, add a smooth bridge to the next paragraph.
- Collect, print and read all references for each paragraph and add them in short alongside the flow chart
- Suitably adjust the flow chart and references until the reasoning and the required literature match optimally.
- This finishes most of the thinking on this section of your paper.
- Now you can concentrate on the language and the actual writing, paragraph by paragraph.
- Language and style should be as if this is going to be the final version: all details should be dealt with now, so you don't have to go over the little things again and again later.
- The writing will progress quickly, because it is barely interrupted by novel ideas or novel references. (If this occurs, it will create not chaos but improvement.)
- One evening later: this part of the paper is finished! You can confidently start with the next section.

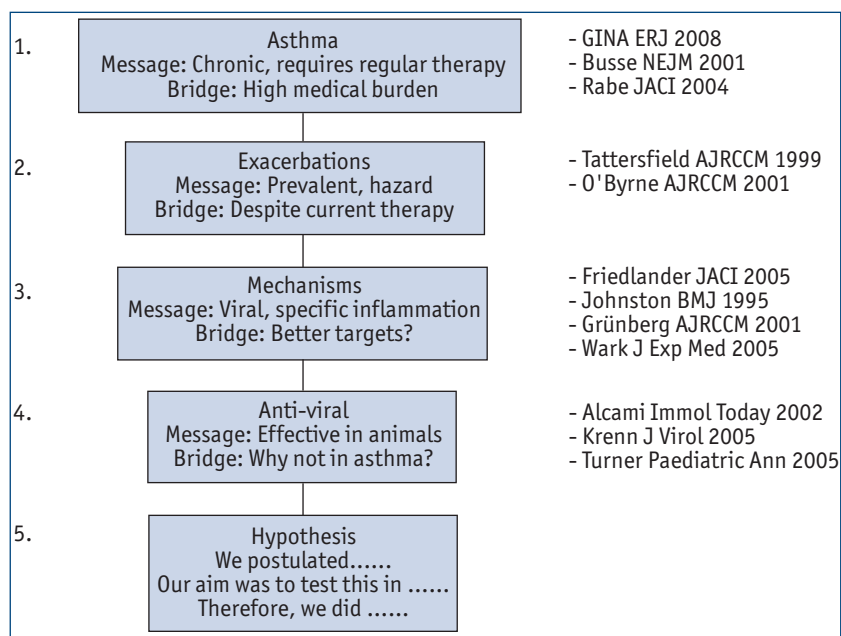
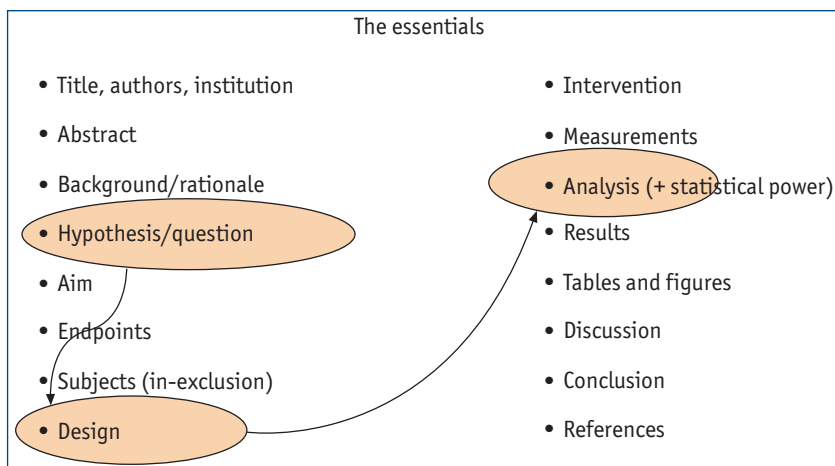


Figure 1
An example flow chart for the introduction to a paper on asthma.

Figure 2
The vital components of a paper.



