2

Drafting the manuscript: Step-by-step guidelines and exercises

CONTENTS

CHAPTER OBJECTIVES

The aims of this chapter are to:

- Consider work flow dynamics, including the all-important project kickoff meeting or teleconference (KOMT).
- Review methods of building structure and cultivating style when drafting and editing manuscripts.
- Walk through "HOW–TWA–ROA" ("How To Write A Report Of A...") exercises. How to write reports of a randomized controlled trial (RCT), observational study, health economic analysis, systematic literature review (SLR), and meta-analysis.
- Offer examples to foster writing quality (including "before/after" exercises).

2.1 WORK FLOW DYNAMICS

2.1.1 Getting started

At minimum, the following resources are strongly recommended.

- Author Guidelines (AGs), Aims & Scope, and a "template" article from the targeted peer-reviewed journal (PRJ), ideally a paper involving a topic similar to your own.
- Author disclosure forms in Word, .pdf, or other readily circulated files (Tables 2.1–2.3; selected forms available at www.icmje.org).
- Microsoft (MS) Office (or Mac-compatible version) including PowerPoint and Excel. SigmaPlot (Available at: http://sigmaplot.co.uk/products/sigmaplot/sigmaplot-details.php.

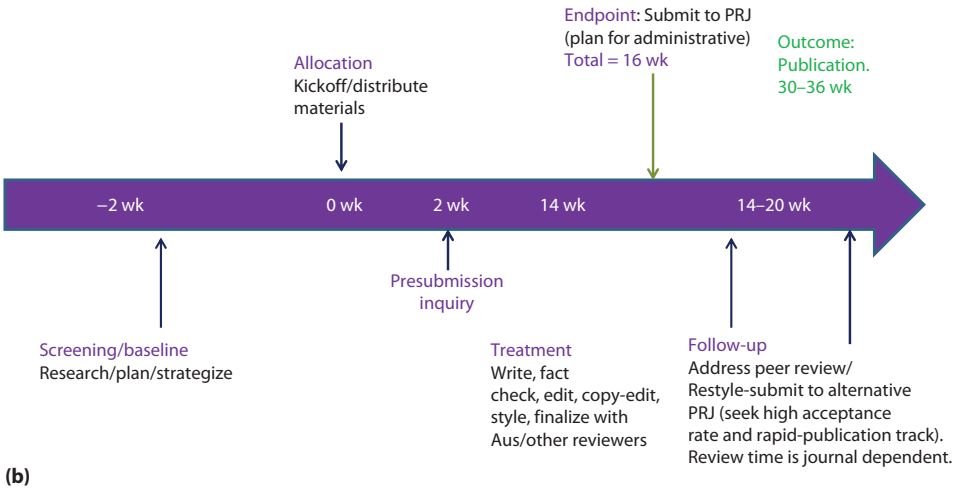
Last accessed December 31, 2017), Prism from GraphPad (Available at: https://www.graphpad.com/scientific-software/prism. Last accessed December 31, 2017), and Smartdraw (Available at: https://www.smartdraw.com. Last accessed December 31, 2017) assist in generating figures and other graphics.

- Open-source or otherwise widely available online statistical software, including R Project for Statistical Computing (Available at: https://www.r-project.org. Last accessed December 31, 2017), Vanderbilt University's P/S for power and sample size calculations (Available at: http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize. Last accessed December 31, 2017), and The Cochrane Collaboration's Review Manager (RevMan) for SLRs and meta-analyses (Available at: http://community.cochrane.org/tools/review-production-tools/revman-5. Last accessed December 31, 2017).
- Off-site/cloud-based file-backup software with automatic saving of new work.
- Antivirus software.
- *American Medical Association Manual of Style*, 10th ed. (or later editions as appropriate).
- Electronic medical and generic grammar-, spell-, and consistency-checking software, including PerfectIt Pro (www.intelligentediting.com) and Grammarly® (https://www.grammarly.com/).*
- A general reference text, such as *Harrison's Internal Medicine* or *Goodman & Gilman's The Pharmacological Basis for Therapeutics*. Find prescribing information online, and cite the URLs where you accessed it (and the date accessed). Throughout the publication process, make sure that these URLs remain active and accurate.
- A textbook on biostatistics. (I recommend, and cite throughout Chapter 3, Riffenburgh's *Statistics in Medicine*, and Kirkwood and Sterne's *Essential Medical Statistics*.[1,2])
- Any other, authoritative specialty reference texts as needed to acquaint you with the disease state being discussed, including, for instance, *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Use these for "deep background." Do not overuse textbooks and/or secondarily cite references in their chapter bibliographies.
- Reference search, retrieval, and management software, such as Endnote or Reference Manager (Available at: http://endnote.com. Last accessed December 31, 2017). Mendeley software (Available at: https://www.mendeley.com. Last accessed December 31, 2017), is highly useful for organizing references. Once you have obtained .pdfs of articles, you can upload them to Mendeley, which not only "reads" but organizes them into searchable content "bits." For instance, if you cannot recall which paper evaluated effects of cetirizine on frequency of sneezing (sternutation), you can type "cetirizine," "sneezing (sternutation)" or, if the database contains mainly references on cetirizine, type simply "sneezing/sternutation." Type the key term into a Mendeley window and the software will open the appropriate reference exactly at the word searched. In a word, "brilliant!"
- A subscription or other access to a high-quality nonspecialty medical journal (e.g., *Ann Intern Med*, *BMJ*, *JAMA*, *Lancet*, *N Engl J Med, The Cochrane Database of Systematic Reviews [CDSR]*) and/or "gray literature" (e.g., Medscape [https://www.medscape.com/], epocrates [http://www.epocrates.com/], UpToDate [https://www.uptodate.com/home]), preferably if they update your e-mailbox to notify you of new and noteworthy articles.
- A thirst and knack for Internet searches, especially via Google Scholar, government, regulatory, and payer websites with data on disease statistics, pharmacovigilance, ongoing clinical and observational trials (e.g., ClinicalTrials.gov and other registries), and approvals and other activities related to investigational and marketed products, and costs.
- Industriousness, self-reliance, attention to detail, a "can-do" attitude, and an abiding respect for your colleagues and their contributions.

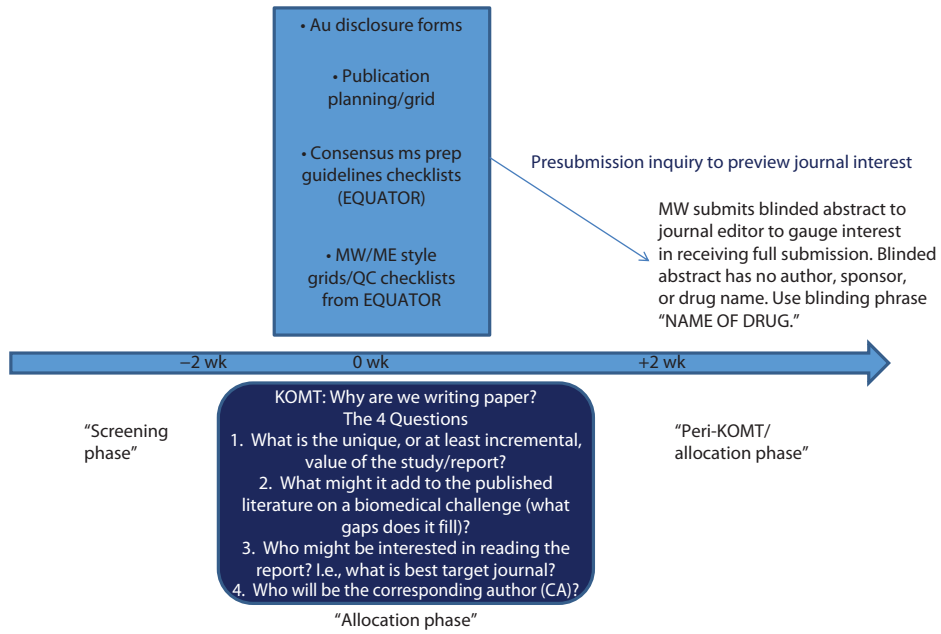
2.1.1.2 MANAGING THE FLOW OF WORK

The term "medical writer" is often somewhat of a misnomer; we are expected not only to draft the manuscript but also "drive" the overall project, from preparing for and running the all-important KOMT to addressing final peer review (Figure 2.1). At the KOMT, distribute forms (Tables 2.1–2.3),

* There are too many spell checkers to endorse a single one. They include Dorland's (https://www.dorlandsonline.com/dorland/home); Medispell (http://medispell.com/); and Spellex (http://www.spellex.com/).



(b)



(c)

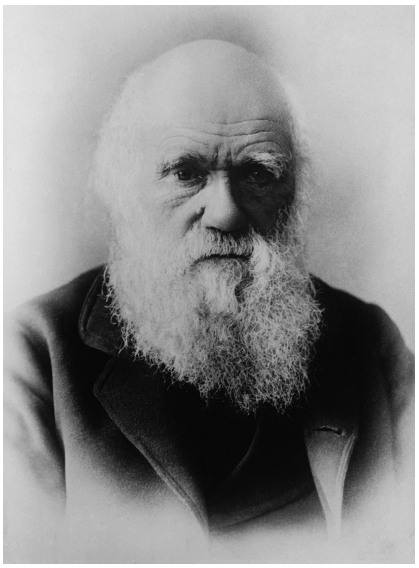
Figure 2.1 (Continued) Organizing, planning, and delivering a publication for a peer-reviewed journal (PRJ). **(b, c)** The KOMT is a pivotal event that allows the authors (Aus), overall research/publication team, medical writer (MW), project manager (PM), and medical editor (ME) to determine the all-important issues of (1) who will serve as the corresponding author (CA)? and (2) which peer-reviewed journal would be the best fit for the research and report (based on publication planning and gap analysis; See Table 2.4). The KOMT answers the broad questions "Why?" (Are we here? Did we conduct the study? Are we reporting the findings?) and "How?" (Will we organize and divide labors to submit the manuscript to a suitable PRJ?) Circulate disclosure forms (Tables 2.1–2.3) to facilitate PRJ manuscript submission, which can be a labor-intensive process. Note that the disclosure form is distributed prospectively but can be completed only retrospectively to ensure that all four International Committee of Medical Journal Editors' criteria for authorship have been met. To become most conversant with key issues addressed by the research and report—and how to engage the PRJ's readers—schedule 1:1 time with the CA.

Abbreviations: EQUATOR, Enhancing the Quality and Transparency of Health Research; QC, quality control.

including Gantt charts, to remind participants of their roles and facilitate submission of the final manuscript to the PRJ. Commercial web portals (e.g., www.pubshub.com) offer details about key parameters of thousands of journals (e.g., impact factor, time from submission to publication). Another, admittedly "old-school," approach that I often adopt is to target the "statistical mode." In other words, examine the bibliography of your outline or manuscript. Which journal is cited most frequently? Consider submitting your paper there.

2.2 STRUCTURE AND STYLE

2.2.1 Finding your voice: From Charles Darwin to Chris Matthews



Statements in your Introduction, Results, Discussion, and Conclusions should not only report data but culminate a thoughtful, fair-balanced consideration of the findings that enables your essay to draw meaningful inferences to either improve, or otherwise inform, readers' practices. (As stated in Chapter 1, "Appraise, then apprise; aggregate, then advocate.")

To capture the essence of writing that is not only evidence based but also engaging and memorable, I refer to two solid minds separated by more than a century: naturalist Charles Darwin, who was an intellectual titan but not eminently accessible to us in modern times, and political pundit Chris Matthews who is more so. To represent the evidence-based aspect, we have the introduction to the *Sterling Signature* (2008, 2011) edition of *On the Origin of Species*. David Quammen states:

> Seldom in English prose has such a dangerous, disruptive, consequential book been so modest and affable in tone. That's because its author was himself a modest and affable man—shy in demeanor though confident of his ideas—who meant to persuade, not to declaim or intimidate. [His prose] might sound like a gentle uncle, clearing his throat, politely, about to share a few curious observations and musings over tea.

As researchers and communicators, we are almost always seeking to persuade readers of a particular point of view. However, we should do so in a Darwinian modest, calibrated, and evidence-based, if not "affable," way. Slightly rewording a famous quotation of US industrialist Henry J. Kaiser (founder of Kaiser-Permanente), "When your data speak for themselves, don't interrupt." For instance, if a therapy reduces hospital LOS from 10 to 7 days, it is better to report the 3-day (rather than a 30%) reduction in LOS. The 3-day reduction is more likely to have subject-matter "hooks" in terms of direct health-care costs.

While striving for an ideal of tempered, evidence-based expression, we also need to engage our readers by being original and, if possible, memorable. The reach and salience of our work are driven largely by its likelihood of being cited by others. To convey the original, engaging, and enduring qualities of desirable medical writing, we turn to Chris Matthews. This former

Table 2.4 Example of a publication/journal options grid ("long list"): Brief report manuscript on adherence to an oral antidiabetic drug

Journal	Impact factor	Circulation	Acceptance %	$T_{Sub \rightarrow Pub}$,* wk	Brief reports? (data provided if yes)?
Acta Diabetologica.	3.34	1,000 (print) 118,247 (downloads)	25	5–12	Max words text = 1,000 No abstract Max. refs = 5 Max. tables/figures = 2
Clinical Endocrinology.	3.327	191 (print)	43	14	No brief reports.
Diabetes.	8.684	1,600 (print)	18	12–26	Max. words text = 2,000 Max. refs = 25 Max. tables/figures = 4
Diabetes and Vascular Disease Research.	3.417	923 (print)	25	7–10	Max. words text = 1,500 Max. refs = 10–12 Max. tables/figures = 1
Diabetes Care.	11.857	6,600 (print)	13	9–24	No brief communications.
Diabetes Research and Clinical Practice.	3.639	23 (print)	39	7–17	Max. words text = 1,000 (w/summary ≤50 words)
Diabetic Medicine.	3.054	854 (print) 16,047 (monthly downloads)	67	18	Max. words text = 1,500 (w/ structured abstract) Max. refs = 20 Max. tables/figures = 2
Diabetes, Obesity and Metabolism.	6.715	11,000 (print)	20	4–13	Max. words = 1,200 (w/180-word unstructured abstract) Max. refs = 12 Max. tables/figures = 2
Endocrine Practice.	2.347	4,400 (print)	35	13–16	Commentaries. Max. words text = 1,500 Max. refs = 15 Max. tables/figures = 1
Endocrine Reviews.	15.745	763 (print)	30	12–24	Commentaries Max. words text = 1,000 Max. refs = 8 0 tables/figures
Endocrinology.	4.286	1,398 (print)	30	24–28	Max. words text = 2,400

(*Continued*)

Table 2.4 (Continued) Example of a publication/journal options grid ("long list"): Brief report manuscript on adherence to an oral antidiabetic drug

Journal	Impact factor	Circulation	Acceptance %	$T_{Sub \rightarrow Pub}$,* wk	Brief reports (data provided if yes)?
European Journal of Endocrinology.	4.101	800 (print)	25	16–18	No brief reports.
International Journal of Endocrinology.	2.510	N/A	25	15	No brief reports.
Journal of Clinical Endocrinology and Metabolism.	5.455	6,925 (print)	25	20	Commentaries Max. words text = 1,000 Max. refs = 8 0 tables/figures
Journal of Diabetes and its Complications.	2.056	9,199 (average monthly visits)	40	4–18	Max. words text = 1,000 (w/summary ≤50 words). Max. refs = 20.
Journal of Endocrinology.	4.706	850 (print)	20	13	No brief reports.
Metabolism.	5.777	38 (print) 17,225 (average monthly visits)	39	5–16	Max. words text = 1,500 (w/structured abstract). Max. refs = 20. Max. tables/figures = 2.
Pancreas.	2.967	12,815 (average monthly visits)	50	9–25	Yes, but no posted max. words (except summary of ≤50 words).
Primary Care Diabetes.	1.381	2,757 (average monthly visits) 850 (print) 40,000 (average monthly users worldwide)	43	11–41	Max. words text = 1,000 Max. refs = 20

Source: Data available from PubsHub, An ICON plc Company. Available by subscription at: https://journalsandcongresses.pubshub.com. Last accessed February 9, 2018.

Note: "Author Team: Journal aims/scope, free recent on-line content, and editorial contact information are provided under separate cover."

Abbreviation: NA, not available.

*$T_{Sub \rightarrow Pub}$, time from manuscript submission to publication or posting ahead of print, including under assumptions of expedited publication.

speechwriter for President Jimmy Carter and chief of staff to Speaker of the House Thomas "Tip" O'Neill closes his MSNBC telecast "Hardball" with a segment that challenges his guests to "Tell Me Something I Don't [Already] Know."

Similarly, by evaluating data and arriving at your own unique and original synthesis—in short, by telling your readers "something they don't know"—you not only engage their interest but also enliven and increase the intellectual currency of your work.

Review literature critically, fashion your own creative synthesis, and then target it appropriately to your likely readers. I find "raw" statistics—millions of patients with a condition; billions of dollars spent on its management—eminently forgettable compared to relationships, trends, and rankings.

2.2.2 Examples of both evidence-based and memorable prose

Take the following statement summarizing clinical data:

> Diaphragmatic bleeding frequency was 6% in the spastex, compared to 12% in the treatment-as-usual (TAU) arm (p = 0.047) of patients with involuntary noisome hiccup syndrome (INHS).*

Is this the most impactful statement for a clinician (e.g., gastroenterologist) caring for many patients with INHS? It would be completely acceptable in the Results section of a study report but perhaps not as consequential in a summary of a prior study presented in an Introduction or Discussion. From these data, we can compute the *risk difference* or *absolute risk reduction* and then easily calculate the number of patients that a clinician would need to treat to benefit one by preventing a single bleeding episode (NNT_B). NNT_B is calculated as the inverse of the difference in absolute risk between the two treatment arms, in this case:

$$NNT_B = \frac{1}{0.12 - 0.06} = \mathbf{16.7}$$

A clinician would need to treat 17 patients with spastex (vs. TAU) to prevent a single episode of diaphragmatic bleeding.

What about incidence rate and prevalence? It is often sufficiently illuminating to report each—as numbers of new cases per 100,000 person-years for the former and as a percentage (not a number of patients) for the latter—in your Introduction. By combining them, you can reach an original creative synthesis:

> Influenza virus has a high incidence and low prevalence, which are consistent with an acute but curable and overall effectively managed condition. Such disorders are not compatible with a crossover or other multiphase study, because many patients will no longer harbor the virus after the first phase. Type 2 diabetes mellitus has a lower incidence and higher prevalence, which are consistent with a chronic, incurable, and suboptimally managed condition. Such disorders are compatible with a crossover or other multiphase study because subjects will continue to have diabetes for a prolonged period (*ad vitam*).

Calculating the attributable proportion of a risk factor in exposed (vs. unexposed) individuals is another way to offer a more meaningfully descriptive and memorable "snapshot" of a cohort or other population. For instance, let us say that we know the following data, under the assumption that highly spiced meals can cause INHS:

> The incidence of INHS was 7/100,000 among patients in the INHS-IV-COHORT study who consumed highly spiced foods at least once weekly, compared to 3/100,000 in those who consumed spicy diets less frequently.

$$\text{Attributable Proportion} = \frac{\text{Incidence}_{\text{exposed}} - \text{Incidence}_{\text{unexposed}}}{\text{Incidence}_{\text{exposed}}}$$

$$\text{Attributable Proportion} = 100 \times \frac{7 - 3}{7} = \mathbf{57.1}\%$$

* Also termed "Smelly Hicupping Disorder," this clinical syndrome has been completely fabricated by me for teaching purposes (and a little levity).

This value can also be computed from the rate ratio (RR; rate in exposed vs. unexposed) as:

$$\text{Attributable Proportion} = \frac{RR - 1}{RR}$$

In the entire INHS-IV-COHORT, approximately 57% of all incident episodes of INHS would be attributable to consuming highly spiced foods (i.e., attributable risk). Approximately 43% of individuals in this cohort would experience episodes of INHS without consuming such foods (i.e., inherent risk). Attributable proportion can also be computed if the incidence and risk or rate ratio are known. Like other methods, this form of analysis has certain limitations.

Consider the following statistics about suicide in the United States. Which do you find more impactful (and why)?

- Each year, 21,334 Americans commit suicide using firearms.
- Suicide is the leading cause of firearm deaths in the United States; each year more than 60% of Americans who die by gunshots are committing suicide.

For most readers, the second sentence has a far more affecting, tangible (almost "moral") dimension, whereas the first is eminently forgettable. (However, some public policy scientists may be more interested in the first sentence; make sure to research your likely readers, as described below.) Another example follows.

- Each year, 44,193 Americans commit suicide.
- Suicide is the 10th-ranked cause of death in Americans (n = 44,193)

Your choice of words (especially active, memorable verbs) and original synthesis of data can make the difference between memorable and forgettable facts. I recently wrote:

> Patients with schizophrenia shoulder a disproportionate burden of suicide. The US prevalence of schizophrenia is only about 1.0% compared to 6.7% for major depressive disorder and more than 10% for anxiety disorders. Yet about 33% of Americans with schizophrenia attempt suicide and 10% ultimately take their own lives. (Centers for Disease Control and Prevention: Available at: https://www.cdc.gov/mentalhealth/basics/burden.htm. Last accessed December 31, 2017.)

Describing the cellular and molecular microenvironment of non–small-cell lung cancer, I recently referred to the fact that the carcinoma recruits fibroblasts to "cement a nearly impervious bulwark that protects against surveillance by host tumor-infiltrating immune cells."

When seeking to introduce memorable facts to engage your readers, be mindful of their clinical and other points of view and likely interests. Though largely "intuitive," this guidance is often ignored. For example, the following epidemiologic data might be of interest to a family physician, who treats patients from infancy through advanced age:

- Suicide is the 3rd-ranked cause of death among persons aged 10 to 14 years, 2nd in those aged 15 to 34, 4th in those aged 35 to 44, 5th in those aged 45 to 54, 8th in those aged 55 to 64, and 17th in those aged ≥65 years.
- In the past decade, the incidence of suicide among Americans aged 35 to 64 increased by nearly one-third. The sharpest increases were observed in men in their 50s and women in their early 60s.

A pediatrician might be especially interested to learn the following:

> Not only is suicide the 2nd- to 3rd-ranked cause of death in US adolescents and young adults (behind only accidents and homicides), but some studies estimate that one-third to one-half of community-dwelling young people also inflict wounds on themselves without suicidal intent.

Psychiatrists may be most interested in knowing that:

- More than 90% of suicide decedents had a diagnosable psychiatric condition (especially major depressive disorder or treatment-resistant depression) at death.
- Veterans of military combat may be more likely than age-matched civilians to commit suicide, because veterans meet criteria of Joiner's Interpersonal Theory, including a perceived low sense of "belongingness" and burdensomeness to others, as well as an ability to endure the discomfort that might be required in killing oneself.

Almost all readers would be interested in learning that:

- Because of medical surveillance bias, suicide is a problem of largely untold dimensions. Many patients, especially members of certain ethnoracial minority groups and veterans of military combat, experience stigma about mental illness and hence do not report or seek medical attention for suicidality.

Readers of a health economics and outcomes research (HEOR) journal might be more inclined to read the following, from former US National Institute of Mental Health (NIMH) director Thomas Insell (Available at: https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2011/the-global-cost-of-mental-illness.shtml. Last accessed December 31, 2017).

> The Agency for Healthcare Research and Quality cites a cost of $57.5 billion (2006) for mental health care in the (United States), equivalent to the cost of cancer care. But unlike cancer, much of the economic burden of mental illness is not the cost of care, but the loss of income [because of] unemployment, expenses for social supports, and a range of indirect costs due to a chronic disability that begins early in life.

Some HEOR readers are payers and chiefly interested in direct health-care costs. Research your targeted PRJ's websites and online publication-planning sites (e.g., www.pubshub.com) to understand the PRJ's circulation and numbers of different types of readers, including physicians (providers), patients, payers, and policymakers. (The "4 Ps" of reader perspectives.)

As a digression related to memorable introductory statistics, I remember once driving with my father along one of the many highways and byways of New Jersey. We observed that roadside sound barriers were being erected, and my dad stated that the project was costing New Jersey taxpayers "$1 million per mile."

Such "neat and tidy" relationships in Introductions (and Discussions) are so memorable that they linger with readers long after being read. Examples in medicine that I have read over the years include the facts that:

- On a population (not necessarily per-patient) basis, there is a 20% reduction in the annual incidence of ischemic cardiovascular disease for every 1-mmol/L decline in low-density lipoprotein cholesterol (LDL-C) on treatment with HMG-CoA reductase inhibitors (i.e., statins).
- Risks of percutaneous ("needle-stick") viral transmission are 30% for hepatitis B, 3% for hepatitis C, and 0.3% for HIV. [These relationships were true when I read the statement but have now been updated.]
- For every 30-day gap in antipsychotic medication adherence, there is a 10-fold increase in the incidence of relapse in patients with newly diagnosed schizophrenia.

Typically, try to exclude from manuscripts statistics such as "every 30 seconds an American experiences a myocardial infarction." Such statements often originate from patient-advocacy groups and shed more heat (emotion) than light (intellect) on a problem. They can, however, confer "gravitas" and command attention. During a recent presentation to a life sciences company (LSC), including several representatives of Medical Affairs, the room grew quieter and the participants more attentive after I announced that, "During my 1-hour talk, 5 Americans will die by suicide [1 every 13 minutes; CDC data]."

2.3 STRUCTURING THE OUTLINE

2.3.1 "Scaffolding": The Gutkin 4 × 4 cogent manuscript structure outline

Using references identified by PubMed/MEDLINE/EMBASE/CDSR and other literature searches, develop a detailed and referenced outline. The "4 × 4" structure refers to four headings (Introduction, Methods, Results, Discussion) with four subheadings each (Table 2.5). If a congress abstract is available, it should be introduced as the Abstract segment of the outline. If figures or tables from an existing congress poster are available, introduce them in the outline (after ensuring with the statistician that they are final and "clean").

Table 2.6 summarizes key considerations when preparing the report of a randomized controlled trial (RCT).

2.3.1.1 INTRODUCTION

The chief aim of the Introduction is to develop the scientific rationale for the study, its objectives, and, in some cases, hypotheses and outcome measures. The Introduction builds to a thesis statement, which sets forth issues or problems that the study and its report uniquely (or incrementally, compared to prior published literature) address.

One formulation or idea flow for the Introduction runs along the lines of typical review articles in the *New England Journal of Medicine*, which cover, in sequence (and often using one paragraph each):

- Disease state definitions and clinical or humanistic dimensions.
- Public health dimensions (incidence, mortality, prevalence, and costs).
- Normal physiology, homeostasis, pathophysiology, and natural history.
- Etiology, risk factors (and protective factors, if applicable), and genetics.
- Consensus diagnostic and treatment embodied in clinical practice guidelines (CPGs).

Readers of specialty journals are well acquainted with such introductory facts. For these readers, craft an introduction that quickly builds to the rationale and objectives of the study and its report.

Aims* of Introductions should be to delineate the dimensions of a disease state; its contemporary consensus diagnosis and management; and any potential ongoing issues or clinical challenges. The Introduction should culminate in clear objectives that guide the rest of the manuscript.

In my practice, I have received draft Introductions that were:

- Vague, "diffuse," and unfocused: did not build to a study rationale and objectives.
- Tangential: did not use key words and themes to link paragraphs and organize the essay.
- Overly argumentative (not gently persuasive in the Darwinian spirit): foretold the findings or a controversy reviewed in the Discussion, in a "defensive" or "strenuous" manner that included value judgments, superlatives, or other non–evidence-based statements.
- Innocuous: not necessarily bad but bombastic and inconsequential, never "hooking" potential readers with ongoing challenges related to their practices in an RCT or failing to characterize the "situation on the ground" in a regional pharmacoepidemiology (real-world evidence [RWE]) paper.

