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Daniel W. Byrne

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In memory of Art Wheeler

Preface

"Worship the spirit of criticism," Pasteur advised his fellow scientists. Today, most scientists recognize the importance of this advice, but nearly all prefer the spirit of praise from one particular group: peer reviewers. The bad news is that each year, reviewers reject hundreds of thousands of medical manuscripts. The good news is that many are rejected for common flaws that can be avoided.

Numerous books have described how to write a scientific paper, notably those by Day and Gastel (2011), Huth (1999), Browner (2012), and Hall (2012). My goal in writing *Publishing Your Medical Research* was to explain how to anticipate and avoid the problems typically encountered in designing a research study and writing a publishable paper.

Many common reviewer criticisms can be avoided simply by understanding the research and publishing processes and by following certain fundamental principles. This book presents more than 200 principles in five sequential phases: Planning, Observing, Writing, Editing, and Revising. Applying these POWER principles will increase the likelihood that your research will be accepted for publication. The information in this book will also help you critically assess new medical information and extract what you need to know.

As background research for this book, I surveyed a number of experts, including editors-in-chief of prominent medical journals, peer reviewers, and Nobel Laureates. I conducted this survey for the first edition and then again recently for the second edition. Additionally, I analyzed hundreds of actual reviews to identify common themes and distilled specific comments into positive guidance. These ideas are arranged into principles presented in an easy-to-read format, with short examples of actual peer review critiques. To protect the privacy of those involved, some of these comments are paraphrased or generalized.

Publishing Your Medical Research is designed to help researchers work effectively with epidemiologists, informatics experts, biostatisticians, technical writers, graphic artists, and other methodologists. It provides an organized collection of solutions to help you publish your medical research paper. For those who manage a research team, these solutions will help you stretch your research funds. Although this book focuses on clinical research, most of the principles can also be applied to nonclinical biomedical research, which is increasingly requiring more of these principles. This book is a guide, not a cookbook, and therefore does not attempt to explain everything you need to know about statistical analysis, epidemiology, or writing. For more complex problems, a suitable modern reference or resource is recommended.

Academic publishing requires time, dedication, practice, and, above all, persistence. If you can muster these resources, you will be rewarded with seeing your article in print and knowing that your work has made a difference. As the clinical psychologist and educator Anne Roe said, "Nothing in science has any value to society if it is not communicated."

—Daniel W. Byrne

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All published work and quotations are referenced as accurately as possible. As promised, the survey responses were kept anonymous, but I am nonetheless grateful to the reviewers and editors who completed and returned my questionnaires.

Gertrude Elion and Robert Jacoby were kind enough to read and find something nice to say about early drafts of the first edition of this book. I continue to be grateful to all of the people who helped with the first edition, including Paul van Niewerburgh, Jane Petro, Harold Horowitz, Jean Morgan, Albert Lowenfels, Chris Hunter, Lawrence Wexler, Luis Bracero, P.D. Reddy, Evan Jones, Michael Blumenfield, Elizabeth Nieginski, Julie Scardiglia, Karla Schroeder, Rosanne Hallowell, Beth Goldner, and Jacqueline Jenks.

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Finally, but most of all, a special thanks to my wife, Loretta, for her insightful editing and almost endless patience.

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CHAPTER 1

Overview: Twenty Key Principles

Success in publishing your medical research paper will largely depend on how well you follow these twenty key principles. Study these points before moving on to the more detailed principles and periodically review these during your research project.

> *"You have to learn the rules of the game. And then you have to play better than anyone else."*
>
> —Albert Einstein

PRINCIPLE 1 • Educate yourself in an aggressive and continuous way regarding clinical trials, study design, bias, and biostatistics.

There are no shortcuts to publishing papers. Clinical trials, in particular, have become a science, and there are plenty of pitfalls for those who are not experts in this science. Table 1.1 provides a reading list that will provide a preliminary plan for this self-education. A formal training program in medical research is also extremely valuable in learning how to write publishable papers, for example, a master of public health (MPH) or a master of science in clinical investigation (MSCI) program.

PRINCIPLE 2 • Select a clinically important problem to solve that will result in a high-impact paper.