The essential parts

We all know that it is customary to write a scientific paper in sections: introduction, methods, results with tables and figures, discussion and references (figure 2). Obviously, this depends on the focus of the study, but it is very useful to check the parts that should not be forgotten. The backbone of your paper is the link between the three vital elements: the hypothesis or research question, the design of the study and the analysis. A particular hypothesis can only be addressed by a

particular design, which brings in a specific way of analysing and presenting the data. The most common reason for rejection of papers is some kind of discrepancy between these three issues. Of course, this point should have been dealt with when writing the protocol, but we know from (too many) of our own experiences that any weaknesses in linking these three parts that we overlooked or accepted at the protocol stage can become very apparent and awkward when writing the paper.

Let us go through each of the sections now one by one. First, carefully check the journal's instructions to authors on the requirements regarding content and layout. As an example,

you can check the instructions for the *European Respiratory Journal* [9].

Title page

Start with this page: within 15 minutes you have written the most important, selling page of your paper, so that you can proudly press "save" for the first time:

- Title page includes: title, authors, affiliations, address for correspondence, grants, sponsors, trial registration number, key words, date and draft number.
- The title is essential, as it primes the reader. It should cover the study adequately, and should also raise interest.

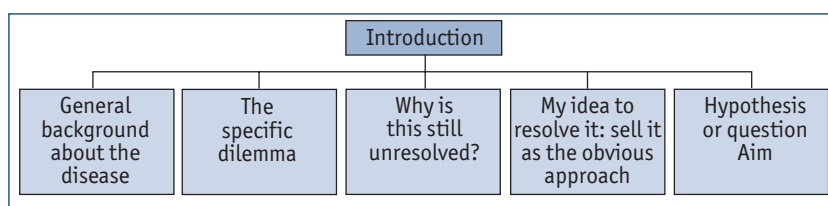


Figure 3
The construction of an Introduction.

Introduction

The general make-up of the introduction has already been summarised in this article. It is shown in figure 3. In fact, the word "introduction" does not cover the meaning of this section. It should deal with the rationale of your study. It is your most important chance to convince the reader that what you did makes a lot of sense. Usually, an introduction does not exceed two double-spaced pages. The bottom line here is: the reader should be increasingly enthusiastic when reading your introduction!

- The general problem: which health problem forms the motive of your study? Give a few facts about it. Highlight its relevance. Even if your biomedical study is a basic science one, it should be embedded into some kind of health problem.
- The specific focus: which part of the problem will you be focusing on? Why is this issue so important? What will be the gain when this is solved? Make plausible the idea that this is within reach.
- Why is the problem still unresolved? Mention whether, and how, others have approached this previously. Why has this not been (fully) successful? Why have others (partly) failed?
- Your idea: indicate why you believe that the specific problem can be solved. Explain why your idea is good, and probably better than what has been attempted previously. Sell your proposal. After reading this your idea should be an obvious thing to do. Provide any data supporting your idea.
- Provide an explicit hypothesis (or a primary and a secondary hypothesis). Second best is to list a few explicit research questions.
- Finally, mention the aim/objectives and outcome measures of the study. That is: testing the hypothesis in this material, in such a way, by measuring these (primary and secondary) outcomes.
- You may close this section by very briefly giving the implications of rejecting or not rejecting the hypothesis. Similarly, highlight the implications of positive and negative answers to the research questions.

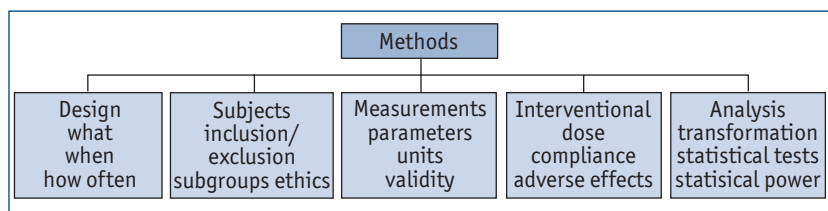


Figure 4
Building the Methods section.

Methods

Regardless of whether you are presenting a basic science, clinical or epidemiological study, the methods will have a similar structure. Usually it starts with Subjects, then Design, followed by Measurements and Analysis (figure 4). You may also start with Design.