Table 2.7 defines key epidemiologic terms frequently cited in Introductions, including incidence proportion, attack rate, secondary attack rate, incidence rate, point prevalence, and period prevalence.[3] Prevalences should be reported as proportions (%) of a population, not as numbers of people with a disease, as is so often encountered even in published articles. Clarify whether you mean point or lifetime prevalence.

* In medical writing, the word "aim" is a noun, not a verb. The "aim" of the study corresponds to its objectives, but researchers do not "aim" to determine one thing or another.

Table 2.5 Gutkin 4 × 4 (4 major headings × 4 subheadings in each) cogent manuscript structure outline[a]

Each Roman numeral below becomes a heading (**H**), and each capital letter becomes one paragraph (¶) or more. Each topic sentence (**TS**) provides "horizontal logic." The reader of your outline or essay should be able to progress from one topic sentence to the next and appreciate the arc of your argument.

I. Introduction (250–500 words) H
- **A.** Disease state, definitions, and basic epidemiology **1–2¶**, each with a **TS**
- **B.** Pathophysiology/etiology/natural history/genetics **1–3¶**, each with a **TS**
- **C.** Consensus diagnostic and management guidelines **1¶** with a **TS**
- **D. Thesis statement**: clinical problem/educational need and unique or incremental value in addressing it study rationale and objectives 1¶/**TS**

II. Methods (250–750 words) H
- **A.** Study design/setting/participants/ethics **1–3¶**, each with a **TS**
- **B.** Interventions **1¶** with a **TS**
- **C.** Assessments/outcome measures **1–3¶**, each with a **TS**
- **D.** Statistical methods **1–4¶,** each with a **TS**

III. Results (250–750 words) H
- **A.** Patient disposition **1¶** with a **TS**
- **B.** Baseline characteristics **1¶** with a **TS**
- **C.** Efficacy outcome measures **1–2¶,** each with a **TS**
- **D.** Tolerability/Safety **1¶–2¶**, each with **a TS**

IV. Discussion (500–1,000 words) H
- **A.** Key findings: $p < 0.05$ and >0.05; expected and unexpected; meeting or not meeting endpoints/MCIDs (and why) **1–3¶,** each with a **TS**
- **B.** Relationship to published literature (narrowly construed, as it relates to study design and findings), as well as potential clinical implications, and alternative explanations, of the data, **1–3¶**, each with a **TS**
- **C.** Potential study strengths and limitations **1–2¶,** each with a **TS**
- **D.** Conclusions: clinical implications and needs for future research **1¶**, with a **TS**

Abbreviation: MCID, minimum clinically important difference.

[a] Consult journal author guidelines and online content. Refer to checklists in Chapter 4 to adapt this basic structure to other forms of study reports (e.g., Consolidated Standards of Reporting Trials [CONSORT] for randomized controlled trials and Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] for observational studies). Collaborate with the corresponding author to formulate the outline. Circulate it to all potential authors, request their feedback, and record/date the input (including deletions). Outlines should be referenced and include newly generated figures and tables or "table shells."

In your Introduction, strive to include (and cite) CPGs, which help to orient readers concerning diagnosis and management of the disease. When doing so, find something specific and not uniformly applicable, trivial, or innocuous. An example of the former is "phosphodiesterase type 5 inhibitors constitute first-line therapies for erectile dysfunction, irrespective of its etiology or concomitant chronic conditions." This statement is consequential to clinical decision making. Conversely an innocuous introductory sentence might include a banality ("throwaway") such as "Objectives of therapy for erectile dysfunction are to enhance quality of life while minimizing adverse effects." This is true of virtually any disease's management!

Leave readers with concepts that they did not learn in medical school or early training. For example, a statement such as "Risperidone is an atypical antipsychotic that functions as a central serotonin ($5\text{-}HT_{2A}$) antagonist at lower doses and dopamine (D_2) receptor antagonist at higher doses" is more valuable to most practitioners than one such as "Schizophrenia results from excess brain dopamine."

Table 2.6 Considerations when drafting a randomized controlled trial report

Disclosures	Introduction	Methods	Statistical issues and methods	Results	Strengths	Limitations
Registration. Clinicaltrials.gov (NCT ID #).	**Historical perspective:** the "saga" of the disease; management advances over the years; and limitations/ ongoing challenges of current modalities.	**Study setting** (e.g., number and locations of centers). **Eligibility criteria. Ethics (IRB/ICD). Study schema/timeline (**Figure 2.5**).**	Attrition (MAR MCAR) and imputation method (e.g., LOCF).	**Baseline characteristics** (Table 2.8). Segregate categorical and continuous variables. Define ITT, PP, other populations.	Random allocation, blinding, and placebo control largely preclude bias or confounding.	Ecological validity/ generalizability to real-world treatment settings.
Previous presentation (all manuscripts).	**If nonspecialty journal:** Allocate 2–4 paragraphs for disease state, then build to problem/objectives (250–750 words).	**Efficacy endpoints** (primary, secondary, tertiary, exploratory). **Prespecified subgroup analyses. Safety/tolerability endpoints.**	Type 1 or 2 Error Multiple comparisons (Bonferroni).	**Efficacy endpoints**: reported in same sequence as "motivated" in Methods: primary, secondary, tertiary, exploratory. **Text: report p values, 95% CIs, and test that generated each p value**.	High quality of patient-level data.	Highly selected patient population (tolerability, adherence, and overall treatment response may be overestimated).
Funding statement and author financial disclosures/ conflicts of interests (all manuscripts).	**If specialty journal:** Build swiftly to problem/ objectives (100–200 words), e.g., 1 sentence on disease state; 1–2 on phase 1–3 development; last 1–2 on problem/issues and objectives.	**Assessments** (can use summary table for assessment schedule by visit) and their biometric/ psychometric properties and implications (e.g., MCID for PROs).	Parametric or nonparametric analyses: plot data, test for skew (Microsoft Excel, see Chapter 4); use Shapiro–Wilk test to determine if distribution is normal or non-normal.	**Efficacy graphics**: tables, figures (e.g., pie, bar, linear regression, forest, Kaplan–Meier, box-whisker).	Guidance on endpoints (FDA).	Protocol-based (inflexible) treatment regimens.
Author contributions (ICMJE; all manuscripts).	• **What is known?** • **What is the issue/ problem/gap?** • **How does this study/report address the issue/fill the gap? What does it add to existing knowledge?**	**Populations** (total, intent-to-treat, per-protocol, safety).	ANCOVA often does not control for disease severity or age.	**Safety/tolerability endpoints**: See Table 2.9 for terminology. **Safety**: narrative text and shift tables. **Tolerability**: frequency table (MedDRA PT/SOC; Table 2.10).		RCTs are typically not powered to determine intertreatment differences in infrequent adverse events and of insufficient duration to determine differences in safety parameters.

Abbreviations: ANCOVA, analysis of covariance; FDA, Food and Drug Administration; ICD, informed consent document; ICMJE, International Committee of Medical Journal Editors; IRB, institutional review board; ITT, intent-to-treat; LOCF, last observation carried forward; MAR, missing at random; MCAR, missing completely at random; MCID, minimum clinically important difference; MedDRA, Medical Dictionary of Regulatory Activities (www.meddra.org); PP, per-protocol; PRO: patient-reported outcome; PT, preferred term; SOC, system organ class.

Table 2.7 Measures of morbidity that are often used—and misused—in introductions

Measure	Numerator	Denominator
Incidence proportion (or attack rate or risk).	Number of new cases of disease during specified time interval.	Number in population at start of interval.
Secondary attack rate.	Number of new cases among contacts.	Total number of contacts.
Incidence rate (or person-time rate).	Number of new cases of disease during a specified time interval.	Summed person-years of observation or average population during time interval.
Point prevalence.	Number of current cases (new and pre-existing) at a specified point in time.	Number in population at the same specified point in time.
Period prevalence.	Number of current cases (new and pre-existing) over a specified period of time.	Number in the average or mid-interval population.

Source: Centers for Disease Control and Prevention. In: *Principles of Epidemiology in Public Health Practice*: *An Introduction to Applied Epidemiology and Biostatistics*. 3rd ed. Atlanta, GA: CDC, 2016. Available at: http://cdc.gov/ophss/csels/dsepd/ss1978/lesson3/section2.html. Last accessed December 31, 2017.[3]

2.3.1.2 METHODS

As mentioned in Chapter 1, the Methods section is the linchpin of "internal fidelity" and represents the "Rosetta Stone of Clarity" for the entire manuscript. The purpose of the Methods section is to enable the reader to understand (and, ideally, replicate) your investigation, with reference to the justifications for, and meanings of, the pivotal efficacy, safety, tolerability, patient-reported outcome (PRO), and/or pharmacoeconomic endpoints. The Methods section delineates the overall logic of the paper and helps the reader or other reviewer (e.g., PRJ referee) to follow it.

In the pre–GPS era, Methods sections were identified as "road maps," in that they elucidated study assessments and outcomes in sufficient detail for the reader to understand if: (1) an increase or decrease signifies an improvement or worsening in function; (2) there are normative values associated with no disease or other impairment; and (3) there are any threshold values that represent minimum clinically important differences (MCIDs).

2.3.1.2.1 Internal fidelity: "Rule of Chekhov's Gun"

> If you say in the first chapter that there is a rifle hanging on the wall, in the second or third chapter it absolutely must go off. If it's not going to be fired, it shouldn't be hanging there.
>
> *Anton Chekhov*

Reporting of scientific findings must be internally consistent (i.e., have "internal fidelity"). If the Methods section mentions a study objective or endpoint, the Results section must include a value for that outcome variable irrespective of whether it is statistically or clinically significant. Conversely, the Results section should not present any value that was not mentioned or "motivated" in the Methods. A cogent Methods section also determines the sequence in which data are presented in the Results.

Statistical methods are considered in detail within Chapter 3 of this textbook. In my practice, I have found that the names of many statistical

tests are "buried" in footnotes or other obscure sections of a CSR or raw statistical output. Only after reviewing these data might you learn the key covariates in an analysis of covariance (ANCOVA) or that, say, Fisher's Exact Test, Student's *t*-test, or Mann–Whitney's U test was performed. Include such data not only in the Methods text but also in footnotes to tables or legends to figures.

2.3.1.3 RESULTS

Report the findings concisely, and in the same sequence as presented ("motivated") within the Methods section (Rule of Chekhov's Gun). One sequence of data flow for RCTs runs as follows: (1) patient disposition (including a Consolidated Standards for Reporting Trials (CONSORT) patient-disposition flow diagram if possible), (2) baseline characteristics (example in Table 2.8), (3) efficacy, (4) tolerability (Tables 2.9 and 2.10), and (5) safety.

Because of the modular organization of contemporary scientific papers (and divergent styles of readers in apprehending information) tables and figures must be self-contained units of meaning (stand-alones). Some readers access information from papers largely by jumping from one table or figure to the next. For these readers, abbreviations and statistical methods used to generate p values (and other statistical details such as covariates in an ANCOVA model) need to be defined within figure legends and table titles or footnotes, as well as in the Methods text. For each endpoint identified in the Methods, a p value should be presented in narrative text, table, or figure, regardless of whether the test result is statistically significant ($p < 0.05$).

Tolerability and safety are often confused but are not synonymous. Tolerability typically includes adverse events (AEs) or treatment-emergent adverse events (TEAEs), which first appear, or are present at baseline and worsen, after treatment initiation. Adverse events should be elicited via open-ended questioning by the investigator or other appropriately trained trial personnel at each study visit. Definitions of different tolerability terms are presented in Table 2.9.[4]

Avoid "judgmental," non–evidence-based modifiers that might make the modest and affable Darwin blush. For instance, the Food and Drug Administration (FDA) has no standard for the term "well tolerated"; it is what I term an "unanchored judgmental" adverb. Rather than use such a loose modifier, convey incidences (usually in descending order of frequency) of the most salient AEs, often in a table.

Safety includes serious adverse events (SAEs). Chapter 4 provides tables to guide you in reporting harms in RCTs.[5] An SAE report in a manuscript should detail how the SAE presented, actions taken, outcomes of these interventions, and whether investigators judged the SAE to be related to treatment. This last inference is based largely on temporal patterns of the patient's taking the medication and then experiencing the SAE, or discontinuing the regimen and then not experiencing it.

Other key safety parameters include mean changes from baseline to end of treatment or study in laboratory parameters (e.g., chemistries, hematology) as well as any outliers, such as numbers (%) of patients with values ≥5 times the upper limit of normal (≥5 × ULN). Individual or group changes (often in so-called "shift tables") in 12-lead electrocardiography (ECG) and vital signs (pulse rate, blood pressure, respiration rate, body temperature) are also subsumed under the rubric of safety.

2.3.1.4 DISCUSSION

A thoughtful, fair-balanced, and well-organized Discussion helps the reader to understand the findings and their ramifications. Such a Discussion should meet the following objectives.

- Recap key findings and probe their implications and relationships to the hypotheses and endpoints **[1–3 paragraphs]**. What is the single statement that will convey the most lasting meaning? Were study objectives or outcome measures met? If not, why not? How do the findings address a scientific problem or controversy and advance the field or readers' practices? Do they confirm or violate hypotheses (e.g., reject the null hypothesis or accept the alternative hypothesis)? Are findings clinically as well as statistically significant? (Do associated effects meet or exceed MCIDs?) If prespecified subgroup analyses were conducted, did any patient segments derive special benefits, or experience more adverse consequences, from treatment?
- Compare the data to results from similarly designed and other recent (past 1–5 years) and pivotal studies using the same agent (or related agents from the same pharmacologic class)

Table 2.8 Example of a baseline characteristics table for a randomized controlled trial. Baseline characteristics of subjects with involuntary noisome hiccup syndrome (INHS) in the NO-MO-BURP-PLS! Trial[a]

Characteristic	Spastex + placebo group (n = 848)	TAU[b] + placebo group (n = 459)	Total (N = 1,307)
Mean (SD) age, yr	55.3 (11.2)	57.2 (9.3)	56.0 (10.6)
Mean (SD) body mass index, kg/m²	28.0 (4.3)	29.4 (4.7)	28.5 (4.5)
Mean (SD) daily hiccup frequency	8.6 (0.6)	7.6 (1.6)	8.1 (1.4)
Mean (SD) INHS severity score[c]	14.9 (6.3)	13.1 (6.4)	14.3 (6.3)
With gastric pH, n (%)			
<7.0	820 (98.7)	186 (41.1)	1,006 (78.3)
7.0–10.0	9 (1.1)	209 (46.1)	218 (17.0)
>10.0	2 (0.2)	58 (12.8)	60 (4.7)
Age (yr), n (%)[b,d]			
<50	274 (32.3)	91 (19.8)	365 (27.9)
50–64	402 (47.5)	274 (59.7)	676 (51.7)
65–74	146 (17.2)	86 (18.7)	232 (17.8)
≥75	26 (3.1)	8 (1.7)	34 (2.6)
Daily treatments, n (%)			
Placebo	250 (29.5)	146 (31.8)	396 (30.3)
Spastex 2.5 mg	79 (9.3)	117 (25.5)	196 (15.0)
Spastex 5 mg	519 (61.2)	196 (42.7)	715 (54.7)
Ethnoracial identity, n (%)[b,d]			
Caucasian	728 (85.8)	367 (80.0)	1,095 (83.8)
African	21 (2.5)	11 (2.4)	32 (2.4)
Hispanic	80 (9.4)	68 (14.8)	148 (11.3)
Native American/other	19 (2.2)	13 (2.8)	32 (2.4)
INHS severity, n (%)[d]			
Mild	313 (36.9)	141 (30.7)	454 (34.7)
Moderate	235 (27.7)	126 (27.5)	361 (27.6)
Severe	293 (34.6)	191 (41.6)	484 (37.0)
Unknown	7 (0.8)	1 (0.2)	8 (0.6)
INHS duration, n (%)[d]			
3–5 mo.	29 (3.4)	9 (2.0)	38 (2.9)
6–11 mo.	70 (8.3)	36 (7.8)	106 (8.1)
≥1 yr	749 (88.3)	414 (90.2)	1,163 (89.0)
INHS etiology, n (%)			
Organic	346 (40.8)	330 (71.9)	676 (51.7)
Psychogenic	127 (15.0)	5 (1.1)	132 (10.1)
Mixed	316 (37.3)	118 (25.7)	434 (33.2)
Unknown	59 (7.0)	6 (1.3)	65 (5.0)
Comorbidity/history, n (%)			
GERD	254 (30.0)	265 (57.7)	—
Hiatal hernia	14 (1.7)	13 (2.8)	—

Note: GERD, gastroesophageal reflux disorder. For Consolidated Standards of Reporting [Clinical] Trials (CONSORT) patient flow diagram related to these data, see Figure 2.6.

[a] Intent-to-treat population; denominators vary across characteristics and reflect numbers of subjects with available data for each.

[b] The treatment-as-usual (TAU) group comprises patients receiving placebo + proton pump inhibitors, histamine$_2$ (H_2) blockers, and/or over-the-counter antacids for INHS.

[c] Lower scores denote more serious disease with worse effects on diaphragmatic function.

[d] Some percentages do not add to 100 because of rounding.

Table 2.9 Common terms in tolerability and safety defined according to the International Conference on (now Council for) Harmonisation (ICH)

Term	Definition
ADR	Preapproval: "All noxious and unintended responses to a medicinal product related to any dose." Postapproval: "A response to a drug which is noxious on and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function."
AE	"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment."
AESI	"An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted. (This definition is covered by ICH E2F guidance.[b])"
SAE[a]	"A serious adverse event (experience) or reaction is any untoward medical occurrence that, at any dose: results in death; is life threatening; requires [hospitalization] or prolongation of existing [hospitalization]; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect."
UAE	"An adverse reaction, the nature or severity of which is not consistent with information in the relevant source documents."

Source: International Conference on Harmonisation. *ICH Harmonised Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A*. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf. Last accessed December 31, 2017.[4]

Abbreviations: ADR, adverse drug event; AE, adverse event; AESI, AE of special interest; SAE, serious AE; UAE, unexpected AE.

[a] The terms "serious" and "severe" are not synonymous. "Severe" signifies a step up in intensity from mild and moderate. "Serious" is based on an outcome or event in a patient that is associated with threats to her survival and/or function.

[b] In characterizing overall adverse reaction experience, nonspecific terms that lack a commonly understood or precise meaning are discouraged, because use of such terms can be misleading. For example, the phrase [well tolerated] is a vague and subjective judgment about a drug's adverse reaction profile for which there are no commonly understood parameters. Specific frequency ranges (e.g., adverse reactions occurring in <1/500) provide more precise information about incidence." (From ICH E2F.)

[1–3 paragraphs]. Which findings are consistent with, or divergent from, published data? Do results in general confirm or violate expectations based on the literature? In what ways do the present analysis and its findings improve on prior methodologies and results?

- Probe the potential clinical implications of the findings and how they might fit into contemporary patient care, referring to recent CPGs if appropriate **[1–2 paragraphs]**.
- Appraise potential strengths and limitations related to study design, statistical methods, baseline patient populations and other factors, which render the study more or less generalizable to populations related to readers' practices **[1–2 paragraphs]**. What questions could the study address or not address? Do error, bias, confounding, or other factors undermine confidence in the findings? What types of future studies are warranted to confirm, reject, or extend them? (See Chapter 3 for more on issues in study design.) Are there any other potential mechanisms or lines of evidence that could provide an alternative explanation of the findings?
- **Conclude the argument,** crystallizing the key information, including pivotal findings, potential limitations, and plausible future research avenues **[1 paragraph]**.

Table 2.10 Example of a tolerability table. Frequencies of treatment-emergent adverse events (TEAEs) in the NO-MO-BURP-PLS! Trial (12-week data)

	No. (%)		
TEAE[a]	Spastex + placebo (n = 846)	TAU[b] + placebo (n = 458)	Total (N = 1,304)[c]
≥1 TEAE	324 (38.3)	166 (36.2)	490 (37.6)
Headache	47 (5.6)	19 (4.1)	66 (5.1)
GERD	44 (5.2)	18 (3.9)	62 (4.8)
Dyspepsia	42 (5.0)	16 (3.5)	58 (4.4)
Nasal congestion	34 (4.0)	14 (3.1)	48 (3.7)
Nasopharyngitis	18 (2.1)	9 (2.0)	27 (2.1)
Influenza	12 (1.4)	6 (1.3)	18 (1.4)
URI	12 (1.4)	6 (1.3)	18 (1.4)
Dizziness	9 (1.1)	0	9 (0.7)
Bronchitis	9 (1.1)	0	9 (0.7)

Note: GERD, gastroesophageal reflux disorder; URI, upper-respiratory-tract infection.

[a] Treatment-emergent adverse events (TEAEs; Medical Dictionary for Regulatory Activities (MedDRA) 14.0 preferred terms), occurring in ≥2% patients in any treatment group (or with higher frequency in the active-treatment group), presented in descending order of frequency, in the safety population.

[b] The treatment-as-usual (TAU) group comprised patients receiving placebo + proton pump inhibitors (PPIs), histamine$_2$ (H_2) blockers, and/or over-the-counter antacids for involuntary noisome hiccup syndrome (INHS). Some patients had more than one TEAE.

[c] The total N value is smaller than that for efficacy (Table 2.8) because the safety population comprised all subjects who were randomized and received at least one dose of study treatment (safety population) rather than those randomized to one group or another (intent-to-treat population).

Chapter 3 delves into potential study limitations, error, bias, and confounding factors, and considers ways in which to account, control, or otherwise adjust for them. In a *New England Journal of Medicine* article, Avorn referred to RCTs and observational studies as the "yin and yang of drug research" (Figure 2.2).[6]

Randomized controlled trials are ideal for establishing a medication's efficacy but are typically conducted in a highly "selected" population that chooses and enrolls patients who tolerate and adhere to medication regimens optimally. Investigators painstakingly maximize the quality of individual patient data. Such studies are also typically not powered or of sufficient duration to discern intertreatment disparities in TEAEs and safety signals, particularly infrequent ones. In addition to a perhaps somewhat exaggerated homogeneous population of study participants, treatment is typically inflexible and protocol driven, rather than dynamic, as in most readers' "real-world" practices. Although ideal to demonstrate treatment efficacy, RCTs have limited ecological validity, or generalizability to typical care settings.

In contrast to RCTs, observational studies are conducted in a more familiar and typical (naturalistic) clinical milieu, enabling enrollment of more subjects who can be monitored for longer intervals. However, such studies may be "associational" in nature, unable to conclusively determine causality and also susceptible to biases, confounding factors, and other statistical issues.

Unlike RCTs, retrospective cohort (observational) studies involving administrative (pharmacy) claims databases typically lack high-quality individual patient-level data. Because of their retrospective nature and failure to randomize patients, such studies may also be subject to various forms of bias and confounding on unmeasured variables. Propensity score matching (PSM) is one statistical approach to limit such biases and adjust for potential imbalances resulting from the failure to randomly allocate patients to treatments.

Methodological heterogeneity may occur when pooling data from studies with fundamentally disparate methods and populations. Measured by the I^2 statistic (among other methods), heterogeneity can undermine the strength of conclusions drawn

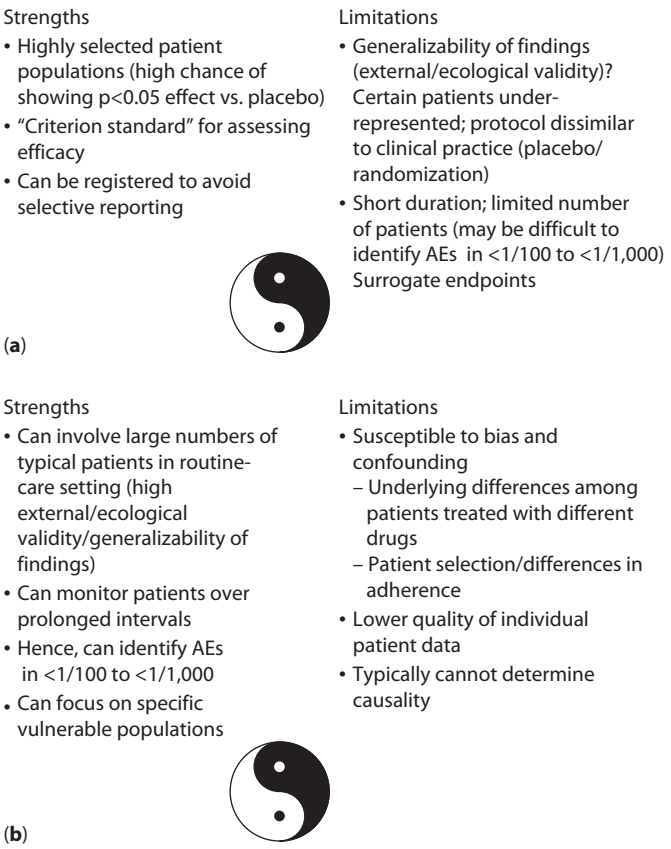


Figure 2.2 Randomized controlled trials **(a)** and observational (also known as "real-world evidence [RWE]) studies **(b)** as the "yin and yang of drug research."[6]

by meta-analyses and other pooled-data analyses. Finally, SLRs may be influenced by publication bias, whereby smaller studies need to report greater treatment effect sizes in order to be published; some journals are less likely to publish study reports of negative (null) findings. Publication bias can be assessed using funnel plots, in which the average treatment effect size in each study is plotted on the abscissa (*x*-axis) and precision (the standard error or number of subjects) on the ordinate (*y*-axis). Asymmetrical funnel plots suggest publication bias.

Most progress in pharmaceutical research is incremental. Hence, even the advent of a new class of medications or an innovative new agent or technology that promises to be "best in class" should not prompt overly zealous or, worse yet, promotional writing. Hew closely to the most up-to-date product labeling. Most medications are members of families (pharmacological classes); writing that "derogates" one member may tarnish the entire family, including the medication being considered in your paper. Discussions that unduly emphasize benefits over risks (e.g., adverse events), are speculative, or bear the merest whiff of promotionality will likely not survive journal peer review.

2.3.1.4.1 Before-after exercises in discussions (and results)

Before (promotional)-after (balanced) exercises follow:

Promotional: The dose of spastex does not need to be reduced in patients aged ≥65 years, whereas other agents in the anticholinergic class must be adjusted in older patients.

Neutral: The dose of spastex does not need to be reduced in patients aged ≥65 years.

Neutral: Agent X has a terminal elimination half-life of 16 hours.
Promotional: Agent X is the only member of its pharmacologic class whose terminal elimination half-life exceeds 10 hours.
Or (worse, speculative and misleading):
Agent X may offer longer-term benefits on patient-reported outcomes and be associated with enhanced convenience and higher adherence because of less frequent dosing.

Not necessarily. On a pharmacodynamic basis, Agent X may confer not only more durable benefits on efficacy endpoints but also longer-lived adverse events, potentially *compromising* patient-reported outcomes in some individuals. Regarding the "enhanced convenience" of "less frequent dosing," I am aware of no well-validated instrument that measures patient convenience. The original publication on adherence and dosing frequency, by Cramer and co-workers,[7] found that adherence fell off substantially when dosing frequency increased from three to four times daily.

Avoid "unanchored superlatives." For example:

According to the American Society of Hematology, the International Normalized Ratio is the criterion standard (or reference standard or method of choice) to measure coagulation.
Not:
The International Normalized Ratio is the gold standard to measure coagulation.

In our study, treatment with Agent X was associated with a reduced incidence of outcome D compared to therapy with Agent Y.
Not:
Treatment with Agent X was superior to Agent Y in reducing outcome D.

Be careful about inaccurate "causal implications" of verbs. Observational studies typically cannot prove causation or its direction.

In our observational study, treatment with Agent X was associated with a lower 5-year disease event rate compared to therapy with Agent Y.
Not:
In our observational study, treatment Agent X reduced the 5-year disease event rate compared to therapy with Agent Y.

Biased writing can also result from narrowly discussing the efficacy profile of a medication (e.g., the one manufactured and/or marketed by the study grantor) without considering its potential adverse effects or other costs (humanistic or economic). However, it is reasonable and appropriate to use study findings to help identify certain patient subgroups who might derive special treatment benefits based on disease-centered, PRO, or other key endpoints.