Focus on answering questions that are important to improving patient-centered outcomes and avoid projects related to trivial correlations or meaningless interactions. Write one polished sentence that clearly defines the precise problem that your study addresses. This problem must describe the specific shape of the niche in the literature that your paper will fill—not a vague background statement, such as "There is an obesity epidemic in this country." A strong problem statement would be "It is unclear from the current medical literature whether an online diabetes prevention program would be as effective as an in-person program with regards to attendance and weight loss." Translate this problem into a testable null hypothesis to include in the Methods, for example, "The 1-year weight loss is no different between participants randomized to an in-person diabetes prevention program and those in an online program."

PRINCIPLE 3 • Invest ample time and money in planning.

"JUST DO IT" was a successful slogan for selling sneakers, but it is a poor approach to conducting medical research. You need both an experienced research team and an extensive understanding of the literature to avoid the common problems encountered in planning the study, designing the measures of outcome, creating the data collection forms, and performing the statistical analysis. An experienced and successful mentor is your best resource for understanding exactly how much time needs to be dedicated to the planning phase of a project.

TABLE 1.1 A Self-Education Reading List for Medical Researchers

Designing Clinical Research by Hulley et al. (2013)
Fundamentals of Clinical Trials by Friedman et al. (2015)
Evaluating Clinical and Public Health Interventions: A Practical Guide to Study Design and Statistics by Katz (2010)
Basic Statistics for the Health Sciences by Kuzma and Bohnenblust (2004)
How to Write a Lot: A Practical Guide to Productive Academic Writing by Silvia (2007)
Medical Uses of Statistics by Bailar and Hoaglin (2009)
Statistics with Confidence: Confidence Intervals and Statistical Guidelines by Altman et al. (2000)
How to Report Statistics in Medicine: Annotated Guidelines for Authors, Editors, and Reviewers by Lang and Secic (2006)
The Man Who Discovered Quality: How W. Edwards Deming Brought the Quality Revolution to America—The Stories of FORD, XEROX, and GM by Gabor (1992)
Epidemiology by Gordis (2013)
Essentials of Medical Statistics by Kirkwood and Sterne (2003)
Clinical and Translational Science: Principles of Human Research by Robertson and Williams (2016)
Statistical Modeling for Biomedical Researchers: A Simple Introduction to the Analysis of Complex Data by Dupont (2009)
Modern Epidemiology by Rothman et al. (2012)
Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating by Steyerberg (2010)
Encyclopedia of Biostatistics: 8-Volume Set by Armitage and Colton (2005)
Essentials of Writing Biomedical Research Papers by Zeiger (1999)
Statistical Issues in Drug Development by Senn (2008)
Experimental Design for Biologists by Glass (2014)
Experimental Design for the Life Sciences by Ruxton and Colegrave (2010)
Thinking, Fast and Slow by Kahneman (2013)

PRINCIPLE 4 • Develop a robust study design and document it completely in the Methods (and Appendix).

It takes a lot of thought to plan a study carefully. Remember, a good paper is not about the prose, it is about both the prose and the science—and for the science you need crisp thinking in the planning phase. Develop a long-term collaboration with an experienced biostatistician and create good open communication at all phases of the research. Poor methodology annoys reviewers and must be avoided at all costs.

PRINCIPLE 5 • Write a detailed study protocol to create reproducible research.

The study protocol is the written plan for your research project. A good protocol provides direction, focus, and structure. An analogy is a cake recipe that includes an appropriate level of detail with ingredients, amounts, duration, and temperature. As you conduct your study, follow this plan and document all decisions and developments. This approach allows you to monitor and describe the accuracy and appropriateness of your methods. Keep the protocol and all documents related to the study organized into files and folders labeled carefully so that anyone on your research team could retrieve and use those files years later.

For examples of modern, professional medical research protocols, see the protocols posted on the journal's website, for example, at The New England Journal of Medicine's website, these can be found under Supplementary Material for each paper.

http://www.nejm.org/toc/nejm/medical-journal

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) is "an international initiative that aims to improve the quality of clinical trial protocols by defining an evidence-based set of items to address in a protocol." The SPIRIT Statement provides protocol recommendations and a checklist.

http://www.spirit-statement.org/spirit-statement/

Another resource is Protocol Exchange, which is an open repository for sharing scientific protocols.

http://www.nature.com/protocolexchange/

PRINCIPLE 6 • Prespecify the analysis and interim monitoring plan in your protocol and register it before you start the study.