Subjects (Materials)

- This includes the patients, the animals, the tissue, *etc.*
- Give the required number (based on the sample size estimation in the Analysis section). The actual number that you ended up with comes in the results section.
- Indicate how the subjects were selected, from what source, by whom and in what way. In the case of patients, give details of the recruitment procedure.
- Give explicit inclusion and exclusion criteria. For human subjects think of demographic, clinical, habitual and functional criteria, medication usage, biochemical criteria, *etc.* If applicable, give the rationale and criteria for control group(s).
- If needed, give criteria for predefined subgroups (these should be logical subgroups, derived from the reasoning in the introduction).
- Define criteria for drop-outs.
- Confirm approval by a human or animal ethics committee, and in the case of humans confirm written informed consent.

Design

- Check current guidelines for presenting, *e.g.* randomised controlled trials (CONSORT Guidelines) [10] and observational studies (STROBE Guidelines) [11].
- For clinical studies: give the registration number of the study in an International Clinical Trial Registry [12].
- Give an exact description of the study design: descriptive, observational, cross-sectional, interventional, follow-up, retrospective, prospective, randomised controlled trial, cohort study, case-control, *etc.*
- Uncontrolled, controlled, placebo-controlled, cross-over, parallel, matched pair. Open, single-blind (who was blinded?) or double-blind. Give method of randomisation and method of matching.
- Mention exactly what was performed, when, how often, and in which sequence. Don't forget what was done prior to (screening, run-in?) and after (run-out?) the study. A figure of the design is always helpful.
- Give the procedure of study monitoring.

Methods of measurement

- This should list each and every measurement of the study.
- Give your rationale for the measurements in view of the study objectives.
- Give apparatus, settings, calibration, resolution and detection limits if applicable.
- Indicate that detailed standard operating procedures (SOPs) were used. If needed, mention key elements from the SOPs.
- Give variable(s) for each measurement, and the units in which you will present those.
- Provide (references about) the validation of the methods (accuracy, precision, repeatability), preferably from your own lab.

Analysis

- Check adequate recommendations on how to present the analysis and statistics [9].
- Indicate whether any of the variables required transformation of the units (*e.g.* log-transformation).
- Mention the structure of the study database and who was responsible for it.
- Indicate when and who broke the code of the study, and who had access to it.
- Indicate who carried out the statistics, using which software and version.
- Provide statistics for each hypothesis/research question. Remember that the tests have to be appropriate to your study design.
- Clearly indicate what was analysed between groups, and what within groups.
- Define the minimally relevant effect size (*e.g.* the minimally important clinical difference) and the type 1 and type 2 error by either single- or double-sided testing.
- Present sample-size estimation or power calculation for the analysis and the number of subjects/animals/*etc.*
- Indicate and explain whether the analysis was performed by "intention to treat" or "per protocol".
- Mention what was done with missing data or drop-outs.
- Was interim analysis planned? If so, why? Was it done? Give detailed consequences of this.

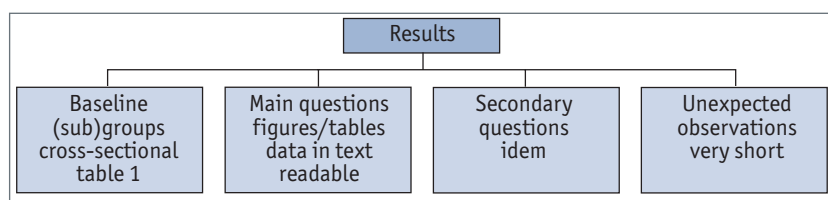


Figure 5
The structure of the Results section.

Results

The Results section presents facts. Do not repeat the rationale of measuring things, nor discuss the findings here. Even though this section is highly factual, it should remain readable. So, present your findings in clear paragraphs, based on the steps in the Analysis. A good way to start writing the Results section is to construct the tables and figures first. This also splits the thinking from the writing. If the tables and figures highlight your major findings clearly, then writing results will be very easy (figure 5).