2.3.1.5 CONCLUSIONS

"Clinch" your essay as concisely and precisely as you began it. As a lesson, I refer to the "Lads from Liverpool" for one of the most elegant "clinchers" ever penned, in music or any other creative endeavor:

And in the end; The love you take,
Is equal to the love...You make.

Paul turned what could have been an afterthought or pastiche into an unforgettable axiom. The last recorded Beatles' album (*Abbey Road*) was arguably the most creative and collaborative, with everyone working "frightfully well" together (according to producer George Martin). To "clinch" the work, Paul penned the above (at least nearly) heroic couplet, drawing deeply from

the roots of English literature, reaching back as far as Chaucer. The phrasing is almost mathematically elegant. You can almost put a "QED" (*quod erat demonstrandum*) at the end of the verse.

One takeaway from this example, apart from the reminder that "brevity is the soul of wit?" Creative work, including medical writing, is enriched by collaboration. Especially when challenged by a problem in a study or its report, reach out to your colleagues early and often, including, most importantly, the corresponding author (CA). In many instances, only a fresh pair of eyes from a peer is needed. In short, "No man [or woman] is an island!"

Avoid conclusions that exceed the scope and aims of the predefined (*a priori*) protocol, including off-label (or beyond-label) claims, conjecture, and failure to distinguish between surrogate measures and hard outcomes such as morbidity and mortality. Undertake the previously mentioned "reckoning" process. How well do the Results answer the study's questions and meet its prespecified objectives (from the Introduction)? Which findings were expected or unexpected and statistically (and/or clinically) significant? Are there alternative explanations for the findings? What future research could help to further evaluate and challenge or extend the findings?

2.4 HOW TO WRITE A REPORT OF A … ("HOW–TWA–ROA") STUDY

2.4.1 Overview

This section focuses on building high-quality study report manuscripts. Like Chapter 4, which provides quality-control checklists for preparing different manuscripts, the next section summarizes my own guidance to prepare diverse types of study reports, organized below in descending order of evidence quality (Chapter 1 evidence pyramid). Types of papers are summarized below in descending order of evidence quality according to the medical evidence pyramid presented in Chapter 1.

2.4.2 HOW–TWA–ROA … Systematic literature review (SLR) or meta-analysis

See Chapter 4, Tables 4.15 and 4.19.[8–10]

2.4.2.1 CONSIDERATIONS WHEN CONDUCTING A SYSTEMATIC LITERATURE REVIEW OR META-ANALYSIS AND INTERPRETING THE FINDINGS

The chief advantage of conducting an SLR or meta-analysis is that it enables the researcher to pool data from multiple trials in order to increase statistical power and hence more readily test hypotheses. Two potential pitfalls are heterogeneity and publication bias. The former occurs if study designs, populations, and other factors are so disparate across the included studies that they are not necessarily all measuring the same treatment effect or other variable being reported. Heterogeneity can also occur if data from patient subgroups differ meaningfully from findings in the overall (general) population.

To evaluate heterogeneity in meta-analyses, Cochran's Q is calculated by summing the squared deviation of each investigation's estimate within the overall meta-analysis and weighting each trial's contribution in an identical manner to the method in the overall analysis. The Cochran Q statistic is then compared with the χ^2 distribution in k number of studies with $k - 1$ degrees of freedom to generate p values.[11]

Of a more recent vintage, and increasingly more frequently employed in meta-analyses to evaluate heterogeneity, is the I^2. One advantage of using this statistic is that it can be directly compared between meta-analyses with distinct types of outcomes and disparate numbers of patients.[11] I^2 ranges from 0 to 1.0 (or 0 to 100%). A score of 0 indicates no observed heterogeneity, whereas higher numbers indicate rising heterogeneity.

In practice, I^2 values exceeding 0.75 (75%) are typically considered to be consistent with an unacceptable degree of heterogeneity. Although I have previously stated that you should avoid such "unanchored" modifiers (e.g., "acceptable, unacceptable"), another similar example is a frequent rule of thumb in the literature on prognostic models: a *c*-statistic (area under the receiver operating characteristics curve [AUC ROC]) exceeding 0.70 is consistent with acceptable model performance in discriminating one predicted outcome from another.

Publication bias may occur because smaller studies must report a greater effect size (vs. larger studies) to be published by a PRJ. In the absence of

such bias, the precision in projecting a treatment effect should increase with rising sample sizes of the contributing studies. In this setting, a plot of precision (e.g., standard error; number of study participants) on the *y*-axis against effect size on the *x*-axis should show that the smallest studies (i.e., with the lowest *N* values) loosely scatter at the bottom, whereas the largest ones cluster narrowly at the top. When a plot has this inverted-funnel shape and is symmetrical, publication bias is unlikely.[12,13] In addition to publication bias, potential contributors to asymmetrical funnel plots include[12]:

- Artifacts related to choice of treatment effect measure
- Citation bias
- Data irregularities, including poor study design, insufficient analyses, and fraud
- Disparate intensities of interventions across trials
- Difference in sample populations' underlying risk
- Location bias
- Multiple-publication bias
- Random probability

When conducting an SLR or a meta-analysis, you may choose to visit the UK National Institute of Health Research's International Prospective Register of Systematic Reviews (PROSPERO) website to register your study or determine if similar ones have been or are being performed (Available at: https://www.crd.york.ac.uk/PROSPERO. Last accessed December 31, 2017). Before conducting your literature search using EMBASE/PubMed/MEDLINE and other, more specifically subject-related databases, electronically scan the CDSR and other published reviews to confirm that a review like your own has not been conducted. If it has, define your objectives to build on (or further evaluate) the prior findings and conclusions.

Of course, it is a fool's errand for you and your colleagues to consider all papers on a particular disease state or therapy. Published papers need to be reduced, consolidated, organized, and prioritized.

A proven way over potentially immobilizing anxiety about covering all relevant papers is to "divide and conquer." This maxim has a twofold meaning concerning SLRs and meta-analyses, from broadest to most specific in nature. First, don't go it alone. Find a few committed researchers who are willing to share the load with you. Second, work with your colleagues to focus your research team on a discrete scope for the review. This scope should in turn be translated into a manageable number of SLR objectives. Limits must be imposed, including English-language articles in PRJs from the previous 5 to 10 years that are related to a limited number of key search words or terms and publication types.

An example of a PRISMA (Available at: http://www.prisma-statement.org. Last accessed December 31, 2017) flow diagram is provided in Figure 2.3. When conducting your literature searches with EndNote or Reference Manager software, use the "tab delimited" function to export the search results into a Microsoft Excel file, then share it with your colleagues to review. It is often wise to include three independent reviewers to determine different articles' relevance and suitability for inclusion in the SLR or meta-analyses, including one to "break ties" (as mentioned above, this can be the CA).

Software from the Cochrane Community (Review Manager [RevMan] 5) is available to generate pivotal data for a meta-analysis (Available at: http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download. Last accessed December 31, 2017). As shown in Figure 2.4, data on each study of a meta-analysis on our hypothetical disease INHS can be entered, after which the software generates odds ratios and 95% confidence interval (CI) values, a forest plot, a funnel plot, and I^2 values. The I^2 value in the example (71%) is consistent with substantial heterogeneity in effects of spastex (vs. treatment as usual) on patients with (vs. without) congenital disease. The funnel plot is somewhat asymmetrical, suggesting publication bias.

2.4.3 HOW–TWA–ROA … Randomized controlled trial (RCT)

See Chapter 4, Tables 4.21–4.25.[14–16]

2.4.3.1 INTRODUCTION

Download recent online content from the target PRJ so that you understand its readers and their likely educational needs and become acquainted with the current issues and approaches to them (Table 2.6). These activities are supported by

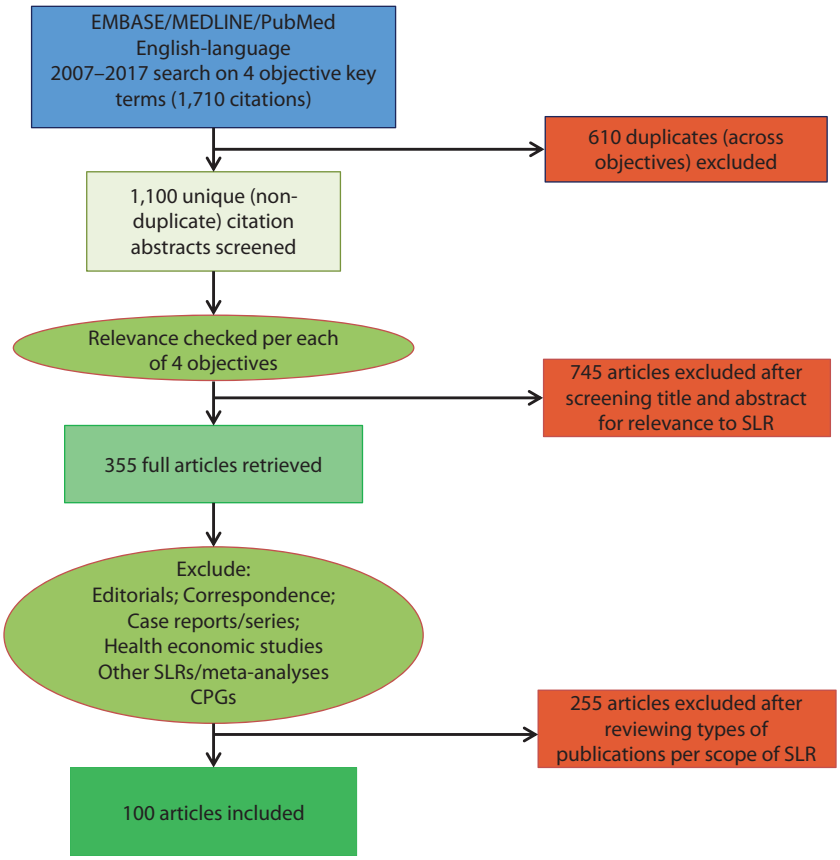


Figure 2.3 PRISMA flow diagram for a systematic literature review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Source: Available at: http://www.prisma-statement.org. Last accessed December 31, 2017.

reviewing the published literature and presented data, and discussing these with the CA.

Typically (for a clinical study), your aim in the Introduction is to (very concisely) summarize a disease and its contemporary management, identify gaps and other limitations in such management, and hence "motivate" the need for (and aims of) the current research and its report. ("This…but that…therefore this study….") Build to a clinical problem and/or deficiency in knowledge and how your study and report are unique or of incremental value in addressing them.

Most PRJs allot approximately 100 to 500 words for the Introduction, especially in the setting of a maximum 2,000-word manuscript. Citing a Cochrane review or other recent SLR or meta-analysis can help to set the stage for your report by providing an overview of previously published data, with an emphasis on the highest-quality studies. If consensus CPGs are available and applicable—particularly if issued by the professional society that also sponsors the targeted PRJ or authored by members of the research/publication teams—try to cite them in an incisive, clinically consequential way.

Even if your introduction focuses on clinical development of a particular medication, including phase 1 to 3 study data related to the grantor LSC's investigational product, strive to render the introduction otherwise "individual-treatment–agnostic." For instance, CPGs often feature stepped-care treatment algorithms comprising classes of medications without emphasizing individual agents. Citing a landmark study that compares multiple therapies for a condition may offer a widely applicable frame of reference for the broadest swath of readers and practitioners. In the field of schizophrenia, for example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study—which compared

Ferrous 2015

Methods	Observational study (electronic medical records [EMR] review)
Participants	1,188
Interventions	Spastex versus TAU
Outcomes	Hiccup frequency (%)
Notes	

Plumbous 2009

Methods	Patient registry
Participants	4,444
Interventions	Spastex versus TAU
Outcomes	Hiccup frequency (%)
Notes	

Stannous 2013

Methods	Open-label extension study
Participants	88
Interventions	Spastex versus TAU
Outcomes	Hiccup frequency (%)
Notes	

(**a**)

	Spastex			TAU	
Study or subgroup	Mean [percent]	SD [percent]	Total	Mean [percent]	SD [percent]
Ferrous 2015	22.2	10.1	0	72.2	36.1
Plumbous 2009	14.1	4.2	0	71.3	8.1
Cupric 2016	17.3	14	0	65.7	60.1
Chromic 2017	28.8	30	0	78.4	54.8
Stannous 2013	19.4	22.4	0	62.3	68.7

(**b**)

Characteristics of studies

Characteristics of included studies

Chromic 2017

Methods	Randomized controlled trial
Participants	150
Interventions	Spastex versus TAU
Outcomes	Hiccup frequency (%)
Notes	

Cupric 2016

Methods	Observational study (administrative claims database analysis)
Participants	425
Interventions	Spastex versus TAU
Outcomes	Hiccup frequency (%)
Notes	

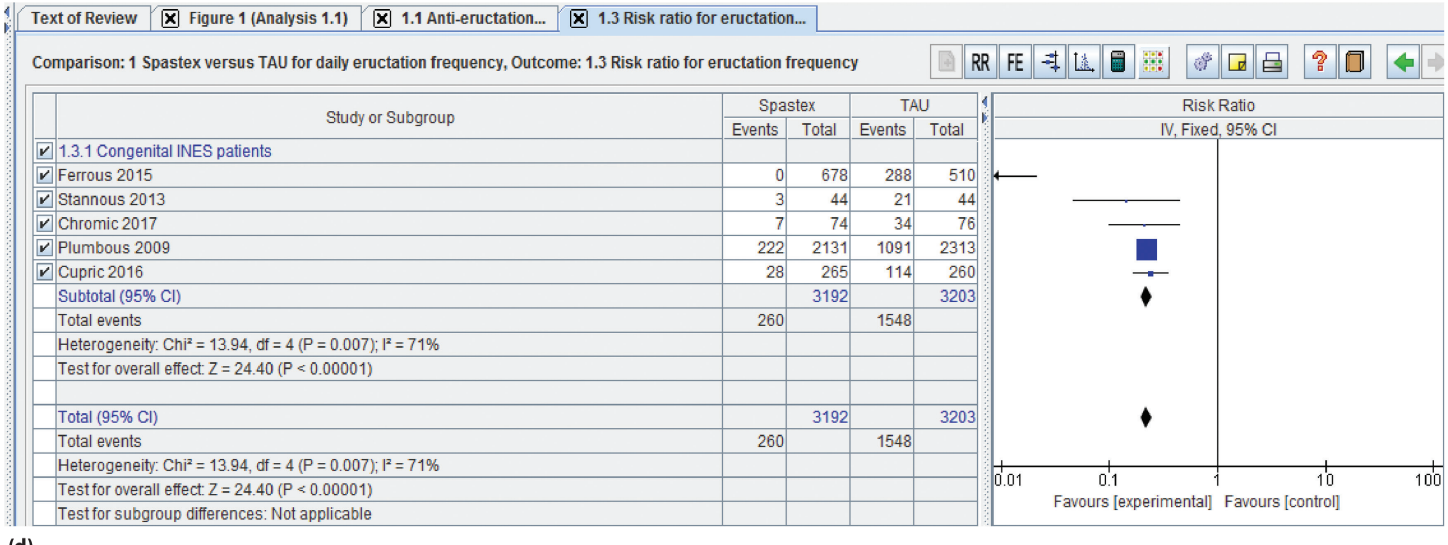
(**c**)

Figure 2.4 Data inputs and outputs for a meta-analysis using RevMan 5 software. **(a–c)** Study inputs.
Source: Images of figures from Cochrane Review Manager 5 (RevMan) [Computer program]. Reprinted with permission from The Cochrane Collaboration (www.cochrane.org).

(*Continued*)

clinical outcomes using a range of first- and second-generation oral antipsychotics in patients with chronic schizophrenia—has been cited more than 5,000 times since its publication in 2005.[17]

You may be provided with a clinical study report (CSR) by the trial grantor, typically an LSC. Although typically useful in outlining the subject matter addressed by the study, the Introduction from a CSR represents the LSC's point of view. To appropriately orient the Introduction and align it with the viewpoint of the PRJ, review recent online content of the PRJ and, if possible (beginning before, during, or soon after the KOMT), discuss the study with the CA and/or other key researchers. Review the Statistical Methods of the CSR, study protocol, or data/statistical analysis plan (DAP/SAP) to understand why certain statistical approaches and tests were chosen. At the KOMT, you may be able



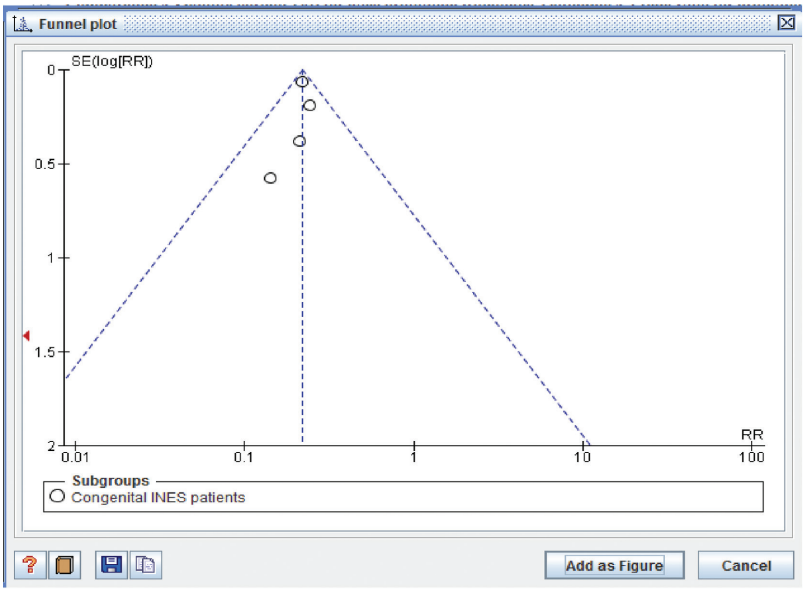
Study or Subgroup	Spastex Events	Spastex Total	TAU Events	TAU Total
1.3.1 Congenital INES patients				
Ferrous 2015	0	678	288	510
Stannous 2013	3	44	21	44
Chromic 2017	7	74	34	76
Plumbous 2009	222	2131	1091	2313
Cupric 2016	28	265	114	260
Subtotal (95% CI)		3192		3203
Total events	260		1548	
Heterogeneity: Chi² = 13.94, df = 4 (P = 0.007); I² = 71%				
Test for overall effect: Z = 24.40 (P < 0.00001)				
Total (95% CI)		3192		3203
Total events	260		1548	
Heterogeneity: Chi² = 13.94, df = 4 (P = 0.007); I² = 71%				
Test for overall effect: Z = 24.40 (P < 0.00001)				
Test for subgroup differences: Not applicable				

(d)

Figure 2.4 (Continued) Data inputs and outputs for a meta-analysis using RevMan 5 software. **(d)** Event frequencies in patients with congenital INHS, including forest plot. The statistically significant I^2 value of 0.71 (I^2 ranges from 0 to 1.0 or 0 to 100%) indicates substantial heterogeneity between patients with acquired versus congenital INHS.

Source: Images of figures from Cochrane Review Manager 5 (RevMan) [Computer program]. Reprinted with permission from The Cochrane Collaboration (www.cochrane.org).

(*Continued*)



(e)

Figure 2.4 (Continued) Data inputs and outputs for a meta-analysis using RevMan 5 software. **(e)** The funnel plot is asymmetrical, suggesting publication bias.

Source: Images of figures from Cochrane Review Manager 5 (RevMan) [Computer program]. Reprinted with permission from The Cochrane Collaboration (www.cochrane.org). RevMan 5 software is available at: http://www.community.cochrane.org/tools/review-productiontools/revman-5. Last accessed December 31, 2017.

to ask the biostatistician about such issues. Perhaps the most important objective of the KOMT is to target a PRJ to publish the findings, because this decision informs manuscript development, formatting. and other key editorial activities.

2.4.3.2 METHODS

If study objectives could not be specified in the Introduction, delineate them at the outset of the Methods section.

Briefly characterize the study setting, including numbers and locations of study sites and study dates, such as dates of first subject enrolled or randomized and last subject followed up. If data on numbers of subjects at each site are available, include them in the Results, not the Methods. Detailing the study setting is especially important for international trials because responses to assessments may vary by culture and certain demographic traits. Detail patient eligibility criteria and ensure that these are consistent with any product labeling in the countries where study sites are located. Graphing a "schema" and timeline may help to summarize study design, especially if it is complex and not the typical parallel-group, randomized, double-blind, placebo-controlled trial (Figure 2.5).

The Study Setting section may include statements about ethics and protection of patient rights and safety. Review the CSR or protocol to identify these. Increasingly, PRJs are requesting that the actual informed-consent document (ICD) be included along with the submitted manuscript. A typical ethics statement runs along the following lines:

> The study was conducted in a manner consistent with ethical tenets originating in the Declaration of Helsinki (DOH; seventh revision, 2013). Each potential subject provided written informed consent after receiving an explanation of the potential risks and benefits of participating in the study but before undergoing any study procedure (assessment or intervention). The informed-consent document (ICD) and study protocol were reviewed and approved by local institutional review boards (IRBs) before study onset.

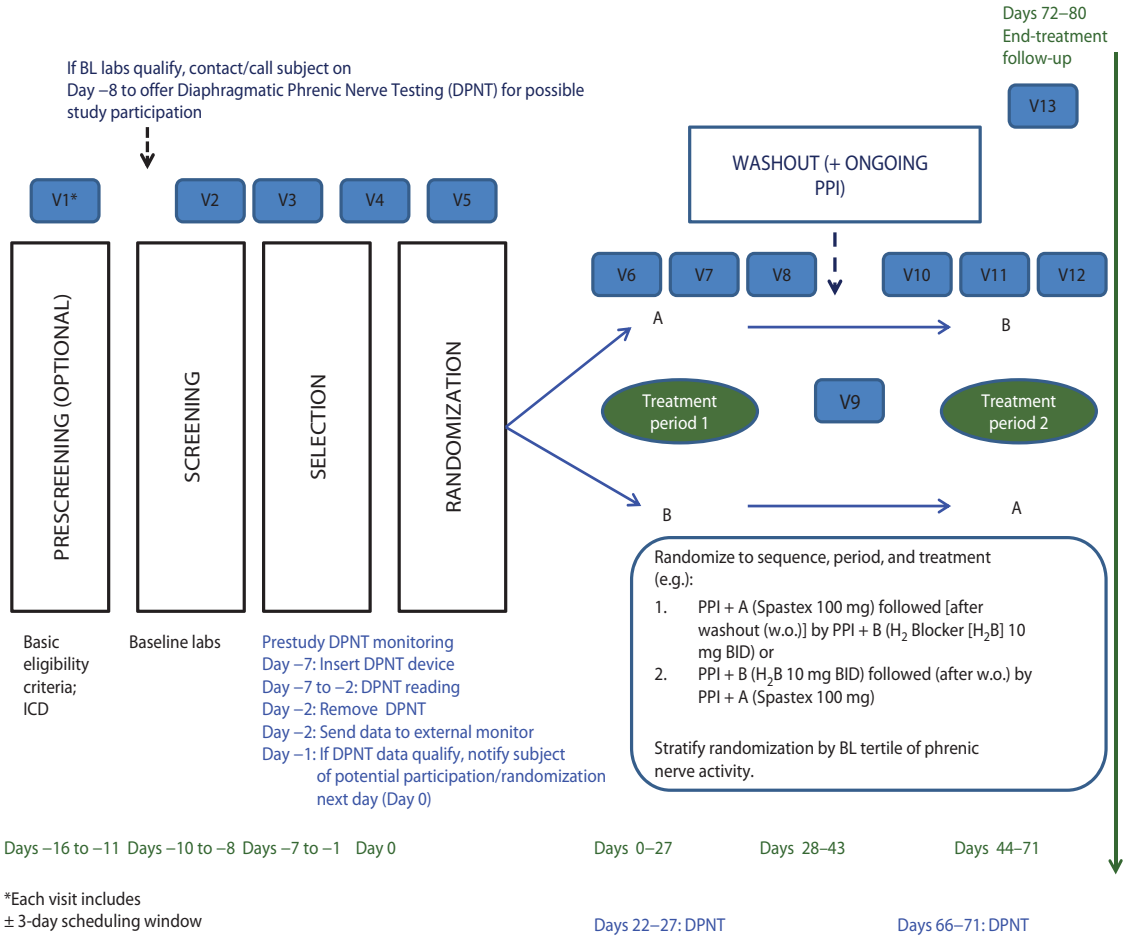


Figure 2.5 Example study schema and timeline for an actively controlled crossover clinical trial involving assessments of diaphragmatic phrenic nerve activity in patients with involuntary noisome hiccup syndrome (INHS). In general, crossover trial designs have greater statistical power (i.e., smaller needed sample sizes) compared to parallel-group studies because each subject serves as his or her own control. Paired statistical tests are warranted because each observation in the same subject receiving two different treatments (e.g., active treatment vs. placebo or usual-care) is not independent of others in the same individual.
Abbreviations: BL, baseline; H_2, histamine type 2; H_2B, histamine type 2 blocker; ICD, informed-consent document; PPI, proton pump inhibitor; V, visit.

The DOH transcends local and national law, falling within the domain of the World Medical Association.

Devote most of the Methods section to assessment measures, including their schedule and attributes. Begin by defining the intent-to-treat (ITT), per-protocol (PP), and safety populations. The ITT population includes all patients who are randomly allocated to one study treatment or another, irrespective of whether treatment is received. Using this population may help to avoid artifacts associated with crossover and attrition due to non-missing-at-random (non–MAR) dropouts. The PP population encompasses individuals who completed the study according to protocol, typically with perfect adherence, and is often used to assess efficacy. The safety population encompasses all subjects who were randomized and received one dose or more of study treatment.

Organize outcome measures by efficacy (primary, followed by secondary, tertiary, and exploratory) and then safety/tolerability. If you are

reporting subgroup analyses, disclose if these were prespecified in the study protocol and/or included statistical adjustment for multiple comparisons (e.g., Bonferroni correction) or were *post hoc*; subgroup analyses are intrinsically hypothesis generating. If pressed for words, include a table detailing the efficacy/safety/tolerability assessment schedule in a supplementary online appendix.

Safety assessments are typically conducted at baseline (e.g., prescreening, screening) and end of treatment or soon afterward. They include a medical history (with concurrent conditions and medications), physical examination, vital signs, laboratory panels (serum chemistries, hematology, urinalysis), and 12-lead ECG. Blood pressure and pulse rate are typically measured at each study visit. Any adverse events (AEs) can be elicited by open-ended questioning, at each visit after randomization.

Are efficacy outcome measures hard clinical endpoints (e.g., all-cause and disease-specific mortality), or surrogate variables? If the former, Kaplan–Meier survival or other (e.g., Cox) analyses may be warranted. For certain PROs and other, more subjective endpoints provide a verbal "legend" or "road map": does an increase or decrease in scores on an instrument indicate improvement, or worsening? Are any changes associated with normal—or otherwise reliably improved—functional status or health-related quality of life (HRQOL) on PROs? These include thresholds for MCIDs.

For an RCT, it is often appropriate to include one or more null hypothesis (NH; often expressed as H_0) as well as an alternative hypothesis [AH; often expressed as H_1 (H_N)] for each. Be careful about using categorical, "responder [or target achievement] analyses" as the major NH. Unless the target or responder criterion is widely recognized as biologically relevant, defining the endpoint as a "percentage of patients with [*choose measure*] greater [or less] than [*choose threshold*]" is not necessarily statistically valid because it categorizes an intrinsically continuous variable. If this sort of analysis is formulated, include (and report) precision limits (e.g., 95% CI) around the threshold for response in the report.