This plan must include a definition of the primary end point and only a very limited number of secondary end points. Any subgroup analysis must also be clearly predefined to avoid the appearance of a fishing expedition—or digging out post hoc subgroups. All projects, even observational studies and animal experiments, should have a detailed prespecified analysis plan. Registration systems vary by country: In the United States, clinical trials should be registered on the website http://www.ClinicalTrials.gov. Failing to register your trial properly may make it impossible to publish your paper in a high-profile journal. For more information, see

http://www.nlm.nih.gov/services/ctwhatis.html

If a trial is registered in more than one registry, it must be cross-referenced. See the International Clinical Trials Registry Platform (ICTRP):

http://www.who.int/ictrp/trial_reg/en/index.html

PRINCIPLE 7 • Build a complete, unbiased, high-quality data set.

Demonstrate that the way you gathered the data is unbiased. Measure a comprehensive set of important variables at baseline and regular intervals rather than assuming perfect compliance with the protocol, blinding, etc. These variables must include covariates, potential confounders, and measures of intermediate efficacy (to understand the mechanism and the mediation model).

PRINCIPLE 8 • Aim to keep the manuscript short, especially the Introduction and Discussion—clarity with brevity.

Plan to submit a paper that is 10% shorter in word count than the maximum limit for the target journal. This will help you avoid the inefficiency of writing and deleting superfluous text. Check the total length of the paper, the length of each section, and the number of references. Having said that, it is sometimes prudent to include slightly more tables and figures than average; reviewers appreciate tables and figures—and your first goal is to keep them happy. Use the appendix to include additional figures, tables, and detail about the methods.

PRINCIPLE 9 • Describe your methods thoroughly for reproducible research.

To show that your findings can be applied to larger populations, clearly describe your study design. Readers and reviewers will scrutinize your methods before they accept your conclusions. Be sure that you can reproduce your own analysis. Save your statistical coding/syntax in the Appendix of your paper.

PRINCIPLE 10 • Describe the rationale for the size of your sample.

Explain how and why you chose to study the specified number of patients. Discuss the implications and statistical power of your decision. Help the reader understand your logic in selecting this group of patients for the study.

PRINCIPLE 11 • Construct tables that are informative and transparent.

The tables should present an honest and complete account of all positive and negative outcomes, complications, and side effects. Provide 95% confidence intervals around important point estimates. Add extensive footnotes to every table to explain which statistical test was used for each *P* value and provide additional detail to make each table stand alone.

PRINCIPLE 12 • Create modern professional graphs/figures that illustrate the conclusions in an honest fashion.

The graphs should stand alone, with everything needed for interpretation self-contained in the figure itself (or in the figure legend). Conduct internal prereviews to test whether others can understand your graphs and then edit for clarity before submitting. For randomized clinical trials, include a carefully constructed CONSORT flow diagram showing the number of participants at each stage of the trial.

http://www.consort-statement.org/consort-statement/flow-diagram0/

PRINCIPLE 13 • Explain for the editor what is new, interesting, and useful about your results.

What do your findings contribute to the medical literature? Explain the importance of the research problem and your findings for both physicians and patients. The editors' mantra is "What's new? And why should I care?" Answer these questions head-on and in a forceful way. Define the knowledge gap and show how you filled it to advance the field sufficiently.

PRINCIPLE 14 • Elaborate further to answer the reviewers' questions: "So what?" and "Who cares?"

Emphasize the points that distinguish your study from other research. Your paper must contain sections anticipating negative reactions from skeptical reviewers. To be accepted, your subject must interest most of your target journal's readers—so tell a story.

PRINCIPLE 15 • Describe the limitations of the study.

Do not force the editors and reviewers to ask for this. Anticipate several areas that reviewers will point out as drawbacks and demonstrate that you thought long and hard about these—and that the conclusions are still valid despite these apparent weaknesses. The 'Limitations' section of the Discussion should be of this form: "Here are all the things that could be wrong with what I just told you. As you can see from our Results, we investigated each of these and found that the conclusions are still supported by the data."

PRINCIPLE 16 • Follow the guidelines and format of the target journal precisely.

Consult the information for authors and several recent issues of the target journal. Be sure that your submission meets the journal's definition of a complete manuscript. Also consider the timeliness of the subject from the perspective of the readers.