- Start with the sample size that was actually obtained. You may use a figure here (trial profile), showing the numbers of subjects included (and excluded) at each step of the selection procedure.
- Present a baseline analysis of your subjects/material, by giving the vital (demographic, clinical) information in table 1. Mention the most striking features in the text.
- Present the results by addressing the hypotheses (or research questions) in a stepwise fashion, separated into logical paragraphs. Be concise and clear, and refer to tables and figures.
- Concentrate on primary outcomes first. Secondary outcomes come later.
- Avoid repetition of data between text, tables and figures. However, if highlighting major findings is necessary, a little overlap is acceptable.
- The reader will be interested in the main findings. These must stand out, even for those not reading the results from the beginning to the end.
- Do not bore the reader by constantly repeating the same structure of sentences. Hence, even the results should read like a logical story – but be thrifty with adjectives.
- Also, be conservative in presenting (planned) subgroup analysis. Follow recent guidelines on presenting subgroup analysis [13].
- You may end with unexpected findings, and the results of unplanned (*posthoc*) analysis. These kinds of results are mostly hypothesis-generating, and should be limited to the absolute minimum. Otherwise, you will be accused of "fishing".

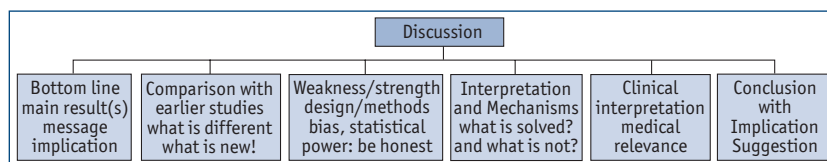


Figure 6
Points for the Discussion.

Discussion

There are many ways of writing the Discussion section. Most of us consider the Discussion section as the most difficult part of the paper because there are so many issues to be dealt with. Again, the best approach is to separate the thinking from the writing. The first step is to distinguish the paragraphs of the discussion. These should be (figure 6):

- Red line and take-home message.
- Comparison with previous literature.
- Strengths and weaknesses.
- Interpretation and mechanisms.
- Clinical relevance.
- Conclusion.

Be aware that each paragraph must have a clear head and tail. The first sentence of each paragraph should guide the reader, by indicating what this paragraph will be about. The final sentence of each paragraph should provide the message, and ideally should form a bridge to the next paragraph. How long should the discussion be? One rule of thumb is that it should be about 3.5 double-spaced pages (and should not exceed 4 pages). Hence, being concise is more important than being complete and exhaustive.

The following system of writing a discussion section may not be the best. However, we do know that it always works well. It comes from Ed Daniel from McMaster University, who taught one of us (P.J. Sterk) how to write a discussion on the back of an envelope. And be aware, there is no one with a broader scientific perspective than Ed [14]!

Again, separate the thinking from the writing. After preparing your flow chart (figure 1), and subsequently writing the discussion part by part, you will be ready within one or two days!

Red line of the findings and take-home message

- Provide the main results in one or two sentences: the main findings only.
- Indicate what one can infer from them.
- Give the implication of the results: this suggests this or that with regard to mechanisms and/or the clinical problem.

Comparison with previous studies in the literature

- Indicate what is novel in your study.
- If your results confirm previous studies: say so.
- More importantly, indicate why your study extends any previous observations.
- Always start with your own findings, and connect these to current literature if available (never the other way around!).
- Discuss only observations, no mechanisms or interpretations here.
- Finally, provide the message of this paragraph: our results are new, different, better, more detailed, etc.

Strengths and weaknesses

- Try to start off with a few strong points in the methods of your study. Do not exaggerate.
- In any study there will have been choices in the methods that might have introduced weaknesses. You should raise these points, otherwise the reviewers will.
- Think of issues related to: selection of subjects, design, and methods of measurements, analysis. Go through your protocol and pick out a few potential weak points.