Graphing data and asking a few basic questions may help to inform your discussions with biostatisticians and other scientists at the KOMT and afterward:

- How was sample size calculated? The main data needed (typically derived from similar previous trials) are treatment effect size, variance, α level, power (1 −β), and nature of data (paired or independent). See Chapter 3 to learn about using P/S software to determine sample sizes.
- How were statistical methods selected? Typically, Fisher's exact test is used for baseline categorical characteristics (descriptive analyses in relatively small numbers of subjects), Student's (Gosset's) *t*-test for continuous variables, and χ^2 for categorical variables. These tests and analysis of variance (ANOVA) can be run using Microsoft Excel, as shown in Chapter 3. However, choice of tests (especially parametric vs. nonparametric) is also dependent on the relative normality or skew of the data, which can be assessed by plotting the data, using Microsoft Excel, or conducting the Shapiro–Wilk test.
- Which methods were used to impute missing data? In the past, the last observation carried forward (LOCF) convention was relied on, but, increasingly, multiple imputation and other approaches are advocated. (See Chapter 3.)
- What methods were used to control for potential covariates? Typically, an ANCOVA with treatment and study site as potential covariates is conducted; however, ANCOVAs often do not include other, potentially influential baseline variables, such as baseline patient age, number of comorbidities, and duration or severity of disease.

2.4.3.3 RESULTS

To ensure "external fidelity (consistency/accuracy)," request original data tables (in Word- or other software-compatible format) from the statistician. Avoid rekeystroking data, which can introduce errors. After "setting" your tables, review with an editor and be alert to any duplication of rows or columns of data, which often indicate human transcription errors.

Include a Consolidated Standards of Reporting Trials (CONSORT) patient flow diagram (Available at: http://www.consort-statement.org. Last accessed December 31, 2017; Figure 2.6); a baseline characteristics table (Table 2.8); efficacy tables or figures that address every endpoint "motivated" in the Methods (and in the same sequence), including numerical data in text for figures that do not include numbers; and a tolerability (AE frequency) table (Table 2.10).

Safety can be covered either in shift tables showing changes in mean values for study populations

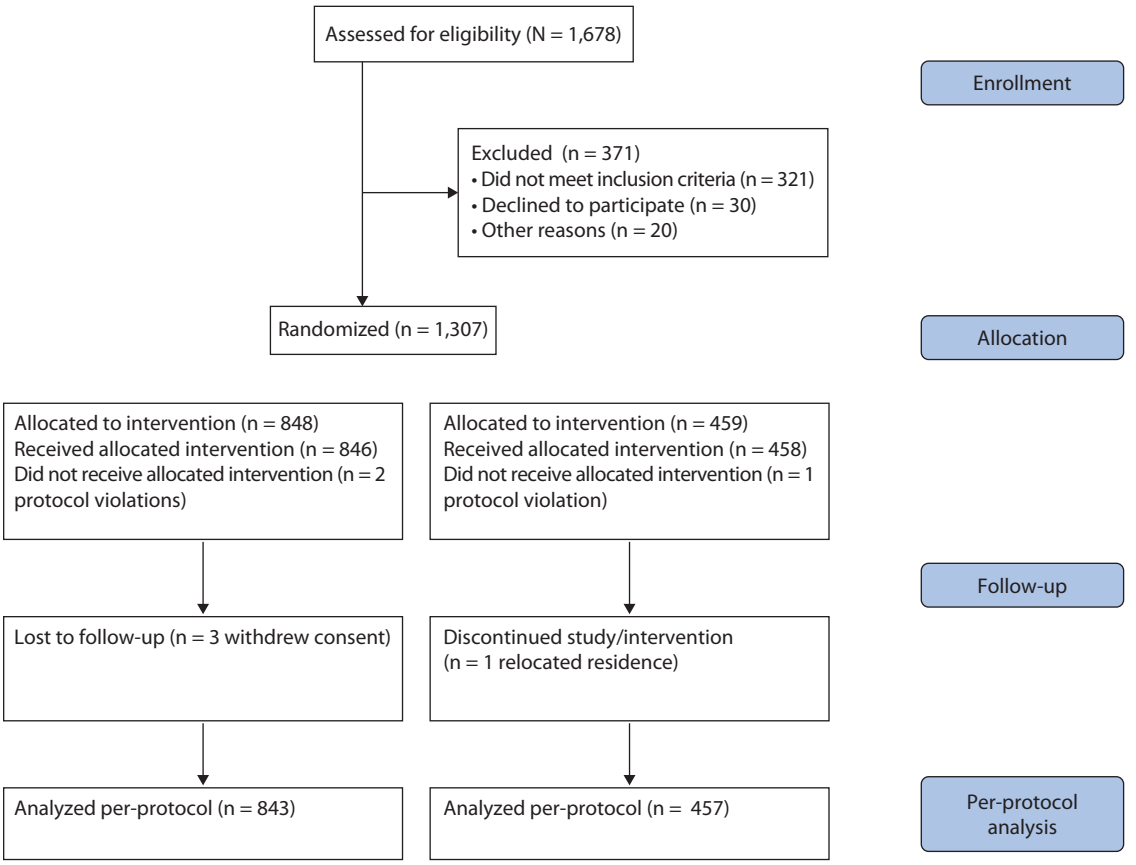


Figure 2.6 Consolidated Standards of Reporting [Clinical] Trials (CONSORT) patient disposition flow diagram for a randomized controlled trial involving spastex for involuntary noisome hiccup syndrome (INHS).

by treatment group and/or in narrative text. Safety parameters include vital signs, 12-lead ECGs, laboratory panels, as well as serious adverse events (SAEs) and how they resolved? Investigators typically decide if SAEs were related to treatment according to their temporal pattern regarding drug administration, dosing, and/or discontinuation.

As appropriate for normally distributed data, report the mean, standard deviation (SD), 95% confidence interval (CI), p value, and the statistical test used to generate it. For non-normal (skewed) distributions, report the median and interquartile range (IQR), or other measure of variability. Physicians may be particularly interested in SD or IQR as indices of treatment variability across different patient subgroups or even within individual patients over time. Make sure that the comparison giving rise to a p value is clear. In many cases you will have pairwise Student *t*-tests between two treatment groups for continuous data and χ^2 for categorical data. In other instances, you are testing effects of a treatment across three or more groups such as different-dose recipients, in which case an ANOVA is typically more appropriate. When effects of treatment are compared in an ANCOVA that controls for baseline covariates, we typically compare least-square means of changes from baseline to visit or study termination.

2.4.3.4 DISCUSSION

Ask yourself the following pivotal questions.

- How well balanced were the groups at baseline? How effective was randomization?
- How representative of, and consistent with, readers' practices (and other larger populations) was the population? Compare baseline characteristics to epidemiologic statistics and/or baseline characteristics of other related studies.

- Which NHs were rejected, which AHs accepted, and which subgroup analyses generated new hypotheses?
- Which study objectives were (or were not) met? If not, why not?
- Were the findings expected, or unexpected? Why?
- What future studies are warranted to evaluate, corroborate, and/or extend (or refute) the findings?
- Are there alternative explanations for the findings?

2.4.4 HOW–TWA–ROA … Observational study

See Chapter 4, Table 4.26.[18]

2.4.4.1 OVERVIEW

Table 2.11 summarizes key considerations when drafting an observational study report.

The main guideline for preparing observational study reports, including retrospective cohort analyses of administrative claims and electronic medical records (EMR), case series, and patient registries, is Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[18] These have been specifically adapted to certain types of studies, including genetic association investigations (STROBE–STREGA).

As mentioned earlier in this chapter, Avorn referred to observational studies and RCTs, as "the yin and yang of drug research."[6] Figure 2.2 illustrates the complementarity of these forms of research. Randomized controlled trials optimize the quality of individual-patient data, often to maximize efficacy in registration trials; however, the findings may not be generalizable to naturalistic treatment settings, including more heterogeneous patient populations treated with dynamic (vs. protocol-based, fixed) regimens. Conversely, observational studies may have lower patient-level data quality but view the patient "in situ," optimizing ecological validity: generalizability to naturalistic care settings of PRJ readers.

By the same token, observational studies may also be subject to certain forms of bias or confounding or residual confounding on unmeasured variables, which the RCT design typically excludes. One frequent finding is confounding by severity, which may result because treatment allocation is not randomized and patient groups differ in systematic, but not necessarily immediately evident, ways. An example might be an observational study's finding that patients with more severe, and/or recurrent, coronary heart disease (CHD) have superior clinical outcomes compared to those with less severe disease who have yet to experience a clinical event (i.e., secondary vs. primary prevention). Patients with more severe CHD may be more likely to receive specialty or other more advanced forms of care that optimize outcomes compared to their less ill counterparts.

With the passage of the 21st Century Cures Act (US HR 34; especially §3022), real-world evidence (RWE) is likely to occupy a more central role in future US biomedical research and even regulatory approval.[19,20] RWE includes retrospective cohort studies such as administrative claims database and EMR database analyses, case series, and patient registries. Like other observational studies, patient registries enable larger numbers of patients to be followed over longer periods of time (vs. RCTs) and hence may be well suited to evaluate infrequent safety signals in pharmacovigilance audits or other studies.

2.4.4.2 INTRODUCTION

As with other Introductions, build to a problem, issue, or gap that your study addresses and follow with the study's (and report's) aims. Whether to draft a longer (clinically comprehensive), or shorter (problem-focused) Introduction depends largely on the subject matter and journal AGs (and online PRJ content). Frequently a published observational study has identifiable objections that a novel study design can overcome.

For instance, I was involved in research comparing two intravenous antibiotics for community-acquired pneumonia. By conducting a de novo PSM procedure, we found that formerly reported differences between antibiotics in terms of health resource utilization (HRU) were biased away from the null by methodological issues in the previous study.[21] I have also contributed to research on rheumatoid arthritis (RA) in a "real-world" cohort (patient registry study) that included many individuals with long durations of illness and otherwise greater heterogeneity of demographic and clinical characteristics compared to recent-onset RA populations in most other clinical trials; many study subjects with recent-onset RA were followed for shorter intervals in RCTs compared to our observational (registry) study.[22]

Table 2.11 Considerations when drafting an observational study report

Disclosures	Introduction	Methods	Statistical issues and methods	Results	Strengths	Limitations
Registration. WHO Registry Network (Available at: http://www.who.int/ictrp/network/en. Last accessed December 31, 2017). US AHRQ Registry of Registries (Available at: https://patientregistry.ahrq.gov. Last accessed December 31, 2017).	• What is known? • What is the issue/problem/gap? • How does this study/report address the issue/fill gap? • "Situation on the ground": local epidemiologic, clinical, and other data and guidelines.	Devote most of the Methods to describe the setting (e.g., which health plan/electronic health claims database/EMR setting/registry) patient profiles (eligibility criteria).	**Biases are possible** given lack of randomization/control/blinding. Propensity score matching (PSM) is one statistical approach to adjust/control. Disclose methods of PSM (e.g., greedy match).	**Adherence** (e.g., MPR, PDC and % with MPR/PDC > 0.80/80%).	**"Real-world evidence":** high ecological validity and generalizability of findings to actual clinical practice: Less "selected" patient populations. Dynamic treatment (vs. rigid, protocol-based in RCTs).	**Associational data:** cannot necessarily infer causality or its direction.
Previous presentation (all manuscripts).		**Explicitly and clearly identify:** 1. the cohort(s) and/or subcohort(s) 2. the baseline or "look-back" period 3. the all-important index date (see Figure 2.7) 4. the follow-up observational period	**Attrition** Use of mixed models may conserve patient data (do not lose a patient from analysis if missing a single datum or small number of observations.	**Health-care utilization** • Hospitalization/LOS • Relapse • DME use • Office visits • Medications prescribed	**Potential statistical power:** can observe many patients "in situ." Because there is no study blind, patients can also be surveyed concerning e.g., treatment preferences.	**Potential biases (see Chapter 3 of this manual):** • Channeling • Treatment by indication • Selection • Immortal time **Possible confounding on unmeasured variables**
Conflicts of interests (all manuscripts).			**Intracorrelated longitudinal data** in registries require special statistical models (e.g., GEE). Disclose the correlational matrix structure.	**Other clinical and subjective outcome measures** (importance of MCIDs for PROs; see Appendix 1 of this textbook).	**Potential value in pharmacovigilance:** can not only observe more patients (vs. typical RCT) but monitor them for longer intervals.	• Lower quality (or limited) patient-level data (e.g., in claims analyses) • Prescription claims ≠ medications taken • ICD-9-CM, ICD-10, and Read (UK) codes are intended for reimbursement, not case ascertainment, purposes (coding errors are possible).
Author contributions (ICMJE; all manuscripts).					Registries particularly useful to study <1/100 to <1/1,000 disease events or safety signals.	Cross-sectional studies: may not be suited to assess frequently waxing and waning disorders.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; DME, durable medical equipment; EMR, electronic medical records; GEE, generalized estimating equation; ICD, International Classification of Diseases; ICMJE, International Committee of Medical Journal Editors; LOS, length of stay; MCID, minimum clinically important difference; MPR, medication possession ratio; PDC, proportion of days covered; PRO, patient reported outcome; WHO, World Health Organization.

One caveat to practitioners: unlike RCTs, RWE studies often do not have neat and tidy CSRs to summarize methods and results. As early as possible, by the KOMT or shortly thereafter, request a protocol, DAP/SAP, and/or "table shells" from the researchers, including the biostatistician.

2.4.4.3 METHODS

The null and alternative hypotheses of RCTs typically give way to assumptions and other premises in observational, and especially health economic (HE), trials. In retrospective cohort studies, it is most important to clearly define the cohorts (and/or subcohorts) being compared as well as the baseline, index, and follow-up periods. Figure 2.7 is an example of a schema and timeline for a hypothetical observational study on INHS. In this example, the index date is the first day on which an electronically linked health claim for INHS—a prescription for spastex—was recorded.

In parallel to the CONSORT patient flow diagram in an RCT (Figure 2.6), observational study reports may include a flow diagram that is based largely on eligibility criteria informed by reimbursement codes (e.g., *International Classification of Diseases, 10th ed* [ICD-10] in the United States and Read codes in the United Kingdom; Figure 2.8). However, eligibility criteria tend to be much less stringent in observational studies, enabling investigations of more heterogeneous, real-world sample populations.

Unlike RCTs, which typically determine medication efficacy, observational studies can provide data on effectiveness in a typical clinical setting. Other measures relate to HRU, including medication adherence. Adherence is typically assessed via the medication possession ratio (MPR) and the proportion of days covered (PDC), which range from 0 to 100%. Acceptable adherence is often defined as an MPR > 0.80 or a PDC > 80%. The PDC may be less susceptible to overestimation of adherence and may be overall more reliable than MPR because the numerator of the PDC is the number of days covered in a given interval, whereas the numerator of the MPR is the sum of days supply for all fills in a given interval. However, prescriptions filled cannot necessarily be equated to medications taken as prescribed. Other HRU data may include hospitalization, length of stay (LOS), relapse/rehospitalization, and durable medical equipment (DME) use. Although some of these data may inform HE and outcomes research (HEOR), indirect health-care cost data are not typically available and/or included.

Observational studies typically are better suited than RCTs to assess PROs. Allowing randomized patients to express treatment preferences might require crossover studies and compromise the RCT study blind. Strive to fully characterize any patient survey instruments, scales, or subscales, including whether an increase or decrease signifies an improvement or worsening; any psychometric data; validation (including any back-translated survey instruments in international studies); normative values; sensitivity, specificity, *c*-statistic, negative predictive value, and positive predictive value; and MCIDs. These data can be omitted if the study report is destined for a journal read by specialists well acquainted with such information.

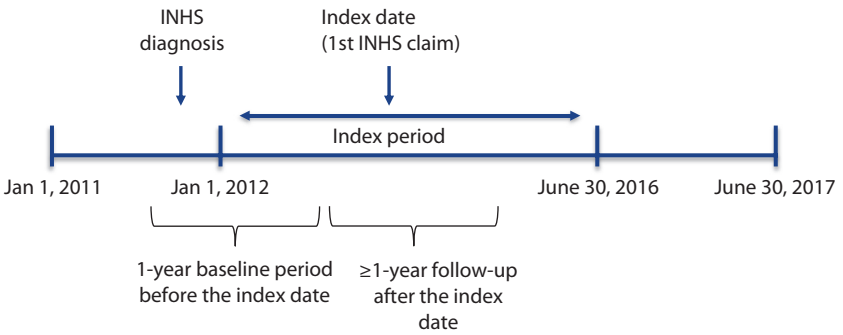


Figure 2.7 Example study schema and timeline for a retrospective cohort study on spastex for involuntary noisome hiccup syndrome (INHS). Ensure that the Methods text defines (1) the study cohorts (and/or any subcohorts), (2) the baseline ("look-back") period, and (3) perhaps most importantly, the index date/period.

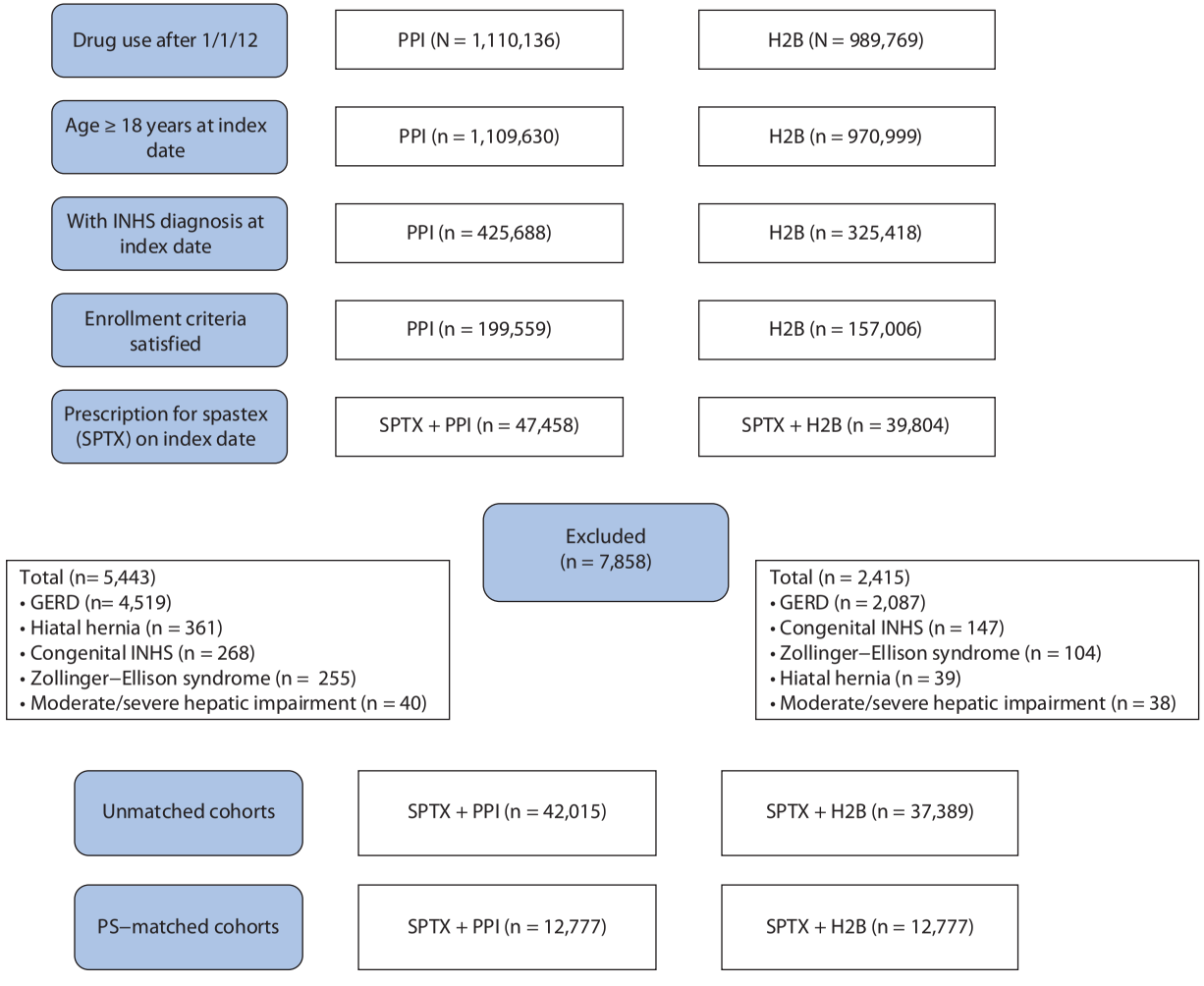


Figure 2.8 Patient flow diagram for the retrospective cohort study outlined in Figure 2.7.
Abbreviations: GERD, gastroesophageal reflux disease; H2B, histamine type 2 blocker; INHS, involuntary noisome hiccup syndrome; PPI, proton pump inhibitor; PS, propensity-score; SPTX, spastex.

To determine this, download recent online content from the targeted PRJ and discuss the matter at the KOMT.

According to the FDA Modernization Act (FDAMA), observational or RWE studies involving marketed products should not violate product labeling, in letter or spirit. For instance, eligibility criteria for patients studied in a claims database analysis should not include individuals for whom medications are contraindicated or in populations in whom the therapy has not been adequately studied; or off-label indications, dosages, or administration routes.

2.4.4.4 RESULTS

Regression analyses are frequently conducted when analyzing observational data. However, correlations between independent and dependent variables (IVs/DVs) do not necessarily imply causation and are most conservatively reported as "associations between," rather than "effects of," IVs on DVs.

2.4.4.5 DISCUSSION

One potential limitation of observational studies can be identified from their study design, schema, or timeline (Figure 2.7). In many cases, the baseline period is relatively short: on the order of 1 to 2 years. Such a relatively brief "look-back" interval may not capture data from patients treated many years before the index date. In our example, patients included during the short baseline period who received spastex on the index date may have overall more severe disease than those whose disease was effectively managed (or even cured) earlier, by older medications such as proton pump inhibitors and H_2-blockers. Channeling (allocation) bias may result when patients with more advanced disease are more likely to receive a new medication (in our case, spastex), hence spuriously associating its use with a previously unknown comorbidity.[23]

Another, perhaps more subtle, and less frequently cited, limitation of certain observational studies relates to adherence. Most health claims database analyses require that a patient be enrolled for at least 1 year before and after the index date. Because continuity of care may be associated with higher adherence, MPR and PDC values may be inflated in some such database analyses.[24–26]

2.4.5 HOW–TWA–ROA … Health economic and outcomes research (HEOR) study

See Chapter 4, Table 4.34.[27,28]

2.4.5.1 INTRODUCTION

The economic value of a health intervention—which is generally understood as a health outcome achieved per unit of currency allocated—may inform decisions at the individual patient, prescriber, health plan, policymaking, or even societal perspective.

Findings from HEOR analyses involving economic modelling often relate to discrete transition states and transition probabilities (TPs), which are in turn informed by published clinical trials—particularly findings from Kaplan–Meier survival analyses. Different forms of modelling may also use stochastic mathematics and other approaches to deal with random probability and project future health outcomes according to different treatment alternatives.

Apart from the model structure (e.g., discrete-time or continuous-time Markov chain [DTMC, CTMC]), model inputs, and model outputs, arguably the most important facet of an HEOR study and its report is the perspective taken. If the analysis is conducted from the societal perspective, both direct and indirect costs are important. Indirect costs include productivity losses due to disability and/or premature mortality. Direct health-care costs include HRU (hospitalization, LOS), prescriptions, DME use, and outpatient care.

Certain prescribers, payers, and policymakers are more interested in direct health-care costs, including incremental cost-effectiveness and cost-utility ratios (ICERs, ICURs) for one treatment compared to another. Health plan administrators are often concerned about the budget impact of introducing a new health technology in the future compared to the current situation in which the new technology has not been introduced. Many of these outcomes fall within the domains of cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and budget impact analysis or model (BIA/BIM).

Transitions between different health states are informed by TPs, which in turn derive from

clinical-trial data, including numbers of subjects available: alive and not censored at several time points within a Kaplan–Meier plot. TPs are described by a transition matrix.

Health economic models typically include a base-case scenario and a sensitivity analysis (SA) in which assumptions are systematically varied and effects on projected outcomes evaluated. One example is the discount rate. Because health benefits of certain therapies may not be realized for several years in the future, costs of these interventions are typically discounted (often at 3%). An SA might vary the discount rate to 1% or 5% and reassess HE outcomes.

2.4.5.2 METHODS

Methods should detail the

- Model structure, perspective, and time horizon;
- Model ratification and/or validation by payers or policymakers;
- Model inputs;
- Model outputs;
- Effects of varying key assumptions (e.g. discount rate) in an SA, including the discount rate;
- Type of SA (e.g., deterministic, probabilistic).

Cost-effectiveness analyses typically compare the incremental ratios of the costs of a clinical benefit divided by the benefit itself, for two or more interventions. When expressing CEA data as ICERs, the numerator is the computed allocation (in US dollars or other currencies) to achieve a clinical benefit, and the denominator is that benefit, including years of life saved (YOLS).

Health is a function of both the quality and quantity of life. If patients rate their HRQOL as better when receiving one health intervention compared to another, we may have the basis for a CEA. The numerator is again the calculated allocation to achieve an HRQOL or other benefit, and the denominator is the number of quality-adjusted life years (QALYs). QALYs are expressed on a scale from 0 (death) or even negative numbers ("worse than dead") to 1.0 (perfect health) and are weighted by time trade-offs. If a patient would prefer to live 5 years while receiving a new medication associated with a health utility value of 0.8 (4.0 QALYs) at an annual cost of $10,000, compared to 6 years on a previous therapy with a utility value of 0.6 (3.6 QALYs) at an annual cost of $800, the ICUR value would be:

$$\text{Incremental cost-utility ratio} = \frac{\$10{,}000 - \$800}{4.0 - 3.6\,\text{QALY}} = \$23{,}000/\text{QALY}$$

Different societies around the world hold different perspectives on the cost-effectiveness or cost-utility of one intervention compared to another. Willingness-to-pay (WTP) thresholds are operative when there is a discrete, positive ICER or ICUR value for the comparison between two treatments. For the example above, the ICER value of $23,000/QALY might not exceed most countries' WTP thresholds. If, on the other hand, one therapy is less expensive than the other *and* is associated with greater clinical benefits in terms of either YOLS or QALYs, that therapy is said to "dominate" the other, and WTP cut points do not come into play. In the "Cavalier argot" of US NBA star LeBron James, we have the proverbial "slam dunk."

A BIM assesses the impact of introducing a new health intervention on the (frequently 5-year) budget of a health plan or other well-defined population, compared to a referent scenario in which the technology is not introduced (Figure 2.9).[28]

One variable that may arise in BIMs that is not typically encountered in a CEA or CUA is that the epidemiologic profile of the disorder in the population can change because of the new technology being introduced to a large number of health plan members. Such a shift may include a reduced incidence of an infectious or other disease after introducing a vaccine, or a decreased prevalence of a chronic disease after introducing a more effective medication. A cohort- or patient-level, condition-specific model can account for patients entering and leaving the eligible population (i.e., changing size of population), as well as changes in case mixes, disease severity, and resultant costs of managing a disorder.

Key elements of a BIM include[28]

- Any restricted access to therapies
- Costs of all therapies and any projected changes
- Time horizon

Figure 2.9 Results from hypothetical budget impact model: effects on prices to a health plan of introducing a new treatment (spastex) compared to the situation before or without doing so (referent or treatment as usual, including proton pump inhibitors and H_2 blockers). **(a)**: Price per patient (with involuntary noisome hiccup syndrome [INHS]) per year (PPPY) after versus before introducing spastex. **(b)**: Price per member (with or without INHS) per year (PMPY) after versus before introducing spastex. **(c)**: Tornado plot showing the effects, on budget impact, of varying key assumptions by 5% in sensitivity analyses.

- Health plan features, including the size of the eligible population and the current and projected case mix after introducing the new intervention:
  - Model inputs;
  - Model outputs;
  - Model ratification/validation, including face validity with decision makers and verification of all calculations;
  - Projected uptake/penetration of the new intervention and any changes in use of already available therapies;
  - Sensitivity analysis (SA): effects of varying key assumptions such as discount rate in an overall analysis that projects alternative scenarios selected using the budget holder's perspective;
  - Type of SA, including deterministic versus probabilistic.

