Writing Up Clinical Research: A Statistician's View

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I supervise a team of statisticians who run analyses for junior investigators undertaking clinical research. The statisticians forward me drafts of the resulting papers for review. As a result, I have seen hundreds of research papers written by junior investigators. What is interesting is that the same missteps occur repeatedly. Here I set out some hints and tips to avoid such missteps. This is a personal view and is not meant to be a comprehensive overview of clinical research reporting. Several other papers provide good general advice on writing introduction and discussion sections.[1–5]

USE REPORTING CHECKLISTS

Expert groups have published checklists detailing what should be reported for a given type of study. For example, the CONSORT checklist for randomized trials includes items such as the eligibility criteria, blinding and the table of baseline characteristics. Other reporting guidelines include STARD (for diagnostic accuracy studies), STROBE (for epidemiology), PRISMA (for meta-analyses) and REMARK (for molecular marker studies). These and other reporting guidelines are available on the Web at http://www.equator-network.org.

MAKE SURE THAT EVERY WORD AND NUMBER IS ACCURATE AND MEANINGFUL

Investigators do not always check every single word and number to ensure that they belong in the paper. For example, statistics are often reported to inappropriate levels of precision, such as a mean age of 45.67 years. It is generally not important to know age to the nearest 4 days and so it is clear that the author did not consider whether it was meaningful to report age to 2 decimal places. A second common error is to lapse into platitude. A statement such as, "surgeons should carefully consider the extent of surgery" cannot reasonably be contradicted. As such, it adds nothing to a paper.

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THE INTRODUCTION SHOULD STATE A COMPELLING CASE FOR THE STUDY OBJECTIVE

Many introduction sections make some general comments about the disease ("rheumatoid arthritis affects 1.3 million American adults"), and then about an intervention or marker ("rheumatoid factor is associated with disease severity"), ending with an imprecise overall study objective ("we aimed to explore the relationship between rheumatoid factor and outcome in patients on disease modifying agents"). Instead, the introduction should consist of a clear, step-by-step argument leading to a specific study hypothesis. This argument can often be usefully written out in bullet point form first. For example: a) disease modifying agents are effective for rheumatoid arthritis; b) response is inadequate in many patients; c) in current practice, pain scores are monitored for some time before a decision is made to change treatments; d) were a marker to be available that could predict treatment response early, this would allow patients to switch treatments decreasing toxicity and improving effectiveness; e) rheumatoid factor is known to be associated with disease severity; f) it is plausible that an early measure of rheumatoid factor could predict treatment response. This argument compels the reader to ask the study question.

STATE A CLEAR OBJECTIVE

One way to think about a paper is that each section follows logically from the previous section: given the introduction, it is obvious what the objective has to be; the methods are determined by the objective; the results section reports the outcomes of applying the study methods; the discussion interprets the results. The end of the introduction section should therefore include a study objective or hypothesis sufficiently clear such that a knowledgeable investigator could make a reasonable

show of writing the methods section based on the objective alone.

THINK ABOUT MECHANISMS WHEN STATING HYPOTHESES

A hypothesis that, say, African American men have poorer prostate cancer survival than whites is specific enough, but is biologically anemic. If there are racial differences in survival, there has to be a reason, such as differences in stage at presentation, access to care, death from comorbid disease or genetics. A more biologically based hypothesis might be that survival is poorer, but not after adjusting for stage at presentation, suggesting that variations in screening are an important cause of racial differences in survival.

BE SPECIFIC ABOUT STATISTICAL METHODS

Many papers say little more concerning statistics than that "t-tests were used for continuous variables and χ^2 for categorical variables". The statistical methods should describe a specific objective (e.g. "to evaluate the relationship between surgical experience and outcome"), the statistical method used to address that objective ("we created a multivariable regression model including the following covariates …") and then any special characteristics of the analysis and the rationale therefore ("as the relationship may be non-linear, we used restricted cubic splines").

PRESENT DATA PREDOMINANTLY USING TABLES AND FIGURES

The text of the results section should point out the main messages of data presented graphically or in tables. Key numbers can be restated in the text, such as the difference between groups along with a 95 % C.I. and p value, but the use of numbers in the text should otherwise be limited.

ANY REVIEW OF THE LITERATURE IN THE DISCUSSION SECTION SHOULD BE CLOSELY LINKED TO THE STUDY FINDINGS

It is common for investigators to include a literature review in the discussion section that constitutes little more than a catalog, ("Jones et al. reported A, B and C … Smith et al. reported D, E and F …"). References to other literature should be directly linked to the current findings. The results of each paper should be described in terms of how they compare to those reported by the investigators (Similar? Larger? Smaller?) and reasons for any differences discussed ("Jones et al. included patients treated in the 1980s, whereas our cohort included only those treated after the stage-shift").

EXPLAIN THE EFFECTS OF ANY STUDY LIMITATIONS

It is all too common for investigators to include in the discussion a throw-away line such as "Limitations of the study include its retrospective nature and small sample size". Study limitations should be evaluated carefully in light of their effects on the results: a small sample size may not be a problem if the null hypothesis is rejected, and a retrospective design is often methodologically sound. Discussion of limitations should include both the likelihood and effect size of possible bias.

DRAW A CONCLUSION

Many investigators avoid drawing a conclusion and merely restate their results. For example, "We conclude that obesity at age 18 predicts death by early middle-age" is a result and is therefore insufficient as a conclusion for a clinical research paper. A good conclusion section might also include, for example, a recommendation that public health measures need to be explored to see how to reduce teenage obesity, or that further research should investigate whether the association between obesity and mortality is causal. On the subject of further research, investigators should avoid concluding merely "further research is warranted", the conclusion should be specific as to the next studies that should be conducted.

DRAW CONCLUSIONS IN THE LIGHT OF THE STUDY QUESTION

A study question involves a specific population, intervention, outcome and, in some cases, comparator. Conclusions should generally be restricted accordingly. For instance, if ultrasound was found to improve mobility compared to placebo in chronic neck pain, it is not the case that "physical interventions" are of benefit, or that ultrasound is "effective for neck pain" or "helps with musculoskeletal conditions". With respect to comparators, one particular mistake is to use within-group comparisons to draw between-group conclusions. If group A has a better response to surgery than group B, this cannot be used to conclude that "group A but not B should be treated surgically". It may be that another treatment is superior

to surgery for group A or that the best option for patients in group B is surgery, even if they do relatively poorly.

DON'T ACCEPT THE NULL HYPOTHESIS

Just as in a court case there is no verdict of "innocent", in a statistical test there is no verdict of "no difference". If a p value is greater than 5 %, conclusions should avoid statements such as "the drug was ineffective" or "there is no difference between groups". Possible alternative phrasings include "no significant difference between groups" or "we failed to find evidence of an effect". Where the null hypothesis is not rejected, confidence intervals can often play an important role. For example, investigators might conclude "the drug is unlikely to have any clinically relevant effect" or, alternatively, "our confidence intervals are consistent with a clinically important 40% decrease in risk".

REJECTING THE NULL HYPOTHESIS DOES NOT OF ITSELF HAVE CLINICAL IMPLICATIONS

Avoid making clinical recommendations on the basis of statistical significance. For example, a finding that a marker is statistically associated with outcome does not imply that treatment decisions should be determined by marker levels.

There are, no doubt, many poorly reported papers that follow the guidelines discussed above. Moreover, there may be good reasons to forgo a specific recommendation. But the hints and tips outlined in this paper should be a good starting point for investigators writing clinical research papers.

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