- What would be factors introducing random errors (noise) and systemic errors (bias) leading to variability in the data? If appropriate (negative results), mention the statistical power here.
- Try to emphasise that some of your choices in the protocol had implicit strengths apart from the (less important) weaknesses.
- You may separate this paragraph in two. On the other hand, don't be too extensive (don't throw yourself away).
- We hope that you can finish by saying that the potential errors have not been that serious. They cannot be the explanation of your (negative) findings.

Interpretation in terms of mechanisms

- How can you explain your findings?
- Which pathophysiological/immunological/*etc.* mechanisms are likely to form the basis of your findings?
- Address these mechanisms one by one: you may need to separate this paragraph into two or even three.
- Again: explain your own findings, and only if it really cannot be avoided explain the findings of others.
- What has been solved by your study, and what has not?
- Speculation is allowed, but be very clear on this: mention the word speculation if you do.
- The final sentence, again, present the main message with regard to interpretation of your data. This or that mechanism is likely to be (or not to be) involved.
- And if there are still open questions here, mention them.

Clinical interpretation

- What is the clinical relevance of your findings? Even biomedical basic science studies should have a link to a medical problem.
- Do your results contribute to improving detection, diagnosis, monitoring or treatment of disease?
- What should physicians do differently in this respect from now on?
- Speculation is allowed, but say so.
- What is still missing in this area?

Conclusion

- This paragraph can be short, because your main message has already been addressed in the first paragraph.
 - You cannot repeat the first paragraph of the discussion, so you have to use a slightly different wording or emphasis here.
 - Be very concise, but crystal clear. This section should contain the take-home message.
 - Hence, summarise the main findings in one or two sentences, and most importantly provide the implication(s) of your findings in relation to the specific and general health problem that you started with. This head and tail closes the circle of the paper.
- After giving your message, you may emphasise the obvious things to do next.

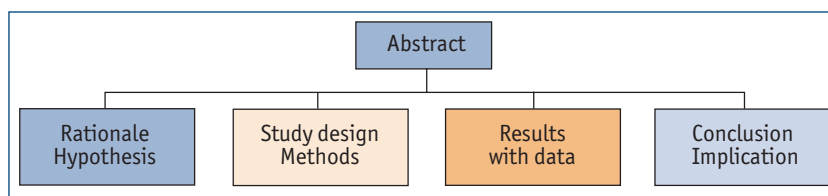


Figure 7
What goes into the Abstract.

Abstract

The structure of the abstract follows the main sections of your paper. You should check the journal's rules for it. The best way of writing the abstract is to use four paragraphs: rationale, methods, results, and conclusion (figure 7).

- The rationale addresses the relevance of the key problem in one or two sentences. It should provide your hypothesis or main research question.
- The methods section is often somewhat longer. Give the essential subject characteristics, the type of design, and the primary outcome parameters. One sentence on the analysis can be very helpful.
- The results section should provide the main outcome of your study, related to the primary hypothesis or research question. Select one or two quantitative results with confidence intervals or p-values (some journals do not appreciate the latter in the abstract).
- The conclusion section essentially presents two aspects. First, one or two sentences on the main finding. Second (and importantly) one sentence on the implication of this. The implication should have relevance to the key problem as mentioned in the rationale (head and tail).

Revision

After submission of your paper and peer review, you may be allowed to submit a revision. There are two main recommendations here. First, take your reviewer seriously. Secondly, take your reviewer seriously. Because editors do.

Make a point-by-point list of your replies, with headings referring to the issues of concern. Be honest, concise and accurate. Try to accommodate most points in the manuscript and indicate where you have done this. If applicable, tell the editor if and why you could not comply with some of the reviewer's requests.

Rejected

Don't panic. It is not you. It is your paper. Journals make a positive selection rather than a negative one. Unless the reviewers have convinced you that your study is flawed, consider submitting the paper to another journal. Do not copy-and-paste your paper. Improve it according to the reviewer's suggestions (if you agree with those). This may include adding new experiments. And then the fun starts all over again...

Accepted

Enjoy it, together with your co-authors! But after one or two days (and nights)... the joy is over. Don't panic. Your keyboard is waiting for the next enjoyable paper.

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