Figure 2.9c shows a "tornado plot" of hypothetical SA data in a BIM. BIMs need to be user friendly. Not only should they present outcomes in familiar ways that are relevant to budget holders and other decision makers, but certain assumptions should be subject to changes by the user; typically, the flexibility is indicated by "drop-down" menu options in a Microsoft Excel spreadsheet. The user can hence examine the effects of changing different combinations of assumptions on model outputs. After constructing a BIM, quality-test it using alternative software platforms or iterations rather than only the one used to develop the model. Users can and will use numerous software applications.

2.5 RHETORICAL EXERCISES AND "BEFORE-AFTER" EXAMPLES TO ENHANCE PROSE STYLE

2.5.1 Motivation

> [Anyone] who wishes to become a good writer should endeavour, before he allows himself to be tempted by the more showy qualities, to be direct, simple, brief, vigorous, and lucid.
>
> *Henry Watson Fowler*

After surveying work by bloggers, I was dismayed to "learn" that there is "grammar you don't have to pay attention to" or "phony grammar." As a dyed-in-the-Harris-tweed (and nearly lifelong) grammarian, I had to take an antiemetic and lie down.

I awoke refreshed to the singularly symmetrical beauty of medical writing: the rigor and conventions of both the "medical," including empiricism and sound scientific logic; and the "writing," including cogent organization and rhetorical elegance.

Both aspects—the medical and the writing—attracted me to the profession before it really was one. I have read and absorbed messages from manuals by not only the American Medical Association and Council for Biology Editors (edited by Edward Huth) but also by great English prose stylists who were not scientists: William Strunk and E.B. White in *Elements of Style*; H.W. Fowler in *Modern English Usage*; and Wilson Follett in *Modern American Usage*, which was completed posthumously by his colleagues (writers, editors, and prose stylists) Jacques Barzun, Carlos Baker, Frederick W. Dupee, Dudley Fitts, James D. Hart, Phyllis McGinley, and Lionel Trilling.

Do the lessons of these great books go to the graves with their authors? Perhaps. There are many niceties on which Follett insisted that are now all but obsolete. I freely concede that medical writing is typically tempered and straightforward. Shorter

is usually sweeter. As a co-worker once said to me, "C'mon, Gutkin, this isn't Proust." Point taken. However, MWs benefit from connecting to the larger tradition of their rhetorical forebears and striving for noble ideals in prose.

Given the advent of newfangled communications, including tweets and texts, some might assert that we are masters of the English language. Perhaps when communicating via PDAs. Medical journals, however, are governed by what is termed "standard written English." In this context, MWs are stewards—not masters—of the language. As with most other distinctions, it is a matter of context. Writing for peer-reviewed journals is compatible with a learned, if not always formal, tenor. The day you find "LOL" or "IMHO" in *The Lancet*, we can talk about "phony grammar."

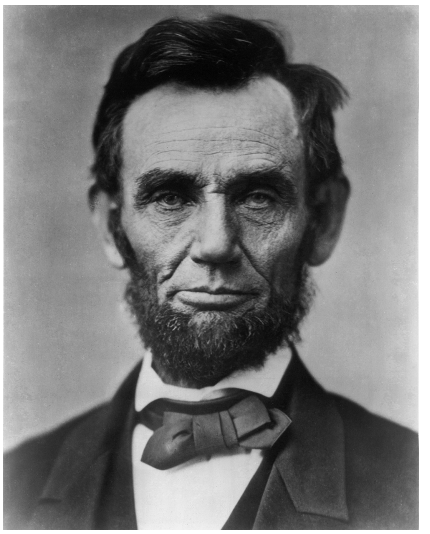
To optimize your written work, seek an editor who shares your passion for not only accurate and precise, but also elegant and memorable, expression. Consider contacting the Editorial Freelancers Association (Available at: http://www.the-efa.org/. Last accessed December 31, 2017.), American Medical Writers Association (http://www.amwa.org. Last accessed December 31, 2017), and International Society for Medical Publication Professionals (Available at: http://www.ismpp.org. Last accessed December 31, 2017.). Carefully review the editor's comments for any patterns of errors in your work, including verbosity, "crutch" phrases, lapses into jargon, and other infelicities.

2.5.1.1 OVERVIEW

The next section will reinforce principles of quality discussed in Chapter 1 by presenting before-after examples and exercises "ripped" from my own practice of nearly 30 years.

2.5.2 Brevity

Our first rhetorical example includes drafts of President Abraham Lincoln's Inaugural Address. Secretary of State William Seward (of "Seward's Folly" fame) seems to have had some difficulty "coming to the point" in his first draft! As usual, Honest Abe both pared down verbiage while elevating the emotional appeal of the rhetoric[29]:



- Draft of Lincoln's Inaugural Address by Secretary of State William Seward: "We are not, we must not be, aliens or enemies, but fellow-countrymen and brethren. Although passion has strained our bonds of affection too hardly, they must not, I am sure they will not be, broken. The mystic chords which, proceeding from so many battle-fields and so many patriot graves, pass through all the hearts and all the hearths in this broad continent of ours, will yet harmonize in their ancient music when breathed upon by the guardian angels of the nation." [82 words; underlined clauses distract!]
- Lincoln's Inaugural Address: "We are not enemies but friends. We must not be enemies. Though passion may have strained it must not break our bonds of affection. The mystic chords of memory, stretching from every battlefield and patriot grave to every living heart and hearthstone all over this broad land, will yet swell the chorus of the Union, when again touched, as surely they will be, by the better angels of our nature." [70 words; underlined clauses build!]

Next is an example from a medical journal article. It strikes me as masterly in its simplicity:

Telephone ownership introduces a bias irreconcilable by recourse to sociodemographic and health status measures.

In the foregoing example, there are no nonessential pronouns or relative clauses. It reads almost like Henry David Thoreau (from the Conclusion of *Walden*):

> **If one advances confidently in the direction of his dreams, and endeavors to live the life which he has imagined, he will meet with success unexpected in common hours.**[30]

The frequent version of the sentence about telephone ownership, which I have encountered all too often in first drafts?

> Telephone ownership introduces a bias that does not have the ability to be reconciled by reverting back to sociodemographic and health status measures.

The first example is simple, elegant, and memorable, manifesting thoughtful organization and expression. The second is a wordy, convoluted, "pseudoprofound" mess. The first example is the pith of sophisticated thought and analysis, whereas the second is quasierudite and a dim assortment of wind-blown chaff.

Write most prose in short, simple declarative sentences, but also try to introduce sentence variety to engage and maintain the interest of readers. Try to mix in some sentences with structures other than "subject-predicate, subject-predicate" *ad infinitum*, *ad nauseam*. If the journal targeted permits, mix in some "lambent flashes" of active voice among the "dense wood" of the passive. However, when mixing in active voice, be cautious about subject-predicate agreement. For instance:

> On further examination, we determined that cortisol levels were consistent with hypothalamic-pituitary-adrenal (HPA) axis disturbance.

Not:

> On further examination, cortisol levels [*this is a borderline dangling participle*] were determined to be [*They were? What was the mark of their determination?*] consistent with hypothalamic-pituitary-adrenal (HPA) axis disturbance.

> Erythema and erosions can complicate visualization of Barrett's esophagus. *[OK: concise but somewhat passive]*

Or:

> When assessing Barrett's esophagus, the clinician may find that erythema and erosions complicate visualization. *[OK: active but somewhat wordy]*

Or:

> Visualization of Barrett's esophagus is complicated, at times, by the presence of erythema and erosions. *[OK but wordy and passive]*

But not:

> When attempting to visualize Barrett's esophagus, erythema and erosions can complicate matters. [!] *[Dangling modifier!]*

Undesired (verbose):

> The rates of recanalization with adjunctive regimens that combined IAT with IVT have been substantially higher than those that have been reported for those patients who underwent IVT monotherapy. [*29 words and cites no numerical data*]

Desired (consolidated):

> Recanalization rates with IAT-IVT (79% TIMI 3–4) exceeded those previously reported with IVT alone (<20% TIMI 3–4). [*17 words and cites key numerical data*]

Undesired (verbose):

> PROACT II was the first randomized trial in which IAT was shown to have benefit in patients who have had an ischemic stroke caused by occlusion of the MCA, as well as in patients whose treatment has been initiated more than three hours after the onset of symptoms. [*48 words*]

Desired (consolidated):

> PROACT II was the first randomized trial showing benefits of IAT in patients with:
>
> (1) ischemic stroke secondary to MCA occlusion and (2) treatment initiation > 3 hours after symptom onset. *[30 words]*

Bulleted lists also foster readers' access to (apprehension of) data and help to rid verbiage. Take, for example, the following drug manufacturers' labels,

before and after the advent of the plain-language movement in government communications.

Undesired (old warning label, verbose):

Do not take this product unless directed by a physician, if you have a kidney problem such as acute interstitial nephritis, or if you have Cogan's syndrome or increased frequency of urination due to enlargement of the prostate gland.

Desired (new warning label, consolidated):

Ask a doctor before use if you have:

- Cogan's syndrome;
- a kidney problem such as acute interstitial nephritis; or
- increased frequency of urination because of an enlarged prostate gland.

In Introductions, make sure that statements are adequately and accurately referenced:

Alleles of single-nucleotide polymorphisms were associated with high plasma levels of Lp(a).[38,119] (Hypothetical references)

Not (unless the number of references is at a critical minimum):

Alleles of single-nucleotide polymorphisms have been shown to be associated with high plasma levels of Lp(a). *[Stating "have been shown to be" without including references raises questions with readers or peer reviewers.]*

In most cases, I advocate dispensing with pronouns and using "ing" verb forms to avoid wordy pronoun constructions.

For instance:

The group randomized to placebo also received usual care.

Not:

Those subjects who were randomized to placebo also received usual care.

Eliminate terms that have been stated or strongly suggested by context, in order to consolidate. For example:

A total of 100 patients received intensive and 75, intermediate, therapy. [*OK*]

Individuals with marked hypo- or hypertension were excluded from study. [*OK*]

But not:

The subject's vital signs were monitored and her chart updated.

The foregoing example of an attempt to consolidate words is prohibited because the subject of the compound sentence changes from plural ("vital signs were") to an implied singular ("her chart was" updated).

Not:

Eligible subjects were randomized to treatment with an ACE inhibitor, angiotensin$_{II}$ receptor blocker, or placebo.

The problem here is that subjects are not "treated with" placebo. Rephrase as follows:

Eligible subjects were randomized to receive an ACE inhibitor, angiotensin$_{II}$ blocker, or placebo.

Or:

Eligible subjects were randomized to the ACE inhibitor, angiotensin$_{II}$ blocker, or placebo arm.

Consider the following expendable (vs. succinct) phrases; many of these are identified in the *American Medical Association (AMA) Manual of Style*, 10th edition.[31]

Expendable phrases

In other words
It goes without saying that
Needless to say
To be sure
First and foremost

Redundant or incomparable/insuperable terms

Adequate enough
Advanced planning
Aggregate (combine, fuse) together
Brief in duration
Completely full (empty)
Consensus of opinion
Distinguish the difference

Redundant or incomparable/insuperable terms

Each individual person
Eliminate altogether
Empty out
Enter into
Equally as well as (should be just "equally"
Estimated at about (approximately)
Evolve over time
Fairly/very/most unique
Fellow colleagues
Fewer in number (quantity)
Filled to capacity
First initiated
Future plan
General rule
Green in color (tint/hue)
Improved [increased] the quality of
Indurated (tender) on palpation (hard/tender)
Interval of time (interval; period)
Large (small, bulky) in size
Lift (raise) up
Near to
Oval (square, round, lenticular) in shape
Own personal view
Perfect circle
Period of time, time period
Personal friend
Plan of action
Precede in time
Predict (project) in advance
Raise up
Reassessed again
Revert back
Rough (smooth) in texture
Skin rash
Soft (firm) in consistency
Sour (sweet, bitter) tasting
Still continues (remains)
Sum total
True fact
Very (quite, most) unique
Uniformly consistent

Be aware of sentences beginning with variants of "It" + forms of the verb "to be." Most are dispensable and "lead burying."

Prolix:

It has been demonstrated that
It is important (interesting) to note that
It may be stated (said, concluded) that
It stands to reason that
It was found (shown, demonstrated) that
The result was noteworthy (remarkable) because...

Prolix versus succinct

As a consequence (result) of	Because/Consequently
As long as	If
At this point in time	Now, while
Brought to fruition	Caused (elicited; but not "produced"; save the "produce" for the market; studies do not "produce" results!!)
Carry out	Conduct (perform)
Commented to the effect that	Said (stated, commented)
Despite (or in spite of) the fact that	Although, even though, though
Draws to a close	Ends (terminates)
Fall off	Decrease (decline, but not "diminish," which has an emotional/moral connotation)
File a lawsuit against	Sue
Following/subsequent to	After (unless "following" is actually meant, and it usually isn't!!)
Have an effect on	Affect (but not "effect," the verb form of which means "to cause")
In advance of	Before
In cases in which	When
In close proximity to (vicinity of)	Near
In order to; in an effort to	To (however, you can use "in order to" if you have already used "to" in a sentence "in order to" avoid repetition...)
In (with) regard to	About (regarding, concerning)

(*Continued*)

Prolix versus succinct (Continued)	
In those areas where	Where
Look at (in Methods or Introductions)	Assess, evaluate, examine, investigate, study
Most well	Best
Not remotely close to	Far from
Prior to	Before
Produce an inhibitory effect on	Inhibit
The majority of	Most

2.5.2.1 CONCISE "*MA NON TROPPO*"

Efforts to communicate tersely should not result in oversimplification or a failure to communicate the intrinsic complexities of a phenomenon—a practice referred to as "pablumizing." Strive for elegance and clarity without oversimplifying descriptions of key scientific details.

Also in the context of oversimplifying, one often encounters a form of "ellipsis" (a sort of shorthanded deletion) in medical communications that runs approximately as follows:

> Study findings support that [*what?*] anti–CRP antibody titers are predictors of rapid radiographic progression in RA.

This, I am afraid, is so terse as to lose sense and should be reworded as

> Study findings support the conclusion that anti–CRP antibody titers are predictors of rapid radiographic progression in RA.

2.5.3 Variety

The best medical writing is varied and engaging while also being direct and forceful. To engage the reader and sustain his interest, seek to mix in different words, sentence structures, and active voice where appropriate.

For instance, be aware of the following sort of defect in a series of paragraphs:

> Par. 1: ED is a source of distress to many men, leading them to withdraw from otherwise fulfilling relationships…
>
> Par. 2: ED often causes rancor with one's partner, compromising interpersonal relationships and quality of life....
>
> Par. 3: ED is commonly caused by endothelial dysfunction in penile vascular beds...

One way around this quadruple repetition?

> Heading: Erectile dysfunction (ED)
>
> Par. 1: A source of distress to many men, ED often leads them to withdraw from otherwise fulfilling relationships…
>
> Par. 2: ED often causes rancor with one's partner, compromising interpersonal relationships and quality of life…
>
> Par. 3: Endothelial dysfunction in penile and other vascular beds is a common cause of ED.

Backward-running sentences (e.g., with predicate preceding subject) can also increase variety and verbal interest. For example:

> This study enrolled patients with a history of myocardial infarction or unstable angina. Also eligible were (*predicate first*) individuals with ST-segment depression. [*Subject second*]

2.5.4 General prose style

In journalistic terms, "Lead with the news" (outcomes); don't "bury the lead (or the journalist's "lede")." While also remembering to vary sentence structure, try to give the reader the "pay-off" (i.e., outcomes) up front, not after a long-winded description of methods via subordinate clauses, unless the journal's AGs, online content, and/or the overall structure and style of the essay dictate otherwise.

> Treatment with dalteparin for 6 days significantly reduced the incidence of pulmonary embolism (vs. placebo) in subjects with deep-vein thrombosis who were enrolled in this randomized double-blind controlled trial. [*OK: Payoff for reader is up front.*]

Not (the lead-burying):

Subjects who were enrolled in this randomized double-blind controlled study in subjects with deep-vein thrombosis showed that treatment with dalteparin for 6 days significantly reduced the incidence of pulmonary embolism (vs. placebo). [*A tough slog*]

Spastex significantly reduced mean BURP scores (by 25%; p = 0.03 vs. placebo) in a multicenter, randomized double-blind, controlled study. *[OK: Payoff for reader is up front.]*

Not (the lead-burying):

In a multicenter, randomized double-blind, controlled study, spastex significantly reduced mean BURP scores (by 25%; p = 0.03 vs. placebo).

In many cases, an intervening clause is nonrestrictive; it adds nonessential information and does not redefine the subject as plural. For instance:

The patient, together with his loved ones, makes the final decision about end-of-life care. [*Correct*]

Comparisons in medical writing can also lead to imprecise agreement, with potential distortions of meaning. Examples follow.

Like other nephrologists, George Bakris is concerned about prerenal azotemia. [*OK*]

Not:

Like nephrologists, George Bakris is concerned about prerenal azotemia. *[Implies that Bakris is not a nephrologist!]*

Or:

Like all nephrologists, George Bakris is concerned about prerenal azotemia. [*Compares Bakris to himself!*]

As a pediatrician, Robert Pantell recognizes his role of educating youngsters.

Not:

As a pediatrician, it is Robert Pantell's recognized role to educate youngsters.

Strive to avoid dehumanizing and jargon-laden prose, even if doing so requires that you add words. Patients are not defined by their diseases.

Most HMG-CoA reductase inhibitor (statins) have not been investigated in children or adolescents (or "youngsters"). [*OK*]

Not:

Most HMG-CoA reductase inhibitors have not been investigated in pediatric patients.

But:

Clinicians should try to educate patients with diabetes (or hypertension).

Not:

Clinicians should try to educate diabetes (or hypertension) patients.

Or (even worse):

Clinicians should try to educate diabetics (or hypertensives).

Another way to enhance prose style is to connect clauses in parallel-structured series. We often miss opportunities to do so. For instance:

Schizophrenia can make it more difficult for patients to reason, learn, interact, and take care of themselves. [*Direct and well constructed*]

Not:

Schizophrenia has the ability to [*wordy construction*] compromise patients' capacity for reason, to attain degrees, and also limits their [*unclear antecedent; whose?*] interpersonal interactions and self-care.

Be mindful of agreement between singular and plural:

Study participants experienced significantly greater health-related quality of life after being randomized to daily treatment with either spastex 2.5 or 5 mg.

Not (implies treatment with both dosages):

Study participants experienced significantly greater health-related quality of life after being randomized to daily treatment with spastex 2.5 and 5 mg.

Sentences differing only in punctuation (commas) may convey vastly different meanings:

LDL-C increased by a mean of 8.3 mg/dL, and TG decreased by a mean of 1.7 mg/dL, from baseline to week 52.

Not:

LDL-C increased by a mean of 8.3 mg/dL, and TG decreased by a mean of 1.7 mg/dL from baseline to week 52. [*By distinct proximities of the phrases, this sentence implies that only TG was measured from baseline to week 52. Commas or parentheses signifying nonrestrictive clauses, as shown in the former example above, are necessary.*]

Predicates often do not match antecedents, and we commit "plural effusions."

Subject-verb agreement is often lacking in first drafts. On some level, this defect is endemic to medical writing, with its fluid shifts between considerations of individuals and groups.

A total of 1,112 women and their husband participated in this placebo-controlled trial. [!]

[*Apologies for my indelicacy here, but he must be very busy!*]

I find that the following plural-singular usage is objectionable:

Each physician inserted a catheter into his patient's pulmonary artery. [*OK*]

Or:

Physicians inserted catheters into their patients' pulmonary arteries. [*OK*]

Not:

Physicians inserted a catheter into their patients' pulmonary artery. [*Hmn? Do the patients share a single, "communal" pulmonary artery?*]

Predicates frequently do not agree with subjects because an intervening clause distracts us. Attention must be paid! For instance:

Treatment with oral antihypertensives, such as calcium channel blockers and β-blockers, were recommended.

Be careful: the subject/antecedent is "Treatment," which is singular. The above sort of disagreement occurs frequently in published papers.

OK:

Treatment with an ARB was at least as effective as, if not more effective than, therapy with an ACE inhibitor.

Or:

Treatment with an ARB was at least as effective as with an ACE inhibitor, if not more so.

Not:

Treatment with an ARB was at least if not more effective than therapy with an ACE inhibitor.

Less than 10% of patients experienced treatment-emergent adverse events.

Should be reworded as:

Fewer than 10% of patients experienced treatment-emergent adverse events.

Although "10%" can be considered as a singular quantity, the fact that "patients" are individuals who can be counted favors the use of "fewer than." However,

Less than 10% of body surface area was affected by plaque psoriasis after treatment.

is also correct because body surface area is indivisible and cannot be counted.

A cohort of 128 patients with RA were followed up for a cohort mean of 10 years.

Should be reworded as:

A cohort of 128 patients with RA was followed up for a cohort mean of 10 years.

because the overall cohort (not the individual participants) is being referenced.

The next example was excerpted from a published paper:

A significant increase in serum total testosterone, prostate-specific antigen, hematocrit, hemoglobin, and total bilirubin were seen in the treatment arm.

Should have been reworded as:

Significant increases in serum total testosterone, prostate-specific antigen, hematocrit, hemoglobin, and total bilirubin were seen in the treatment arm.

unless the intended meaning was that there was a (singular) significant increase in all components combined, in which case the verb form should have been "was."

The tolerability of both patches was also evaluated in this study.

Should have been reworded as:

The tolerability profiles of both patches were also evaluated in this study.

The singular "tolerability" in the first sentence suggests that both patches were worn at once. The plural "tolerability profiles" suggests that more than one patch was evaluated and/or compared.

However, added, nonrestrictive clauses offset by commas do not imply a plural antecedent:

The patient, together with his physician, family, and other caregivers [*nonrestrictive clause*], chooses the treatment course.

is correct, but so is the following (restrictive clause):

The patient, his physician, family, and other caregivers [restrictive clause] choose the treatment course.

However:

The presence of anti-citrullinated protein antibodies are powerful predictive factors for development and progression of RA.

Should be reworded as:

The presence of anti-citrullinated protein antibodies is a powerful predictive factor for development and progression of RA.

Or:

Anti-citrullinated protein antibodies are powerful predictive factors for development and progression of RA.

By convention, certain fundamentally plural medical terms warrant use of the singular:

In the case of ectopic pregnancy, D & C is indicated.
H & E is used to stain granulomas.
The H & P is warranted to discern histories of comorbidities.

However,

Hemoglobin and testosterone levels were determined, and QOL [*omission of form of the verb "to be"implies continued use of "were" even though "QOL" is singular*] surveyed, at regular intervals for 24 months.

Should be reworded as:

Hemoglobin and testosterone levels were determined, and QOL was surveyed, at regular intervals for 24 months.

In each of the preceding sentences, commas are placed before "at regular intervals" to signify nonrestrictive clauses. Absent these commas, the sentence would imply that only QOL was surveyed at regular intervals.

Dangling and "Warring" Clauses: "You Had Me at Hello; You Lost Me at Although."

Be leery of long introductory clauses, including those beginning with "Although."

From a published paper, we have the following:

Although the prognosis of patients with CHF is poor even with optimal management, suboptimal diagnosis, investigation, and treatment of heart failure and comorbidities (e.g., coronary artery disease) in community-dwelling patients contribute to poor survival.

[*The reader gets lost after "optimal management."*]

Should have been reworded as:

Suboptimal diagnosis, investigation, and treatment of heart failure and comorbidities (e.g., coronary artery disease) contribute to poor survival in community-dwelling patients, even though the prognosis of patients with CHF is poor even with optimal management.

Or recast as two sentences:

Suboptimal diagnosis, investigation, and treatment of heart failure and comorbidities (e.g., coronary artery disease) contribute to poor survival in community-dwelling patients. On the other hand, the prognosis of patients with heart failure is poor even with optimal management.

More egregious (and often risible) are long introductory clauses that dangle:

After scrubbing in for the surgery, our eyes noticed that there were no size 7 latex gloves. [!]

2.5.5 Before-after examples on general prose style from my practice

I consulted with an author of a review and offered the following revisions (among others). Notice how my edits to "lead with the news" (and not "bury the lead") not only reduce verbose sentences but also help to organize paragraphs, by moving otherwise buried concluding sentences to the fronts of paragraphs (as topic sentences).

Before: "Buries the Lead"

In one of the largest, the long term prospective Malmo study (19), baseline serum creatinine, incidence of smoking and low BMI, plasma glucose, pulse pressure, and frequency of antihypertensive therapy were all higher in the subpopulation of 40- to 55-year-old men who had orthostatic hypotension at the onset.

After: "Flips the Script," Uses Last Sentence in the "Before" as the Leading (Topic) Sentence in the "After"

The Malmo study (19) showed that the following factors were elevated in a subpopulation of men with OH at study onset:

- baseline serum creatinine
- incidence of smoking and low body mass index (BMI)
- plasma glucose
- pulse pressure
- frequency of antihypertensive therapy.

The Malmo trial was among the largest long-term prospective trials of men aged 40–55 years with OH.

Before:

Since hypertension is associated with orthostatic hypotension, and the target organ damage associated with hypertension (left-ventricular hypertrophy with impaired diastolic filling, central vascular rigidity, stroke and other cerebrovascular changes, and congestive heart failure) may all contribute, in a causative fashion, to OH, even the directionality of the association is uncertain.

After:

Even the directionality of the association between OH and target organ damage (TOD) is uncertain.

Hypertension is directly associated with OH. Findings of TOD associated with hypertension may also contribute in a causal manner to OH. These manifestations include left-ventricular hypertrophy (LVH) with impaired diastolic filling; central vascular rigidity; stroke and other cerebrovascular changes; and congestive heart failure.

2.6 BEFORE-AFTER EXERCISES, BY MANUSCRIPT SEGMENT

2.6.1 Article title

This section illustrates principles of high-quality writing and editing, using "before" (raw; red font and hypothetical author queries to address errors) and "after" (refined; green font) exercises and examples. When drafting titles avoid declarative sentences that convey the study's results because they can reduce the reader's motivation to read the paper. Do include the study design if possible.

Not:

Treatment with spastex improves diaphragmatic function without causing

off-target anticholinergic effects in patients with involuntary noisome hiccup syndrome: a randomized controlled trial

But:

Can treatment with spastex improve diaphragmatic function without causing off-target anticholinergic effects in patients with involuntary noisome hiccup syndrome? A randomized controlled trial.

Or (most simple and preferred):

Effects of treatment with spastex on diaphragmatic function in patients with involuntary noisome hiccup syndrome: a randomized controlled trial.

2.6.2 Abstract

2.6.2.1 "HELP READERS TO FIND YOUR ARTICLE"

Major considerations are summarized in Box 2.1. Structured abstracts are typically 250 to 300 words, represent a microcosm of the overall essay, and may include (1) Introduction/Background; (2) Objectives; (3) Methods; (4) Results; (5) Discussion; (6) Study Limitations; and (7) Conclusions. The chief requirement is to include your key words and other terms that search engines will locate. I always try to include at least one comparison and/or p value.

2.6.3 Acknowledgments: Before and after editing

Before: Raw

Acknowledgment

We are indebted to Ms. Smyrna Smulewicz for preparing the manuscript and to Dr. Hamish Heimstich for reviewing and commenting on it.

This is all very nice on the surface but woefully deficient overall.

After: Refined

Acknowledgments

Financial disclosures

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C.R. has served as a paid consultant to, and a recipient of honoraria, lecture payments (service on speakers' bureaus), and travel support from Apex Pharmaceuticals. She has received lecture payments from, and served on speakers' bureaus for, Astragal Pharma (Cleveland, UK) and T-farma Technologies (Hoddesdon, Hertfordshire, UK). She is also a board member for Kittrec Kickyzer (Marske-by-the-Sea, UK). W.G. is the recipient of a grant from the US National Institutes of Health (NIH; Grant # 24-88482). He has also served as an expert witness for Kittrec Kickyzer. R.D. and T.M.I. are employees of, and stock or shareholders (minor) in, Apex Pharmaceuticals. Z.Q. has received fees from Apex Pharmaceuticals for participating in review activities such as data safety monitoring boards, statistical analysis, and endpoint committees. A.M. has served as an expert witness for T-farma. J.K. has no financial interests to disclose.

Assistance in manuscript preparation was provided by Ms. Smyrna Smulewicz, Bristol University (UK), with support from Apex Pharmaceuticals, Inc. Hamish Heimstich, MD, PhD (Bristol University, UK) reviewed and commented on the manuscript.

Author contributions

Category 1

All authors made substantial contributions to the conception and design of the work, as well as acquisition, analysis, and interpretation of data.

Category 2

(a) Drafting the article: W.G. with assistance from Ms. Smulewicz.

(b) Revising it for intellectual content: All authors and Dr. Heimstich.

BOX 2.1: Before-after exercise to enhance search engine (and hence reader) access to your article via its abstract

THE IMPORTANCE OF SEARCH ENGINES

Google and Google Scholar are the principal search engines by which people find your article online. The search engine is now the first "port of call" for researchers, and it is of paramount importance that your article can be found easily in search engine results. Taking some simple steps to optimize your article abstract for search engines can help your work to be discovered, read, used, and cited in others' work. This, in turn, helps with the ISI Impact Factor of the journal in which your article is published, further raising the visibility of your article.

There are more than 100 factors that a search engine will look at before deciding how to rank your article in their search results, but the starting point is the content that you write.

WHAT DO SEARCH ENGINES SEEK?

Today's search engines use complex, proprietary mathematical algorithms that change every month to keep their search results as accurate as possible. They take into account more than 100 different factors and do not disclose the weighting or importance of each. Below are a few of the elements considered today by search engines:

- the volume of incoming links from related websites
- page titles
- quality of content
- relevance
- page descriptions
- quantity of content
- technical precision of source code
- functional vs. broken hyperlinks
- volume and consistency of searches time within website
- page views
- revisits
- click-throughs
- technical user features
- uniqueness
- key words
- spelling

WHAT CAN YOU DO TO HELP?

Repeat key phrases in the abstract while writing naturally

Search engines look at the abstract page of your article, which is free for everyone to review online. Your abstract is not only the "sales pitch" that tempts researchers to read your article, it is also the information that gives a search engine all the data it needs to be able to find your article and rank it in the search results page. Try to repeat the key descriptive phrases. Try to imagine the phrases a researcher might search for if your paper would be of interest to him or her. Focus on three or four key phrases in your abstract.

Get the title right (see also above)

Ensure that the key phrase for your topic is contained in your article title. Make sure that your title is descriptive, unambiguous, accurate, and reads well. Remember that people search on key phrases, not just single words, e.g., "women's health," not "health."

Choose your key words carefully

Include your three or four key phrases and add at least three or four more. Where more than one phrase (or abbreviation) is often used to describe the same thing, include both/all variants, e.g., drug names (proprietary and generic).

Summary

- What key phrases would you give a search engine if you were searching for your own article?
- Write for your audience, but be mindful of how search engines work also.
- Write a clear title with your main key phrase in it.
- Write an abstract and choose key words reiterating three or four key phrases.
- Keep it natural. Google will un-index your article if you go overboard in repeating terms.

The better you write your abstract, the better chance you give your article to appear high up in the search results rankings. This is vitally important, because researchers will rarely investigate beyond the first 20 results from Google.

BEFORE: EXAMPLE OF AN ABSTRACT NOT OPTIMIZED FOR SEARCH ENGINES

The following abstract's article could not be found in Google Scholar after searching on a variety of phrases around the subject of the article: the representation of youth anti-war protests. The words highlighted below are the only terms repeated, and these were unlikely to help someone researching this subject to find this article via Google.

Peace Children

Debate over the role that young people should play in politics reflects different conceptions of childhood and adult concerns about loss of authority and political hegemony. Coverage of demonstrations against the Second Iraq War by the British national press echoes adult discourse on the nature of childhood and exposes the limits set on political activity. Analysis of news-text and images reveals concerns about the political competence of youth, their susceptibility to manipulation and the requirement for social control. Approval of youth's right to protest was often conditional on the cause espoused.

Key Words: childhood • Second Iraq War

Key points:

- The title is meaningless outside the context of the printed journal issue. It might appeal to certain readers but not to online search engines.
- The title does not include key terms or phrases such as "youth anti-war protests."
- The Abstract does not repeat key phrases used within the title or article and presents Google with no patterns to search.
- Key words play a reduced role in SEO [search engine optimization] but still have influence. In the above Abstract, only two key words were provided, and the article's key phrases were not listed.
- Many other factors influence ranking, but the content above was written in a way that offered the article a very poor chance of being found online through search engines.

AFTER: EXAMPLE OF AN ABSTRACT OPTIMIZED FOR SEARCH ENGINES

The following abstract's article emerged at the top of Google Scholar's search of "depression X folic acid." These are words that researchers are likely to search on. The search terms are highlighted below so that you can discern the patterns of repeated phrases that Google searches.

Treatment of depression: Time to consider folic acid and vitamin B_{12}

We review the findings in major **depression**: of a low plasma and particularly red cell folate, but also of low vitamin B_{12} status. Both low folate and low vitamin B_{12} status have been found in studies of **depression**, and an association between **depression** and low levels of the two vitamins is found in studies of the general population. Low plasma or serum folate has also been found in patients with recurrent mood disorders treated by lithium. A link between **depression**: and low folate has similarly been found in patients with alcoholism. Hong Kong and Taiwanese populations with traditional Chinese diets (rich in folate), including patients with major **depression**, have high serum folate concentrations. However, patients in these countries have very low lifetime rates of major **depression**. Low folate levels are furthermore linked to a poor response to antidepressants, whereas treatment with **folic acid** is shown to improve such responses. A recent study also suggests that high vitamin B_{12} status may be associated with better treatment outcome. Folate and vitamin B_{12} are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAM) is formed. SAM donates methyl groups that are crucial for neurological function. Increased plasma homocysteine is a functional marker of both folate and vitamin B_{12} deficiency. Increased homocysteine levels are found in patients with **depression**. In a large population study from Norway increased plasma homocysteine was associated with increased risk of **depression**: but not anxiety. There is now substantial evidence of a common decrease in serum/erythrocyte folate, serum vitamin B_{12} and an increase in plasma homocysteine in **depression**. Further, the *MTHFR C677T* polymorphism that impairs homocysteine metabolism is over-represented among depressive patients, which strengthens the association. On the basis of current data, we suggest that oral doses of both folic acid (800 μg daily) and vitamin B_{12} (1 mg daily) should be tried to improve treatment outcomes in **depression**.

Key Words: cobalamin • **depression:** • diet • folate • **folic acid** • homocysteine • one carbon-metabolism • S-adenosylmethionine • vitamin B_{12}

Key points:

- Clear and descriptive title includes main key terms or phrases.
- Abstract repeats key phrases in a contextually natural way.
- Key terms or phrases are repeated in the Key Words field.
- Many other factors influence ranking, but the foregoing content was written in a way that gives it the best chance of being found online through search engines.

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Category 3
(a) Final approval of the completed article: All authors.
Category 4
All authors agree to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Following are major ICMJE categories for authorship or contributorship. Categories 1, 2, 6, and 8 must be met to qualify for authorship. It is not sufficient to approve each draft; some substantive intellectual contribution must be made (e.g., addition, deletion, or other revision of text).

(1) Conception and design of the study and/or acquisition of data; Analysis and interpretation of data; (2) Drafting the manuscript or critical revision for important intellectual content; (3) Obtaining of funding; (4) Provision of study materials or patients; (5) Administrative, technical, or logistic support; (6) Final approval of the article; (7) Statistical expertise; (8) Agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.[32]

2.6.4 References

Before: Raw (with author queries)

1. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209–1223.
2. Wessels T, Grunler D, Bunk C et al. Changes in the treatment of acute psychosis in a German public hospital from 1998 to 2004. *Psychiatr Q* 2007;78:91.
3. World Health Report 2001 on mental health.
4. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209–1223.
5. Weiden PJ. Discontinuing and switching antipsychotic medications: understanding the CATIE schizophrenia trial. *J Clin Psychiatry* 2007;68:S12–S19.
6. Kane J, Canas F, Kramer M et al. Treatment of schizophrenia with paliperidone extended-release tablets: A 6-week placebo-controlled trial. *Schizophr Res* 2007;90:161–147.
7. Hamish Heimstich, personal communication, May 4, 2013.
8. DOF, Astragal Pharma.

After: Refined

1. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209–23. [Note: 1/N dash, not hyphens, for page ranges.]
2. Wessels T, Grunler D, Bunk C et al. Changes in the treatment of acute psychosis in a German public hospital from 1998 to 2004. *Psychiatr Q* 2007;78:91–9.
3. World Health Organization. The World Health Report 2001. Mental health: new understanding, new hope. Available at: http://www.who.int/whr/2001/en/whr01_en.pdf?ua=1. Accessed January 29, 2014.
4. Weiden PJ. Discontinuing and switching antipsychotic medications: understanding the CATIE schizophrenia trial. *J Clin Psychiatry* 2007;68(Suppl 1):S12–S19.
5. Kane J, Canas F, Kramer M et al. Treatment of schizophrenia with paliperidone extended-release tablets: A 6-week placebo-controlled trial. *Schizophr Res* 2007;90:147–61.

2.6.5 Tables: Before and after editing

Before: Raw

Table X Baseline characteristics of patients with involuntary noisome hiccup syndrome

Characteristic	Placebo (n = 69)	Spastex 5 mg (n = 146)
Age	51.9 ± 10.4	52.2 ± 10.9
BMI	27.7 ± 3.4	27. 9 ± 4.7
Race, n (%)		
Caucasian	69 (100.0)	144 (98.6)
Black		
Hispanic		
Asian	0.000 (0.000)	2 (1.4)
Disease etiology, no. (%)		
Psychogenic	9 (13.0)	22 (15.1)
Organic	23 (33.3)	40 (27.4)
Mixed	27 (39.1)	61 (41.8)
Unknown	10 (14.5)	23 (15.8)
Disease duration (time since diagnosis), n (%)		
3–6 months	6 (8.7)	10 (6.8)
6–12 months	14 (20.3)	33 (22.6)
>12 months	49 (71.0)	103 (70.5)
Mean ± SD INHS severity domain score	15.9 ± 6.2	15.5 ± 6.0
Categorical severity (categories of severity domain scores), n (%)		
Mild (17−30)	31 (44.9)	64 (43.8)
Moderate (11−17)	22 (31.9)	47 (32.2)
Severe (1−11)	16 (23.2)	35 (24.0)
Comorbidities, no. (%)		
Gastroduodenal ulcer	20 (29.0)	46 (31.5)
Gastroesophageal reflex	6 (8.7)	17 (11.6)
Zollinger−Ellison syndrome	6 (8.7)	19 (13.0)
Barrett's esophagus	1 (1.4)	1 (0.7)
Mean ± SD phrenic nerve parameters		
DPNT > 1.0; no. (%) with values (AU)		
≤1.67	26 (38.8)	63 (43.8)
1.67−2.07	18 (26.9)	50 (34.7)
≥2.07	23 (34.3)	31 (21.5)

Note: Margin and queries and highlights indicate author-remediable defects that should be flagged and/or addressed.

Many questionable items need to be footnoted in the above table to explain internal inconsistencies. See the footnote in the "after" example below.

After: Refined

Table X Baseline characteristics of patients with involuntary noisome hiccup syndrome (INHS)[a]

Characteristic	Spastex 5 mg (n = 146)	Placebo (n = 69)
Mean ± SD age, yr	52.2 ± 10.9	51.9 ± 10.4
Mean ± SD body mass index, kg/m^2	27. 9 ± 4.7	27.7 ± 3.4
Mean ± SD INHS severity score	15.5 ± 6.0	15.9 ± 6.2
Race, no. (%)		
Caucasian	144 (98.6)	69 (100.0)
Asian	2 (1.4)	0
Etiology, no. (%)[b]		
Psychogenic	22 (15.1)	9 (13.0)
Organic	40 (27.4)	23 (33.3)
Mixed	61 (41.8)	27 (39.1)
Unknown	23 (15.8)	10 (14.5)
Disease duration (time since diagnosis), no. (%) with[b]:		
3–5 mo.	10 (6.8)	6 (8.7)
6–11 mo.	33 (22.6)	14 (20.3)
≥12 mo.	103 (70.5)	49 (71.0)
Severity (categories of severity domain scores), no. (%) with:		
Mild (17–30)	64 (43.8)	31 (44.9)
Moderate (11–16)	47 (32.2)	22 (31.9)
Severe (1–10)	35 (24.0)	16 (23.2)
Comorbidities, no. (%)		
Gastroduodenal ulcer	46 (31.5)[c]	20 (29.0)
Gastroesophageal reflex	17 (11.6)[c]	6 (8.7)
Zollinger–Ellison syndrome	19 (13.0)[c]	6 (8.7)
Barrett's esophagus	1 (0.7)	1 (1.4)
Mean ± SD phrenic nerve parameters		
DPNT > 1.0; no. (%) with values (AU)		
<1.67	65 (44.5)	28 (40.6)
1.67–2.07	50 (34.2)	18 (26.1)
>2.07	31 (21.2)	23 (33.3)

Abbreviations: AU, arbitrary units; DPNT, direct phrenic-nerve test.

[a] Intent-to-treat (ITT) population (N = 215): placebo (n = 69), spastex (n = 146); 2 subjects without follow-up data were excluded from all outcome analyses except for adverse events.

[b] Some percentages do not sum to 100 because of rounding.

[c] $p < 0.05$ by Fisher's exact test.

2.7 PUTTING IT ALL TOGETHER: A REPRESENTATIVE (FICTITIOUS) STUDY REPORT FOR A MULTISPECIALTY JOURNAL*

Effects of the anticholinergic agent spastex in patients with involuntary noisome hiccup syndrome: A randomized controlled trial in a naturalistic setting

INTRODUCTION

[1 DISEASE DEFINITIONS/EPIDEMIOLOGY:]

Involuntary noisome hiccup syndrome (INHS) is a neuromuscular disorder of the thoracic diaphragm. Also termed smelly hiccupping disorder (SHD), INHS represents the second-ranked cause of reduced quality of life among diners in Eastern European restaurants.[1–3] Noisy, fetid, and often frankly offensive hiccupping (often with purulent sialorrhea) is virtually pathognomonic for INHS.

[2 NORMAL PHYSIOLOGY:]

The diaphragm receives blood supply from branches of the internal thoracic, superior phrenic, lower internal intercostal, and inferior phrenic arteries. It is innervated mainly by the (cervical) phrenic nerve (C3, C4, C5).[4]

[3 DISEASE STATE: ETIOLOGY/NATURAL HISTORY/GENETICS:]

Smelly hiccupping disorder has a complex etiology. Potential causes result in slowed digestion and can be divided by their propensities to occur postprandially. Non–meal-related causes include gastroparesis, pyloric obstruction, and pregnancy, whereas meal-related causes include acid reflux, hiatal hernia, and hypochlorhydria potentially secondary to *Helicobacter pylori* infection.[5] Meal-related belching is especially frequent after patients consume heavily spiced Hungarian Gulyás (goulash) and more often becomes chronic. The disorder has an autosomal recessive inheritance pattern, with a carrier allele frequency of 0.04%.[6]

[4 IDENTIFY "GAPS" IN RESEARCH AND BUILD TO PROBLEM/THESIS STATEMENT/STUDY RATIONALE AND THE UNIQUE/INCREMENTAL VALUE OF THE STUDY AND ITS REPORT:]

Largely because of halitosis and embarrassment, most patients with INHS do not seek health care. It has been difficult to recruit them for clinical studies, and there are as yet no consensus practice guidelines to manage INHS. A *Cochrane Collaboration* review[7] found only three high-quality studies[8–10] supporting the clinical utility of anticholinergic medications in general[8,9] (and spastex hydrochloride [HCl] in particular[10]) in reducing the frequency and severity of INHS. Another study,[11] with a small and atypical sample population, found no significant difference between treatment with spastex and placebo (+ usual care [UC]). However, the overall unadjusted odds ratio (OR) was 0.78 ($p = 0.04$; 95% CI = 0.74–0.82) for the likelihood of audible diaphragmatic spasms across these four studies, which involved 288 patients receiving anticholinergic agents compared to placebo and/or UC (referent; OR = 1.0).

[5 THESIS STATEMENT AND OBJECTIVES:]

Because of the challenges in motivating individuals with INHS to seek medical attention, the present study uniquely assessed large numbers of subjects by examining them "in situ": within a Budapest restaurant serving heavily spiced Hungarian goulash to Eastern European families. The chief aim of this study was to determine if once-daily treatment with spastex could reduce the frequency and severity of hiccupping in an Eastern European population.

(*Continued*)

* This text of a hypothetical study report cites references and calls out graphics that would likely be part of an actual manuscript but are not included here, to keep the exercise brief.

(*Continued*)

METHODS

Study design and setting

This randomized double-blind placebo-controlled trial (RCT) was conducted in a reserved and temperature-controlled private room of the Budapest restaurant Éshpítészpince from April 1, to June 30, 2018.

Participants

Study candidates were recruited from five large Hungarian gastroenterologic practices but were not specifically compensated for participation (apart from free suppers at Éshpítészpince). Previously untreated patients with ≥2-year histories of noisy, loathsomely smelling hiccupping, before or after meals, with or without purulent sialorrhea, were eligible. Consistent with draft labeling for spastex, exclusion criteria comprised: patients who were ages 18–25 or >65; had ulcerative colitis, Crohn's disease, inflammatory bowel disease, or porphyria; or had renal or hepatic disorders. Also ineligible were pregnant women. Also excluded were patients with congenital INHS, Barrett's esophagus, certain neuromuscular disorders (e.g., myositis), and a history of hospitalization for disabling hiccups.

Ethics

The trial was conducted in accordance with Good Clinical Practices and ethical tenets originating in the Declaration of Helsinki. All study participants were explicitly apprised of the study's potential benefits and risks, then provided written informed consent before any study assessment or treatment. Both the informed-consent document and study protocol were reviewed and approved by local institutional review boards.

Interventions

Subjects were randomized 1:1 (by computerized block randomization) to receive spastex 1.0 mg or placebo (+ UC) once daily for 12 weeks.

Assessments and outcome measures

The primary efficacy outcome measure was change in the frequency of audible hiccups (by trained assessors posing as wait-staff) by each patient, assessed as number of audible hiccups within 3 hours after a standardized test meal, from baseline to week 12. The severity of belching was determined by assessor ratings of noise (secondary efficacy endpoint) and smell (tertiary efficacy endpoint), as graded on a scale from 0 (no noise or smell) to 10 (unbearable noise or smell). Decreases in these measures are compatible with reduced hiccup severity. According to prior field work in Eastern European populations,[12] the minimum clinically important difference (MCID) threshold for decreases in hourly hiccupping frequency associated with increased health-related quality of life (on the SF-36) is 25%. As an exploratory endpoint, we conducted a responder analysis to compare changes from baseline to week 12 in proportions of subjects experiencing a ≥25% (95% CI = 20%–30%) decrease in hiccupping frequency. Treatment adherence was assessed by pill count at week 12.

Safety and tolerability

Laboratory panels (chemistries, hematology), vital signs (pulse rate, blood pressure, body temperature, respiration rate), and 12-lead electrocardiograms (ECGs) were assessed at baseline and week 12.

(*Continued*)

(*Continued*)

Any adverse events (AEs) were elicited at each study visit using open-ended questioning and categorized by preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA 17.1). The study design and timeline are depicted in Figure 1 (study schema).

Statistical methods

Baseline characteristics were designated as continuous (mean ± standard deviation [SD]) or categorical (number, %) variables. Intergroup differences in baseline characteristics were assessed using Fisher's Exact Test.

For inferential statistics concerning efficacy endpoints, we put forth three null hypotheses (NHs): H_{0a}: There is no significant difference in changes in hiccupping frequency (H_{0a}), subjective ratings of noise (H_{0b}), or subjective ratings of smell (H_{0c}) from baseline to week 12 in patients randomized to once-daily spastex or placebo for 12 weeks. Alternative hypotheses were that there were significant changes on active treatment compared to placebo.

Previous studies[13–15] documented that frequencies of hiccupping are normally distributed. Mean (± SD) changes in hourly hiccup counts from baseline to week 12 in the actively treated and control groups (primary endpoint) were compared using Student's *t*-tests.

Hiccupping severity data are asymmetrically distributed because many patients who have INHS with predominant purulent sialorrhea have less noisy and smelly belches; median severity is greater than the mean. Hence, intergroup comparisons for changes in assessors' ratings of noise (secondary endpoint) and smell (tertiary endpoint) from baseline to week 12 were conducted using Mann–Whitney's U Test. The exploratory efficacy endpoint was evaluated using a χ^2 test.

No RCT of pharmacotherapies in untreated patients has been conducted, largely precluding sample size calculations in the present trial. Efficacy analyses were conducted in both the intent-to-treat (ITT) population (subjects randomized to either treatment) and per-protocol population (subjects who completed the protocol without violations). Safety analyses were conducted in subjects who received at least one dose of active treatment or placebo. All statistical tests were two-tailed at $\alpha = 0.05$. Statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition

A total of 108 study candidates were screened, 100 (92.6%) randomized, and 90 (90%) completed the protocol (45 in each group; Figure 2). [CONSORT patient flow diagram.[33]]

Baseline characteristics

Sociodemographic and clinical characteristics were well balanced in the two treatment groups at baseline (Table 1).

Efficacy

Treatment with spastex significantly reduced 3-hour hiccup counts from baseline to week 12. The mean (SD) change was −11.2 ± 1.1 in the spastex group compared to +0.8 ± 0.2 in the control group ($p = 0.024$ by Student's *t*-test; Table 2). However, reductions in hiccupping severity (ratings of noise and smell) did not differ significantly between groups (Table 2).

(*Continued*)

(*Continued*)

Significantly higher proportions of subjects in the spastex (vs. control) group experienced ≥25% reductions in hiccupping frequency (Figure 3). For all endpoints, findings in the per-protocol population were similar to those in the ITT population. Treatment adherence was similar in the actively treated (79%) and placebo (82%) groups.

Tolerability and safety

The most frequent AE was dyspepsia, but no single AE occurred in ≥5% of subjects in either group (Table 3).

There were no clinically significant differences between groups in mean frequencies of abnormal laboratory results, vital signs, or ECGs. A single subject (in the placebo + UC group) experienced a serious adverse event at the baseline assessment, after consuming his meal: emesis and diarrhea requiring hospitalization. A fecal culture returned *Clostridium perfringens*, but triplicate immunologic fecal occult blood tests were negative. After rehydration and rest, the patient recovered within 36 hours and completed the study protocol. The investigator considered the event to be unrelated to study treatment.

DISCUSSION

For the first time to our knowledge, we conducted a trial in a controlled yet naturalistic setting to determine whether daily treatment with the investigational oral anticholinergic agent spastex significantly reduces the frequency of hiccupping (vs. placebo + UC) in previously untreated patients with INHS. Significantly higher proportions of actively treated (vs. control) subjects achieved ≥25% decreases from baseline in hiccupping frequency, an emerging MCID threshold.

The severity of hiccupping, by subjective assessment of noise and smell, was not significantly decreased by spastex (vs. placebo + UC) from baseline to week 12. One potential reason for this somewhat unexpected finding is that measures of noise and smell on the 11-point rating scale varied widely in all subjects both at baseline (SD for noise = 4.3; SD for smell = 3.6) and 12 weeks (SD for noise = 5.2; SD for smell = 4.1). In fact, even in the relatively controlled setting of a private room, Éshpítészpince is a busy and noisy eatery redolent of spices. Baseline values of Cronbach's α (0.34 for noise and 0.18 for smell) and the more recently developed ω coefficient[16,34] (corresponding values of 0.36 and 0.20) for reliability of ratings were low. We hope that the overall favorable experience reported by our subjects in this study will enable other investigators to examine hiccupping severity under more controlled settings better suited to discriminate noise and smell, ideally by more objective methods.

During the 12 weeks of this study, no safety or tolerability issues were identified. The leading AE (dyspepsia) was likely attributable to off-target (extradiaphragmatic) effects. However, certain patients with higher susceptibility to anticholinergic effects were excluded; many of these individuals had congenital INHS and/or received treatment with atropine, phenothiazines, or antispasmodics. Our study was also underpowered to discern infrequent (<1/100 to <1/1,000) adverse events, such as lower-limb paralysis, which has been observed in some Eastern European patients with INHS dining frequently in Budapest eateries. This phenomenon was observed mainly in the 1990s and was ascribed to the unscrupulous practice of restaurateurs who spiked their paprika with lead oxide to enhance the spice's color.

Many patients with INHS are embarrassed and halitotic, and hence do not seek medical attention, let alone volunteer for clinical trials. Only four high-quality trials have been conducted in patients with INHS; findings from three were broadly consistent with our results,[8–10] whereas data

(*Continued*)

(*Continued*)

from the fourth did not include hypothesis testing.[11] This last study's population included an arguably more difficult-to-treat population, with a higher mean age, median number of comorbidities and concomitant medications, and mean frequency of congenital INHS.

POTENTIAL STUDY STRENGTHS AND LIMITATIONS

A unique strength of our trial was its RCT design, which largely excludes biases. At the same time, our study was pragmatically executed in a naturalistic setting, which promotes ecological validity and generalizability of the findings to actual social settings in which patients are often troubled by their signs and symptoms. The fact that we were able to randomize 100/108 (93%) study candidates—of whom 90 (90%) completed protocol—attests to the acceptability of the experimental paradigm to the subjects.

A high degree of error in subjective ratings of the noise and smell associated with study participants' hiccups may have limited the precision of severity assessments. Our study did not assess effects of INHS on those most adversely affected, apart from patients: their loved ones. We have fielded a new subjective rating scale (NO–MO–BURPS–PLS) to evaluate such effects.[17] These individuals may be better able to discriminate changes in levels of noise and smell associated with their loved ones' hiccups compared to highly educated and trained study personnel who were unacquainted with subjects. Our eligibility criteria were also somewhat stringent, resulting in a relatively homogeneous sample population. Finally, the duration of the present study was only 12 weeks, arguably too short an observation window to discern intertreatment differences in adverse events and safety signals occurring in <1/100 to <1/1,000 subjects. The long-term safety and tolerability profiles of spastex are being evaluated in a 52-week extension study (NCT # 108Σ984; available at www.clinicaltrials.gov).

CONCLUSIONS

For the first time in both a controlled and naturalistic experimental setting, this study demonstrated that once-daily treatment with the investigational oral anticholinergic agent spastex significantly reduced the frequency of hiccupping compared to placebo (+UC) from baseline to 12 weeks. Future studies, in larger and more heterogeneous sample populations, are needed to reject, corroborate, or extend our findings. An ongoing 52-week extension study, which is being conducted by our group (NCT # 108Σ984), should provide complementary long-term safety and tolerability findings.

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APPENDIX: "DICTION-ERR-Y"—A GUIDE TO BETTER USAGE

"Diction-Err-Y": Of "plural effusions" and other peculiarities of medical writing's "singular" syntax and semantics

IUVIF: Infrequently used verbs that I favor (often to introduce greater rhetorical variety).

FUVIA: Frequently used verbs that I abhor (when overused).

Abate: IUVIF. What transient effects do with time or continued treatment.

Accident: This term may be imprecise or misleading. What is usually meant? Injury, trauma, shooting, or collision.

Do not use "cerebrovascular accident" to mean stroke. Stroke is preventable and not an accident. Prefer cerebrovascular incident (CVI).

Acquaint: IUVIF, e.g.,

This review will acquaint the reader with emerging diagnostic methods.

Acronyms vs. abbreviations: Acronyms are abbreviations that spell words (or easily spoken "quasi-words"). AIDS, CONSORT, NASA, RANKL, and SARS are examples. All others (e.g., MI, NIDDM) are just abbreviations. All acronyms are abbreviations, but not vice versa; being an abbreviation is a necessary but not sufficient condition of being an acronym. If permitted by the targeted journal, include a list of abbreviations and acronyms at the front of your manuscript. Try not to exceed a 0.5% abbreviation: text ratio (e.g., ≤10 abbreviations in a 2,000-word paper). Define/expand all abbreviations in tables and figures, even if they have been defined in the text. Tables and figures need to function as discrete/self-contained units of meaning for readers who apprehend most or all information from graphics.

Active voice; Use, misuse: Most journals encourage you to use passive voice, which has a solid foundation in medical writing. To encourage sentence variety and reader interest, however, I advocate that you introduce active voice when you can. Do it carefully, however, maintaining parallel structure and subject-predicate agreement.

Not:

After controlling for covariates, women were more likely than men of all ages to respond to β-blockers.

But:

After controlling for covariates, we found that women were more likely than men of all ages to respond to β-blockers.

Acute, chronic: These terms describe diseases or conditions, not treatments. Treatment may be longterm but not chronic; urgent but not acute. In at least two major disorders, the term "acute" has a specific physiologic definition not completely encompassed by its meaning of "short-term": "acute abdomen" refers to severe abdominal pain within 24 hours that has an unclear etiology, with a differential diagnosis that includes abdominal aortic aneurysm, appendicitis, pyelonephritis, pancreatitis, cholecystitis, diverticulitis, ovarian torsion, ectopic pregnancy, and ischemia. A more precise term in some cases is acute peritonitis, which results from infection of the peritoneal lining of the abdominal cavity. "Acute coronary syndromes" refer to cardiovascular conditions associated with acute myocardial ischemia, including 12-lead electrocardiographic ST-segment-elevation myocardial infarction (STEMI).

Additionally: PLEASE AVOID. PLEASE?! For example, "Additionally, we reviewed study report data." Additionally? As opposed to "Subtractionally?" Ditto "Hopefully, I will write a sound paper" (unless you are filled with hope). "Historically, elders have received suboptimal care," and others.

In general, be leery of connecting introductory modifiers such as "Moreover" and "Further." If one sentence or paragraph flows organically from the last, these "verbal crutches" are not only unnecessary but potentially distracting. "On the other hand," use an expression such as this one (or "However") to mark a departure in logic from the previous sentence or paragraph.

***Ad libitum*:** (or *Ad lib*) At liberty, freely, at one's pleasure, as much as desired.

Laboratory animals drank water *ad libitum*.

Adverbs vs. conjoined adjectives:

Don't hyphenate adverbs (which modify the verb "to be"):

Thank you, waiter; this steak is well done. [*correct, no hyphen*]

Conjoined adjectives (two words modifying a noun) do require a hyphen:

Waiter, please bring me a well-done steak.

Never hyphenate an adverbial ("-ly") construction. Hyphenate only conjoined adjectives.

This is a smoothly flowing sentence.

Not:

Smoothly flowing sentences drive any argument.

But:

Enjoy your hard-earned paycheck [*conjoined adjective requires hyphen*].

Having perused many of my reviews, my readers are well informed [*adverb does not require hyphen*].

Not:

Having perused many of Gutkin's reviews, our readers are well-informed.

But:

Gutkin's reviews have built a well-informed readership.

Involuntary noisome hiccupping syndrome has an adverse effect on well-being.

[***Stet the hyphen because it appears this way in the dictionary.***]

***Ad vitam*:** For life.

Attempt to optimize treatment adherence because the medications will be taken *ad vitam*.

Affect/effect: Affect (n.): the patient with major depression often has a flat affect.

> **Affect (v.):** to influence. Treatment affected disease incidence.
>
> **Effect (n.):** One adverse effect of treatment was rash.
>
> **Effect (v.):** Treatment effected a favorable outcome.

Age referents: Seniors, elders, or the elderly are ≥65 years of age.

Adults (men, women) are ≥18.

Adolescents are 12 to 17 years of age.

Children (not "pediatric patients") are below the age of 18 or 21 (depending on location/society) years, infants 5 weeks to 1 year; and neonates (newborns) birth to 4 to 5 weeks. Toddlers are 1 to 3 years of age and preschoolers 3 to 5.

Agreement: Subject-predicate disagreement often occurs in medical writing because of the high frequency of intervening phrases and shifts in voice from plural to individual (and back!); only in our field could I coin the term "plural effusion" to characterize these defects.

Not:

The rising incidence of stroke, congestive heart failure, and end-stage renal disease has signalled a need to increase awareness and treatment of hypertension. [***Unless you mean that the incidence of the combined outcome of stroke, CHF, and ESRD, in which case the sentence should specify "incidence of the combined outcome of…"***]

But:

The rising incidences of stroke, congestive heart failure, and end-stage renal disease have signalled a need to increase awareness and treatment of hypertension.

Introduction of nonrestrictive clauses, which add information but do not define or limit their antecedents, does not change the number of the subject, e.g.,

The patient, together with his partner, is capable of making a decision about ED therapy.

And:

The patient and his partner are capable of making a decision about ED therapy.

Difficulty with gender issues often can be resolved by switching from a singular to plural subject.

Physicians must make up their own minds.

Or:

A physician must make up her own mind.

Not:

A physician must make up his or her own mind. [***grammatically correct but unwieldy***].

However, indiscriminately rendering plural subjects that would be better handled as singular can also create distracting connotations (even if strictly correct).

Each patient with ED and his wife gave informed consent.

Not:

Patients with ED and their wife gave informed consent.

Aim (n., not v.): Typically use as a noun but not a verb.

Our aim was to evaluate anti-inflammatory effects.

Not:

We aimed to evaluate anti-inflammatory effects.

All: ≠ each.

Compared to patients treated by FPs, those receiving care from specialists had significantly lower frequencies of emergency-department visits (22% vs. 87%), hospital admissions (10% vs. 38%), and durable-equipment use ($p < 0.05$ for <u>each</u>).

[$p < 0.05$ for "all" would imply that endpoints were combined or that the test was for the overall trend.]

Alleviate vs. ameliorate: The verb "alleviate" means to lessen or relieve.

"Ameliorate" signifies improvement.

Treatment with spastex alleviated symptoms of involuntary noisome hiccup syndrome (INHS).

Not:

Treatment with spastex ameliorated symptoms of INHS.

But:

Treatment with spastex ameliorated diaphragmatic function in patients with INHS.

Also: Also frowned upon is the use of "Also, (with a comma)" as an adverbial at the head of a sentence. The use of "Also" (without a comma) in the prior sentence is the only permissible exception.

Although: Use at the head of a sentence to introduce a subordinate clause.

Not:

I have never received a speeding ticket, although I typically drive my Ferrari at 154 mph.

But:

Although I typically drive my Ferrari at 154 mph, I have never received a speeding ticket.

Amenable: For example, "amenable to treatment" is an antonym of "refractory to treatment." Both are IUVIFs!

Among: For comparisons involving more than two entities (between is suitable only for two entities).

Among patients with impaired glucose tolerance, losing weight is frequently recommended.

Amongst: Archaic (avoid). Others include "proven" (in the sense of "this study has proven" but not in the sense of "this medication has proven benefits in elderly patients") and "towards."

Ampersand: Prefer "and" to &. Exceptions include company names and certain medical terms, such as D&C, H&P, and H&E.

Anatomic terms, implied: Be sensitive to possibly distracting medical connotations of otherwise commonplace modifiers.

Not:

Undergoing <u>knee</u> replacement should be a <u>joint</u> decision of the surgeon and patient.

[The word "joint" is distracting in this context.]

Patients with <u>rotator-cuff</u> injury in the active treatment <u>arm</u> received the new device.

[The word "arm" is distracting in this context.]

and/or: Think carefully about whether you mean "and," "or," or "and/or." Frequently, "or" will suffice.

About 10% of patients randomized to spastex 5 mg or phragoph 50 mg experienced treatment-emergent dizziness.

or

Use of nitrates or nitric oxide donors contraindicates spastex treatment.

Spastex treatment may improve quality of life for the patient and/or his caregiver.

Appraise: IUVIF.

Apt/liable: In most cases, prefer "likely" as a more neutral descriptor.

As (≠ because): "As" has a time connotation. (So does "since," which should not be substituted for "because," and "while," which should not be substituted for "whereas.")

Not:

Please confirm the veracity of this statement as the backup patient listing differs. *[This may take some fortunate "timing!"]*

***But*:**

Please confirm the veracity of this statement because the backup patient listing differs. [*This usage is time neutral*.]

As (vs. so): "As" is used for positive comparisons, "so" for negative ones.

Warfarin is as effective as LMWHs in preventing DVT in elderly ACS patients.

Or:

Esteemed Professor Eliot Bookbinder was not so patient as to indulge questions from uninformed students.

Ascribe: IUVIF for "attribute."

Assent: Adults give informed consent; children/minors, verbal assent.

Assure: ≠ ensure. "Ensure" is a neutral term meaning "to make certain." "Assure" carries a psychological connotation ("the physician assured his patient that the injection would not hurt"). Insure is restricted to the meaning of indemnifying against loss.

As though: See "like."

Attend, attended: ≠ "seen." A patient is attended by a physician. This involves much more than "being eyeballed." ("Seen" is also jargony.)

Back formations: Avoid.

Because of hypervolemia, diuresis was instituted. Patients who received surgery fared better.

Not:

The patient was diuresed due to [*this is also wrong usage of "due to," which needs to follow the verb "to be"*] to hypervolemia.

The operated group fared better.

Based on: Avoid at the head of sentence. Substitute "On the basis of" in most instances.

On the basis of these findings, the MIRACLE investigators concluded that biventricular pacing enhances survival in heart failure patients with low ejection fractions.

Not:

Based on these findings, the MIRACLE investigators concluded that biventricular pacing enhances survival in heart failure patients with low ejection fractions. *[How can the "MIRACLE investigators" be "based on" anything?]*

Because: Not synonymous with "since," which has a time connotation.

Because of: Substitute this for "due to" or "since" when causal attribution is intended.

Before: One word versus "prior to" (two words) or "in advance of" (three)!

"Borderline-significant": Avoid. A p value is either below its prespecified critical value (usually < 0.05) or it is not. This type of phrase amounts to a "statistical apology." Instead, simply report p values and confidence intervals, and allow the reader to judge.

Breastfeed: ≠ the verb "nurse" (i.e., connotation of RN, NP).

Bullet points: Useful to augment reader apprehension of data, especially when clauses are "buried" in longer sentences.

Burning: Unless we actually imply a scalding, we typically mean "a burning sensation."

Can: Preferred over the wordy "has the potential to," "has the capacity to," or "has the ability to."

Cause: IUVIFs:

- Elicit
- Induce
- Precipitate
- Prompt
- Spawn
- Trigger

FUVIA: "Produce"

Center around: Sorry, no. Something "centers on" or "revolves around" but does not "center around."

Claudicant: A patient with intermittent claudication.

Clinician: Person who works in clinics, not just a physician (e.g., RN, NP, PA).

Comparable: ≠ "similar." In its strict sense, comparable means "able to be compared." Virtually any two entities are "comparable." Vexed by "apples-to-oranges" comparisons? Why? Both are fruits. Both are nutritious and promote digestive health. Both grow on trees.

Ergo, totally comparable, though not entirely similar!

Compared with: "Compared with" or "compared to" is acceptable. If a sentence is short (<15 words), use "than"; if longer, use "compared to" or "as/when compared to."

It is often preferable to use "compared to" in order to avoid repetition of the word "with" in the same sentence.

On average, men with below-normal dihydrotestosterone levels grew significantly more new hair on the vertex compared to their counterparts with elevated DHT. ***[Writing "to" here avoids triplicate use of "with" in same sentence.]***

Comprise/compose: Groups either *comprise* their elements or are *composed of* them; they are not "comprised of" them.

Concur: One concurs *in* an opinion or *with* another person (not *vice versa*).

Conduct: IUVIF. Studies, electrocardiography, and laboratory analyses are "conducted" (also "performed," or "carried out").

Confer [to/on]: IUVIF.

Confidence interval/CI: Because CIs may contain negative values, and both the "minus" sign and range symbol can be 1/N dashes, there are different styles for CIs.

For intervals with positive values: The odds ratio was 4.9 (95% CI, 3.8–6.1).

For intervals with negative values: The treatment effect was 0.2% (95% CI, –0.1%, 0.3% or –0.1% to 0.3%).

Comparisons: If one of the items being compared already has the word "with," use "compared to" or "as against" (British). It often works out nicely to start a sentence with "Compared to."

Examples:

> **Patients with metabolic syndrome are, on average, at higher risk of adverse cardiovascular events compared to their age-matched counterparts.**

Consolidate words using short parentheses to set off data in the correct location within sentences:

> **Compared to placebo (12%), drug Y enabled a significantly higher proportion of patients to achieve goal (48%; p<0.001).**

Comport (with): IUVIF.

The data do not comport with the prevailing biological theory.

Others: The data are not "compatible" or "concordant" with prevailing biological theory. Commensurate has a slightly different meaning:

Salary for either gender should be commensurate with experience.

Conjoined adjectives: Adjectives comprising more than one word often need to be hyphenated, e.g.,

The late Charles Janeway was well informed [*not "well-informed"*] about immune effector cell mechanisms. It was difficult to find someone better informed.

Or:

To learn more about immune effector cells in the aftermath of Janeway's passing, we will now need to consult other well-informed scientists.

and

drug-induced effects

not

drug induced effects (*which has a vastly different meaning!*)

The medication was well tolerated; it was a well-tolerated medication.

Controlled: Diseases, not patients, are "controlled" or "managed" ("cases" are also managed). Avoid such dehumanizing language.

Currently: ≠ "presently" (which means "soon"). "At present" is also OK.

Dashes:

em (1/M) dash: Don't overuse. Strive to keep clauses within these dashes (and parentheses) short (<10 words). Sentences with unwieldy clauses enclosed in (1/M) dashes often need to be recast as two (or more) sentences.

en (1/N) dash: Use with unequally weighted three-term conjoined adjectives. Non–insulin-dependent diabetes.

But:

very low density lipoprotein cholesterol

Negative symbols and ranges (in parentheses) are expressed using en dashes, not hyphens.

Data: Data *are* plural; *datum* is singular. Alt.: findings.

These data need to be confirmed in a RCT.

Not:

This data needs to be confirmed in a RCT.

Decrease: IUVIFs:

Attenuate

Downregulate

Lessen

Lower

Note: "diminish" ≠ "decrease."

Diminish has a non-numeric/subjective connotation:

Stroke survivors report diminished self-esteem.

or

The death of any patient diminishes morale on the entire ward.

not

Treatment with losartan diminishes blood pressure in patients with hypertension.

Dehumanizing: Patients should not be defined by their diseases, ages, or other clinical data. Diseases and cases are managed, not patients.

Children and adolescents (or "youngsters") provided verbal assent rather than written informed consent.

Not:

Pediatric patients provided verbal assent rather than written informed consent.

Patients with diabetes and hypertension were randomized to intensive therapy.

Not:

Diabetes and hypertension patients were randomized to intensive therapy.

Or (even worse!):

Diabetics and hypertensives were randomized to intensive therapy.

Patients also do not "fail to achieve" or attain certain potentially disease-reducing cut points. After all, is the failure all theirs, or does the health-care system not deserve to shoulder some of the "failure?"

Not:

Despite intensive therapy with medications from three pharmacological classes, the patient failed to achieve JNC-V target blood pressure.

But:

Despite intensive therapy with medications from three pharmacological classes, the patient's blood pressure remained above the JNC-V target.

I also object to the term "treatment-naïve" or, worse, just "naïve." Patients either have or have not been treated.

In most instances, you can substitute "untreated" (or unexposed) for "naïve."

Demonstrated/demonstrable/documented (*argumentative*): Clinical trials test hypotheses and address research questions. They are not designed *a priori* to "demonstrate" or "document" anything. However, if these terms must be used, please observe the following.

Clinical trials of medications, not the medications themselves, demonstrate effects. Hence:

Clinical trials have demonstrated the efficacy of antisense agents.

not

Antisense agents have demonstrated efficacy in clinical trials.

However, an agent may have "demonstrable" efficacy or effectiveness on the basis of clinical trials or experience.

Denote: IUVIF. Also: "signify." Strict definition, as opposed to "connote."

Depressor: Adjective. Blood pressure–lowering. Antonym is "pressor."

Despite (or, worse, in spite of) the fact that: Use "even though" or "although." "Despite the fact that" is wordy (four words vs. one or two).

Determined: Sometimes this verb is combined with forms of the verb "to be," in a passive construction that is not only wordy but also distracting:

Not:

> **The mean systolic pressor effect of aerobic exercise in the placebo group was determined to be +5.8 mmHg.**
>
> ***[There is no stopping that pressor effect when it is "determined to be" +5.8 mmHg!]***

But:

> **The mean systolic pressor effect of aerobic exercise in the placebo group was +5.8 mmHg.**

***df*:** Degrees of freedom; no need to expand this abbreviation, SD, or SE (and certain other oft-used abbreviations, e.g., DNA, RNA).

Diabetes: I prefer type 2 (with "mellitus" at first mention only; DM2) over non–insulin-dependent (NIDDM), which defines the condition by what it isn't.

"Diabetic" (n.) and other objectionable (dehumanizing) labels: Use "patient with diabetes" rather than "diabetic" per American Diabetes Association. Ditto "asthmatic," "epileptic," and "hypertensive." People are not defined by their health problems. They also should not be referred to as "cases" unless you intend the limited statistical sense (e.g., number of "incident cases"). Diseases, not patients with these diseases, are managed. Other dehumanizers include "patients on a drug" rather than "patients using [or taking] a drug."

Diagnose: Diagnose a condition, not a patient; the patient is evaluated or examined.

Disclose: IUVIF.

Discrete vs. discreet: "Discrete" means "independent" or "separate." "Discreet" signifies a sense of care or caution.

Different: One effect may be "different from" another but is not "different than" it. UK usage permits both similar and different "to."

Disinterested: A disinterested party is impartial. Someone without interest is uninterested. If you're quite uninterested in this, you may not be disinterested.

Document: Never use this verb (or "well documented") without citing references! As a noun, this is an imprecise term for which article, study report, case series, or other names of communications should be substituted.

Argumentative. As mentioned above, I have encountered published articles referring to a study's aim being to "document" effects of a medication. Remember, the prospective aim of a study is typically to test hypotheses or address research questions, not to "document" anything. Testing hypotheses is in the appropriate, fair-balanced province of "clinical equipoise," whereas documenting findings or conclusions reaches into the dangerous realm of deductive argument. In hindsight, however, we can say that a study "documented" effects.

Double verbs (*"pseudoprofoundly passive" clutter*):

Not:

> **Sound interpretation of data can be achieved when all observations are independent. *[12 words]***

But:

> **Data can be interpreted soundly when all observations are independent. *[10 words]***

Due to: Can be used as an adverb, typically after the verb "to be." However, it should not be used in other instances because it implies a false modification. In most cases, substitute "because of" or "owing to."

> **Cough is largely due to the effects of ACE inhibitors on kinin levels.**

Not:

> **Due to patient attrition, the ITT population was larger than the evaluable population. *[Was the ITT population "due to" patient attrition?" No.]***

But:

> **Because of patient attrition, the ITT population was larger than the evaluable population.**

and:

> **Coughs due to cold can be managed using OTC medications.**

"Due to" is often used in the same lazy manner as "which" (see below):

Not:

Epidemiologic data such as the point prevalence of dyspepsia are difficult to interpret due to heterogeneity between studies and, particularly, differences in disease definitions. *[The phrase "due to" "floats" without an immediately identifiable antecedent.]*

But:

Epidemiologic data such as the point prevalence of dyspepsia are difficult to interpret because of heterogeneity between studies and, particularly, differences in disease definitions.

The other permissible use of "due to" is outside of the realm of "to be" verbs. In a sentence such as "Coughs due to cold are manageable": "due to" is acceptable because it is functioning as an adverb modifying the verb "to be": Coughs that are due to cold….

Echo: IUVIF. To signify agreement of data or opinions.

Echoing data from previous trials, the present study demonstrated that C-reactive protein is a reliable risk marker for inflammatory disease.

Editorializing: Do not "spin" data.

Rhabdomyolysis occurred in 0.1% of patients.

Not:

Rhabdomyolysis occurred in only 0.1% of patients.

Effects (title): Be careful when using this term to summarize study results. If a study is observational, the results are typically of an associational, not causal, nature; in this setting, the term "effects" may be inappropriate and warrant replacement with more "associational" language.

e.g., i.e., etc.: *exempli gratia, id est, et cetera*

Each should be enclosed in parentheses and separated by a comma (not the word "and"). Never use "etc." if the remaining/implied conditions are not clearly understood. Use "e.g.," "i.e.," and "etc." only in short parentheticals. Never combine "e.g.," and "etc.," in the same parenthesis.

Examples follow.

We treated patients with upper-airway inflammatory diseases (e.g., PAR).

Or:

The results were consistent across sexes (i.e., male, female).

Not:

We evaluated reproductive-tract inflammatory conditions (e.g., PID, etc.).

Not:

We treated patients who had chronic illnesses (e.g., major depressive disorder consistent with the definition established by the Diagnostic and Statistical Manual [DSM IV] and not by the American Psychiatric Association [APA], which is subject to industry bias). [*This parenthesis is much too long and needs to be recast as a separate sentence.*]

Ellipses: Omitting a verb (often of the infinitive "to be") where it is understood in a series is fine if the subject of the verb does not change.

The diagnosis was established and intervention [was] instituted.

And:

Tests were performed and the results [were] noted in the chart.

Not:

Tests were performed and the report updated. (*The word "report" is singular; hence it requires the singular verb "was."*)

Endpoint: Used chiefly to signify an outcome measure. If you are using this term to signify the date of completion of a study, it is preferable to state:

The present study was conducted from August 11, 2010 (first patient enrolled) to August 10, 2011 (last patient follow-up visit).

Not

The endpoint of the present study was August 10, 2011. *[Distracting by connotation of "endpoint" to "outcome measure."]*

Epidemic: A condition that affects many persons in a defined area and is temporary or time limited is an epidemic. A pandemic spans more than one geographic region (e.g., continent).

Be careful not to overuse. For example, some journal peer reviewers object to statements such as "Because of the growing diabetes epidemic [or pandemic]…." These are not true epidemics/pandemics. In most settings of evidence-based study reports, restrict the use of these words to their intended, infectious-disease contexts.

Eponyms: Use the singular together with a brief parenthetical descriptor, such as:

Turner syndrome (gonadal dysgenesis)

Oppenheim disease (amyotonia congenita)

Follow contemporary standard usage (journal or other style guides) for use of possessive.

The patient developed Parkinson's disease at the age of 61.

Or:

The patient developed parkinsonian signs and symptoms at the age of 61.

Not

The patient developed Parkinsonian signs and symptoms at the age of 61.

Eskimo: Unacceptable racial designation (by analogy to American Indian, which should be replaced with Native American). Substitute "Alaska Native," "Aleut," or "Inuit" (as appropriate).

Etiology: ≠ "cause." Etiology is the study or overall perspective on causes.

Sternutation (sneezing) has a complex etiology.

Not

The etiology of sternutation is antigen-induced irritation of the mucous membranes lining the nose and throat.

***Ex ante*:** Literally "before the event": based on or referring to predictions rather than actual data.

Exculpate: IUVIF. Antonyms = impugn, inculpate.

Follow: Patients are observed or monitored, not "followed." Cases and clinical courses are followed. Avoid patient and reader paranoia.

Following: If you mean "after," use "after." And you usually do mean "after" unless something is truly being followed, in a spatial rather than temporal sense. See also "prior to" (before).

For: Often sets up wordy or passive expressions. As an example, see the text below, from a major consensus guideline concerning manuscript preparation:

Not:

Describe any methods for inferring genotypes or haplotypes.

But:

Describe any methods to infer genotypes and haplotypes.

Fore (overused): Even nongolfers understand that the expression "fore" alerts those ahead of a player that an errant ball is on its way.

"Fore" as a prefix relates to events in the future, e.g., "forewarned is forearmed."

However, the correct spellings of other similar words that have the sense of "doing without" rather than a future event do not include the "e." Examples include "forbear" (verb), "forfeit," "forgo," "forsake," and "forswear."

***Forme fruste*:** An attenuated or atypical disease manifestation.

Antonym is *forme pleine*.

Foster: IUVIF. Others: facilitate, promote.

Gave (provided) the ability to: Allowed or enabled.

Gender: Don't overuse the terms *male* and *female*. Substitute the age-appropriate terms for "male patient" and "female patient," i.e., men and women (≥18 years old) or girls and boys (or youngsters) if ages <18.

Gerund/participle: Use "ing" expressions to economize words. Be careful, because these may set up run-on sentences:

Write the journal requesting an investigation into ethical issues related to a submitted or published manuscript.

[Who is doing the requesting, the person being directed by this sentence, or the journal?]

Greek symbols: Generally, use Greek symbols for generic scientific concepts but not in proper nouns (e.g., drug names). Examples follow.

There is no convincing evidence to support first-line use of β-adrenoceptor blockers [*at first mention; "β-blockers" thereafter*] to manage uncomplicated hypertension.

Statistical significance was computed at a two-sided $\alpha = 0.05$.

But not:

Patients with hepatitis C were randomized to placebo or interferon-2-α *[Should be "alfa" as a proper noun (drug name).]*

Or:

Some patients with respiratory diseases are eligible for treatment with β-methasone. ***[Should be "betamethasone."]***

Has been shown [demonstrated] to: Redundant at worst, wordy at best; delete if you are citing references and use only if you are not or cannot (e.g., in an abstract).

Bivalirudin is an effective and well-tolerated treatment for acute coronary syndromes.[1–4] (Hypothetical references, here and below.)

Or:

Studies have shown that bivalirudin is an effective and well-tolerated treatment for acute coronary syndromes. ***[In the abstract, where references cannot be cited.]***

Not:

Bivalirudin has been shown to be an effective and well-tolerated treatment for acute coronary syndromes.[1–4]

Has the ability to; has the capacity to: Can.

Healthily vs. healthfully: Only a patient is healthy. His or her diet or other regimen may be healthful, in the sense of promoting health, but not healthy.

Heart/kidney/liver failure: A patient is encountered "in" (not "with") heart (cardiac), kidney (renal), or liver (hepatic) failure.

Homogeneous: Don't forget that second "e." People often write or say "homogenous" (*does it have something to do with milk?*).

Hyphen vs. dash: Most prefixes, including "non," "de," "co," "post," "anti," "ultra," "under," and "over" should not be hyphenated unless the same letter follows.

A hyphen is not the same as a "minus" sign. The minus sign is a (1/N) dash (–), which you access from the "symbols" tool in MS Word.

Never hyphenate an adverbial: a "highly publicized study," never a "highly publicized study." See also conjoined adjectives. Use (1/N) dashes to express ranges or to "weight" a conjoined adjective (e.g., "non–drug-dependent," "obsessive-compulsive–like symptoms").

Hyphenate if failing to do so leads to an unintended meaning:

> **Our management approach given these symptoms was to re-treat.** ***[Not "retreat"]***
>
> **Given the major salary increase and many fringe benefits in the new contract, I decided to re-sign.** ***[Not "resign"]***
>
> **A lesion may form and "re-form."** ***[Not "reform"]***

Remember also that you can be "detail oriented" (not "detail-oriented") in the adverbial sense, or a "detail-oriented person" in the conjoined adjectival sense.

Avoid lengthy clauses enclosed by (1/M) dashes (or parentheses).

Use a 1/N dash if more than word is modifying another (even when abbreviated):

Nitric oxide–mediated vasodilation reduces total peripheral resistance.

NO–mediated vasodilation reduces total peripheral resistance.

(See also "Dashes," page 105.)

Impart: IUVIF (also: confer [to]).

Imperatives: Avoid expressions such as "the physician should [can]." These read as "preachy" or condescending. Rephrase in passive voice if possible.

Imply/infer: The writer or speaker implies. The audience or reader infers.

Impugn: IUVIF. Synonym = inculpate; antonym = exculpate.

The close temporal association with serious adverse events impugned [inculpated] active treatment as a cause.

Improve (ameliorate) the quality of: Redundant/wordy. Improve or ameliorate means to increase the quality. One can "increase the quality" but not "improve the quality."

Indeed: "A friend in need is a friend indeed." I object to beginning many sentences with "Indeed." Doing so may represent a verbal crutch and a facile attempt to confer "gravitas." Avoid.

Including: Use a comma before if introducing a list.

Increase: IUVIF (depending on context):

> Augment
>
> Elevate
>
> Heighten
>
> Potentiate
>
> Raise
>
> Upregulate

Inculpate: IUVIF. Antonym: "exculpate." Synonym "impugn."

Infinitives, split: Strive to avoid them and not to promote their use.

Inflate (or exaggerate): IUVIF to reduce words compared to, e.g., "bias may have spuriously elevated our estimates."

In order to: Use just "to" in most cases. Use "in order to" if "to" is used earlier in the sentence and there is no way to avoid having a second "to" in the sentence.

Institute: IUVIF. Treatment, therapy, or care is instituted. For example,

In the event of rhabdomyolysis, institute mannitol diuresis.

Insuperable attributes: Each of the following uses is incorrect because the adjectives are categorical rather than continuous in nature (present or absent but not different degrees):

We sat in a perfect circle.

This trial had a very [most] unique design.

Intended: Be careful. Use of this modifier may imply that an objective was established but not met.

Interrogate: IUVIF. One may interrogate a clinical database to seek answers to problems.

Irrespective: Or "regardless," but not "irregardless."

It (starting sentence): In a letter to me, the late rhetorician William Safire stated, "Sentences beginning with 'It is' are boring." Try to avoid and/or recast.

Pomposity, not zeal for clear communication, prompts writers to be verbose.

Not:

It is pomposity and not zeal for clear communication that prompts writers to be verbose.

Niacin causes untoward cutaneous effects.[1–5] **(Hypothetical references)**

Not:

It has been demonstrated that [*or "It is important to note that; It should be observed that; It is undeniable that; It has been shown that; It has been found that"*] niacin causes untoward cutaneous effects.

When composing a style manual, it is the tendency of some authors to excessively rely on the guidance of Luddites.

[This sentence has two defects. Can you detect them? Take a moment, then examine the sentence below.]

But:

When composing a style manual, some authors *[in the above, the phrase "it is the tendency" was not only wordy but also did not agree with its antecedent ("authors")]* tend to rely excessively *[split infinitive in the above]* on the guidance of Luddites.

Italic vs. Roman: Do not italicize expressions that have been well assimilated into English (e.g., in vivo, in vitro, vice versa). Italicize panel letters in more exotic Latin or foreign phrases (e.g., *ex ante*, *forme fruste*).

Lead/led: I hate to do this but have to!

Get the "Lead" Out!: The past tense of the verb "to lead" is "led."

You might be surprised to learn how many times we encounter this as "lead," e.g., "Our study lead to the following conclusions." Oh, really? Elemental lead (Pb), or alloyed with something else?

Please come down from the "ferrous wheel" and spell the word correctly!

"Leading": There is only one leader. Avoid examples such as "obesity is the third-leading cause of cardiovascular disease." How can this be so? Substitute the verb "ranked" for "leading."

Leading zero: I include this in all decimals, including p values. However, defer to the prevailing style of the journal targeted.

In a table, avoid using, e.g., 0.0, 0.00 even if these are consistent with the number of significant figures elsewhere in the table. Doing so strikes me as the height (or nadir?) of pedantry. Zero is just that: 0!

Like: In the 1970s, grammarians had a field day with an advertising campaign purporting that a tobacco product "tastes good, like a cigarette should." Use "as" in most such cases.

Not:

Like I said, the data are inadequate to draw a conclusion.

But:

As I said, the data are inadequate to draw a conclusion.

Look at, looking at: In my world (standard written, not colloquial, English), reviews and studies don't "look at" anything. They evaluate, assess, evaluate, investigate, test, examine, probe, ascertain, or appraise.

MACE: A terrific medical acronym.

Major adverse cardiac events—typically CAD death, nonfatal MI, and/or revascularization. Expand at first mention.

MACE rates declined in actively treated subjects.

Manage (dehumanizing): Diseases, disorders, conditions, syndromes, or cases are managed. Patients receive treatment, therapy, or care, but are not "managed."

Matching placebo: Redundant. If it doesn't match, it's not a placebo.

Mathematical operators, numbers: Use whenever you can (next to units of measure) to reduce numbers of words…See journal style.

Unless expressly prohibited by journal style, use Arabic numerals to express quantities of 10 or higher (≥10) or with units (of time or other measure), the 1/N dash for ranges, and mathematical operators (>, <) in parentheses. Avoid these practices when the entity is unitless or the context dictates Roman numerals.

Treatment with more than two [not >2] agents in this class is not recommended.

The normal range for LDL cholesterol is 0–130 mg/dL.

Not:

Normal values for LDL cholesterol range from 0–130 mg/dL.

Not:

Platelet counts in the range of 100,000/mm^3 are considered normal. [*One value does not constitute a range.*]

Spell a number when in opposition to another digit, even if the first number is zero to nine:

On the third day of Christmas, my purchasing manager gave to me: three 25-mL syringes, two 5-L bags of O negative, and a partridge in a pear tree.

Me vs. my: American users of gerunds/participles tend to use the possessive "my," whereas British users tend to use "me." Adapt according to journal style:

> **US:** I hope you don't mind my taking your patient's pulse.
>
> **UK:** I hope you don't mind me taking your patient's pulse.

Medical misspellings: Some misspellings "fly under the radar" of electronic spellcheckers because they are also valid words:

Complaint (compliant), compliant (complaint), creatine (creatinine; *and vice versa, check meaning*), dairy (diary), infraction (infarction), inoccuous or inocuous (*should be "innocuous"*), innoculate (*should be "inoculate"*), relive (relieve), and trail (trial).

Menopause: Menopause, or the climacteric (cessation of menses), is a time of life and not a medical condition. Are there signs and symptoms associated with the virtual cessation of estrogen output? Of course. Is there possibly even a manageable "postmenopausal syndrome," including acute hot flushes and vaginal atrophy? Arguably. But "menopause" or "post-menopause" as a medical condition? I am not persuaded. Ditto "partial androgen deficiency of the aging male." Each of these expressions is, on its face, potentially judgmental, refers to populations (rather than individual patients), and may spuriously suggest a "need to replenish" "deficient" levels of the reproductive hormone.

Mild-to-moderate: ≠ "mild or moderate." Use only to imply a continuum.

Minimum effective dose: Like "coronary heart disease," this term is so misleading that one almost needs to rethink it to fathom the users' true intent. Substitute "minimum dose effective."

Minuscule: This is the preferred (first-listed) spelling, not "miniscule."

Mitigate: ≠ "militate against." The former has a favorable resonance (e.g., to lessen or "commute" something noxious), whereas the latter suggests an undermining or countervailing force.

Modifiers: dangling, misplaced, wayward:

> **Walking down the ward, our pagers went off simultaneously.**
>
> **Driving through Boston, our eyes saw Brigham and Women's.**

But:

Driving through Boston, we got carsick and went to Brigham and Women's.

Not:

As a nurse practitioner, it is my obligation (no antecedent) to write correct prescriptions.

But:

As a nurse practitioner, I have an obligation to write correct prescriptions.

And:

Trials using statins to lower LDL cholesterol have reported 25% to 35% reductions in CHD events, including death, nonfatal MI, revascularization, and unstable angina, after 5 years of treatment ….

Not:

Trials using statins to lower LDL cholesterol have reported 25% to 35% reductions in CHD events after 5 years of treatment, including death, nonfatal MI, revascularization, and unstable angina….

Braunwald reported at the American College of Cardiology congress that 12 placebo controls with atrial fibrillation in the WARSS trial experienced strokes.

Not:

Braunwald reported that 12 patients with atrial fibrillation in the WARSS trial experienced strokes at the American College of Cardiology congress. (?!)

Monitor: Patients are not monitored or "followed"; adverse events and clinical conditions are monitored, whereas patients receive follow-up. The use of "elevated index of clinical suspicion" is permitted if there is no "monitoring" of "suspicious" patients.

Mortality/mortality rate: Sorry to be grim, but mortality is 100%; death is inevitable. (However, watch this space for future developments!)

No medication or other intervention can reduce mortality, though it may reduce "premature mortality" or mortality over a certain time span (i.e., "mortality rate"). Therefore, only a mortality rate (or mortality over some time interval or age-standardized mortality rate) should be reported.

The 2-year crude mortality rate was 75% lower in the actively treated compared with the control study arm.

Not:

Mortality was 75% lower in the treated group compared with controls.

Conversely, "longevity" and "survival" are not categorical variables (dead, or not dead?) but continuous ones (how many years lived?). Hence, it is permissible and even desirable to state that a medication increased longevity (expressed as mean [SD] or median [IQR] years of life). Longevity has an unfixed, variable upper (right) limit, unlike mortality, which is fixed. Hence, a medication can increase longevity but cannot reduce mortality (only premature mortality, death over a specified interval, or the mortality rate).

Most well: = Best.

The Lowry method is the best-known protein assay.

Not:

The Lowry method is the most-well-known protein assay.

Nadir: Useful antonym to "peak."

Nauseous vs. nauseated: A person can be nauseated or experience nausea. However, the term "nauseous" refers to something causing disgust or nausea, not the state of being nauseated.

Neither, nor: "Neither, nor" constructions often warrant singular verb forms (unless each entity is plural). Do not use "nor" without "neither." Nor should you start a sentence with "nor" (unless it's "Nor-... epinephrine!")

Number at front of sentence: Avoid spelling out, particularly if you then must also spell the unit of measure. Rephrase to introduce the Arabic numeral.

A total of 66 (22%) of 300 patients had fever.

In all, 66 (22%) of 300 patients had fever.

Or:

Of 300 patients, 66 (22%) had fever.

Not:

Sixty-six (22%) of 300 patients had fever.

Object (n.): A topic is the "object" (not "subject") of consideration, because it is the entity that is being considered or debated.

Of the: Wordy and usually can be deleted. Yet, it is amazing how frequently one finds this in writing, even in highly authoritative consensus guidelines. It adds nothing but verbal clutter!

Not:

All of the items in the CONSORT guidelines should be followed.

But:

All items in the CONSORT guidelines should be followed.

Or (more active and concise)

Follow all items in the CONSORT guidelines.

Optimalization [*sic*]: I have seen it published. Should be "optimization."

Or (restrictive): To signify nonrestrictive clauses, each of the following sentences should have a comma before the word "or":

Are the data paired or unpaired? ***[Yes, they must be!]***

But:

Are the data paired, or unpaired?

"Mr. Gutkin, would you like the lobster bisque or the coquille St. Jacques?" ***[Yes, please!]***

Pancreata: Plural of pancreas.

Parallel structure: I cherish elegant serial expressions, which reflect thoughtful analysis with adroit synthesis by the writer. In a serial expression, use the same forms of verbs throughout:

> **Exercising at or near VO_{2max} augments collateral circulation, lowers heart rate, and builds lean muscle mass.** ***[Lovely!]***

Not (what one usually encounters:)

> **Exercising at or near VO_{2max} augments collateral circulation, heart rate is lower, and lean muscle mass is increased.**

Patient vs. subject: Individuals become patients after developing illnesses. Once enrolled in clinical trials, they become study participants or subjects. The generic "individual" covers all contexts, although it represents an adaption of an adjective as a noun and may hence be objectionable to some.

"Patient" vs. "data": In observational studies, it is sometimes tempting to write "patients were eligible if…." or "patients were censored if…" In fact, such intransitive verbs often relate only to patients' data. To state that "patients were eligible if" may connote a prospective study design rather than an actual retrospective design, misleading readers.

Regimens [*not patients*] are switched.

I also too frequently see patients dehumanized in the following type of usage:

We treated only patients <u>that</u> *[should be "who"]* **were eligible.**

Pediatric patients (dehumanizing and imprecise): Avoid. Substitute age-appropriate terms (e.g., infant, adolescent; see "**Age referents**"on page 101)..

Pauci-: This prefix signifies a small number, by analogy to "paucity." (E.g., "Late Lyme disease often presents with pauciarticular arthritis.")

Phagocytose: Not "phagocytize." (I have encountered the latter in published papers.)

Place on (*dehumanizing and jargony*): Do not use when referring to administering or instituting treatment.

Not:

For pain management, the patient was placed on a PCA pump.

[In the words of former US talk-show host David Letterman, "and you know how painful that can be!"]

But:

For pain management, the patient received a PCA pump.

Potentiate: IUVIF. Approximate antonym of "attenuate."

Practicable: An action that can be practiced is "practicable."

Presently: Means "soon." "Currently" means now.

I will visit the metabolic ward presently.

At present, I am evaluating a patient for diabetic ketoacidosis in the metabolic ward.

Pressor: Adjective. Blood-pressure–raising effect. Antonym is depressor.

Presume vs. assume: Presumption has a lower level of certainty compared to assumption. An American has the "presumption (not "assumption") of innocence until proven guilty."

Prevalence: Should be expressed as a percentage or ratio, not a number.

Need to specify point versus period versus lifetime (see Table 2.7).

The point prevalence of whooping cough is 0.1% of the immunized, and 1% of the nonimmunized, US population.

Or:

Approximately 1 million Americans will experience whooping cough at some time in their lives.

Not:

The prevalence of whooping cough in the United States is 750,000.

***Primum non nocere*:** Latin for "First do no harm." This phrase is not found anywhere in the Hippocratic Oath.

Prior to, in advance of: Substitute "before." Also "after" instead of "following" or "subsequent to."

Principal vs. principle: The "principal" is your "pal." Principle is a belief or property.

Probability (observed): I once committed the following to a manuscript and was scolded (and "scalded!") by an über-statistician:

> **"The observed probability differed widely from the projected probability."**

The problem? Only frequencies (not probabilities) are observed.

I reworded to:

> **The observed frequency differed widely from the projected probability.**

Proclivity/propensity: The evidence-based and more neutral (non anthropomorphic) term is "imbalance." For instance

The study population had a slight imbalance [*not "proclivity" or "propensity"*] of women (female: male ratio = 1.18).

On the other hand,

Veterans of foreign military conflicts may have a lower propensity of reporting major depressive disorder because they experience stigma.

[Or:]

Veterans are less apt to report major depressive disorder because they experience stigma.

Produce (v.): FUVIA. If you want to be a "producer," go to Hollywood (or Bollywood!). This is a grossly overused verb in medical communications. Avoid "these studies produced the following results…" or, worse, "this drug has produced favorable efficacy and tolerability data."

Proper nouns/names: Avoid capitalizing nouns that are not names.

The Framingham Heart Study was highly influential.

But:

As shown by the Framingham study, low HDL cholesterol is associated with increased cardiovascular risk.

Dr. Morton Pram is chief of pediatrics [*not "Chief of Pediatrics"*] at Immaculate Conception Hospital.

But:

Dr. Morton Pram is the Donna Shalala Distinguished Chair of Pediatrics at Immaculate Conception Hospital. *[Given the pediatric discipline, this may be a "High Chair" if not a "high-chair!"]*

Proven: Archaic as the past form of the verb "to prove."

However, the use of "proven" in the adjectival form is permissible.

This study has proved that positive inotropes are indicated in emergent care of low-output syndrome.

Or:

Positive inotropes have proven benefits in emergent care of low-output syndrome.

But not:

This study has proven that positive inotropes are indicated in emergent care of low-output syndrome.

Providing that: Should be "provided that" if used in this limited logical/rhetorical sense.

Punctuation: Use the serial comma before "and." [Don't be a "serial killer."] Place both commas and periods inside quotation marks and reference numbers, semicolons, and colons outside (unless otherwise stipulated by PRJ AGs). Use a semicolon to separate two very closely related sentences or to help punctuate longer or complex series, especially those with components including "and" or "or." Use a colon to introduce a series.

Symptoms of seasonal allergic rhinitis include:

- **congestion**
- **runny nose and**
- **itchy eyes.**

Or:

Symptoms of seasonal allergic rhinitis include

- **congestion, which is believed to be secondary to histamine-induced vasodilation with increased perfusion;**
- **runny nose, which may be related to leukotriene- and histamine-induced rises in secretory activity; and**
- **itchy eyes.**

p value: Unless otherwise advised, use roman lower case "p" because it is the most efficient way (even after factoring in the time to program a "macro"). Use p = 0.04 with the leading 0 and space on either side of the operator. Many journals require that p values be preceded by the test used (e.g., ANOVA, Student's *t*-test) and degrees of freedom, which is indicated as a subscript, e.g., $\chi^2_3 = 15.5$; p = 0.02. Report both the p value and the 95% CI or other prespecified confidence interval.

Always try to report the actual p value rather than a category, e.g., p = 0.039; not p < 0.05

p = 0.067; not p > 0.05 or p = NS.

Prefer two-tailed/sided over one-tailed/sided p values; there is usually no statistical benefit of using one-tailed/sided tests.

Race/ethnicity: Racial characteristics are genetic; ethnicities, cultural.

What makes a group an ethnicity is that they are not in the majority of a population.

Persons of African descent include African Americans and Afro-Caribbeans.

Persons of African descent, of course, are not necessarily African *Americans* (e.g., in a European population!).

"Asian" encompasses East Asian (Islander) and Southeast Asian (Islander).

"Eurasian" includes persons from India and Pakistan.

"Alaska Natives" include Aleuts and Inuits.

"Latino" or "Hispanic" is a term of ethnicity, not race.

Conversely "non-Hispanic white (or black)" is a racial term.

Ranked: See "leading."

Rash (redundant): "Skin rash" or "cutaneous rash" is redundant.

Rather than, Instead of: Maintain parallel construction before and after.

Rather than escalate the dose of either drug, introduce an adjunctive treatment with a complementary MOA.

Not:

Rather than escalating the dose of either drug, introduce an adjunctive treatment with a complementary MOA.

Redundant, wordy
Advanced planning
Brief in time (or duration)
Consensus of opinion (or general consensus)
Draws to a close [*concludes*]; brings to fruition [*completes*]
Due to the fact that [*because*]
During the time that [*during, while*]
Each individual person
Fellow colleagues
Fewer in number
Fill to capacity
General rule (or general consensus)
Green in color (or hue, tint)
Had (or exerted) an effect on [*affected, influenced*]
Heralds the onset of [*predicts*]
In close proximity to [*near*]
In terms of, in regard to [*about or concerning*]
Major breakthrough
Majority of [most]
Matching placebo
Mild or moderate in severity
Out of: 4 (10%) of 40, not 4 (10%) out of 40
Precede in time
Produce an inhibitory effect on [*inhibit*]
Skin (or cutaneous) rash
Small in size (or extent)
Smooth in texture
Soft in consistency
Sour tasting
Sum total
Tender to palpation (or to the touch)
Uniformly consistent

Refractory (dehumanizing): A condition, not a patient, may be refractory to treatment.

Regimen: Fine alternative for a pharmacotherapy. It should include both the drug and dosage (with administration route and frequency). Do not confuse with "regime," which does not always carry a health connotation. Regimens ("not patients") are switched (or altered).

Registrant: A participant in a patient registry.

Regurgitate (figurative): Don't. If numerical data are reported in Results tables, there is no need to repeat them in the Results text. Instead, point out the key relationships (e.g., trends, directions, p values) and refer readers to the table. If, on the other hand, the only data are contained within a figure that does not disclose numbers, but you have numerical data used to generate the figure, try to include them.

Relative to: Unless someone is truly related (e.g., a kindred to a proband), do not substitute "relative to" for "compared to/with."

Repeat (adj.): ≠ "repeated." If a test is repeated, state the number of repetitions.

A second MRI suggested a meningeal lesion.

Not:

Repeat MRI suggested a meningeal lesion.

Repeated words, prolix: ***Not:***

Results from this study and from published reports support the same conclusion.

But:

Results from this study and published reports support the same conclusion.

From an online policy:

Not:

"We protect your privacy, your data, and put you in control."

[Nonparallel construction and needless repetition of "your!"]

But:

"We protect your privacy and data, and put you in control."

However, in the "Amidah" of the Jewish prayer book is the phrase "G-d of Abraham, G-d of Isaac, and G-d of Jacob." Why? The repetition signifies that each prophet had his own, individual relationship with the deity.

Respectively: Avoid such constructions. Forces the reader to go back in sentence to find the antecedents.

Restrictive clauses: A restrictive-clause riddle:

Q: How would you survive in the desert with no food?

A: On the "sand which is" there!

Be careful when using restrictive clauses. They can undermine meaning and set up infelicitous expression (e.g., run-on sentences).

Not:

The patient was referred to the operating room (OR) where he underwent open reduction and internal fixation for a fractured right femur. ***[Implies that the patient visited more than one OR.]***

An errant US bomb exploded in a Kunduz, Afghanistan hospital killing 100 patients. ***[Implies that the hospital was killing patients!]***

Robust: Prefer to use mainly in the strict biostatistical sense of not being affected by changes in assumptions. Do not overuse as a way of exaggerating the importance of findings.

Run-on sentence (ROS): Often set into motion by repetition of "ing" forms of verbs and relative pronouns.

Two witches make a curse, whereas two "whiches" often make a ROS.

Salt: ≠ "sodium." Typically, we mention the salts with which drugs are formulated only at first mention unless a complex formulation might otherwise be confused.

Define at first mention, then use chemical name afterward. For example, "Sildenafil citrate has been available to men with erectile dysfunction for nearly 20 years. A contingent agonist of the male sexual response, sildenafil was the first US–approved PDE5 inhibitor for this indication."

Salubrious: Healthful.

Salutary: Favorable, especially to patients' health. Antonym: deleterious

Saw, seen: ≠ attended or treated. A patient is attended or treated by a physician, which constitutes much more than "being seen" (which is also jargony).

Sign (vs. symptom): Symptoms (or complaints) are experienced by patients, whereas signs are observed by clinicians and/or via tests.

Marked rises in CK are signs of statin-induced myopathy.

And:

Myalgia that cannot be attributed to physical exertion may be a symptom of evolving statin-induced rhabdomyolysis.

Not:

Ipsilateral pupil dilation is a symptom of elevated intracranial pressure and/or cerebral edema after stroke.

Not:

Myalgia is a sign of incipient rhabdomyolysis.

Set (singular/plural): Because of a strong connotation of singularity, each of the following is correct:

> **A battery of tests was administered.**
>
> **The H&P did not raise suspicion of tropical infection.**
>
> **D&C is indicated to assess a potential ectopic pregnancy.**

Since: ≠ "because"; use the latter to signify causality. "Since" has a time connotation. See also "whereas"/while."

SI Units: Use Standard International Units (e.g., mmol/l) for most, non–US or non–UK publications. Consult peer-reviewed journal Author Guidelines (PRJ AGs).

If the PRJ AG permits, provide SI–English unit conversion factors, especially in table footnotes.

Subject: Individuals or patients enrolled in a study are subjects or study participants. Also useful as a verb.

The study design was subject to bias.

Writers drawing conclusions from biased findings may be subjected to a scolding by the journal referees!

A topic being debated is the "object," not "subject," of consideration. (It is the thing being considered, and hence an object, not subject.)

Such as: Use a comma before if introducing a list in the nonrestrictive (adding, nonessential) sense (first example below) and no comma if introducing a particular quality or attribute in the restrictive (naming or defining) sense (second example).

Symptoms of asthma, such as wheezing and cough, are amenable to inhaled corticosteroid treatment.

But:

Lower-airway symptoms such as bronchiectasis are often refractory to antihistamines.

Technique (vs. method): Technique is the level of one's prowess, not a method.

The methods relied on enrollment of surgeons with acceptable technique.

Tense: What bad writing makes me! Be as consistent as you can but not so rigid as to preclude rational shifts. For instance, you may use the past tense when discussing data in a study and the present tense when describing or reporting a stable or persistent quality or attribute.

A CDC registry showed that indiscriminate use of broad-spectrum antibiotics increased the likelihood of vancomycin-resistant staphylococci.

But:

Indiscriminate use of broad-spectrum antibiotics increases the likelihood of vancomycin-resistant staphylococci, according to a CDC registry.

The Scandinavian Simvastatin Survival Study demonstrated that statin therapy significantly reduced the probability of recurrent MI (vs. placebo and usual care) and was well tolerated.

But:

Statin therapy significantly reduces the probability of recurrent MI (vs. placebo and usual care) and is well tolerated, according to findings from the Scandinavian Simvastatin Survival Study.

That: Often can be deleted in the interest of verbal economy (as can the pronoun "who").

Aspirin was both effective and well tolerated in a double-blind trial of 38 patients discontinuing therapy because of adverse events.

The: In general, I object to the practice of capitalizing "The" ("The Johns Hopkins Hospital") unless this is the actual institutional identity. In many instances, "the" can be omitted. The article in "The Netherlands" is "The" national identity and hence should not be omitted.

The (*wordy*): The (hospital, clinic). American users tend to state, "The patient was admitted to the hospital (or was hospitalized)" or "The patient was seen in the clinic." UK users tend to leave out what Americans (wrongly, in my

view) believe is a necessary article ("the"). I prefer the UK version because it is more concise and equally clear:

The patient was seen in clinic, then admitted to hospital.

Patients were randomly allocated to receive spastex or placebo.

Not:

The patients were randomly allocated to receive spastex or placebo. ***[What purpose does "the" serve?]***

Not

Aspirin was both effective and well tolerated in a double-blind trial that involved 38 patients who had discontinued prior therapy because of adverse events.

Also

Thomson Reuters warrants that, if used properly, the *Physicians' Desk Reference* should help to prevent prescribing errors. ***[The comma "that" is needed.]***

It is often possible to remove relative pronouns:

Medication-adherent patients ***(not "Patients who adhered to medication regimens")*** **had superior outcomes.**

Those which (who; ***wordy*****):** Avoid. Use the word "those" freely to economize:

Patients receiving PUVA exhibited lower PASI scores than those receiving topical coal tar.

Or (much better because more consolidated):

Patients receiving PUVA (vs. topical coal tar) exhibited lower PASI.

Not:

Those patients who received PUVA exhibited lower PASI scores compared with those patients who received PUVA alone.

To (caveat): Positioned at the head of a sentence, this preposition often sets up a dangling modifier:

Not:

To evaluate the effects of spastex on belching frequency, patients were randomized (2:1) to active treatment or placebo.

But:

To evaluate the effects of spastex on belching frequency, we randomized patients (2:1) to active treatment or placebo.

Toward: Favor over the archaic "towards."

Toxic/dehumanizing: Toxicity is a condition. As with "case," "diabetic," or "hypertensive," a patient is not reducible to his or her "toxicity."

The patient's acitretin toxicity manifested as cheilitis.

Not:

She was toxic from her retinoid, so we lowered her acitretin dose. ***[This is also jargony.]***

Trade (proprietary) names: Avoid unless journal style calls for these, in which case include in parentheses only at the first mention of the generic/chemical name, along with the manufacturer. However, do not use a trade name in an article title unless expressly permitted or required by the journal.

Treatment/treated: Only the active-treatment group is "treated." The control group "receives placebo (or usual care)."

Utilize/employ: FUVIA. These have specific connotations. If you mean "use," use "use." (!)

Vasodilation: Preferred over "vasodilatation." Adjectival is "vasodilator," not "vasodilatory."

Versus/vs.: Use abbreviation "vs." only in parentheses or tables. Avoid using "vs." or "versus" in text, especially display type (e.g., manuscript titles). Substitute "compared with," "compared to," "as compared with" (in longer sentences), or "as against" (UK). In short comparisons, it is permissible to use "than." See "Comparisons" above.

Which: The antecedent of "which" must be clear. Typically, it is inferred to be the immediately preceding clause. "Which" is often used in a rhetorically lazy manner:

Not:

Cholestyramine is nonsystemic, which suggests that it will be better tolerated by many patients. ***[Huh? There is no antecedent.]***

But:

Ezetimibe has a favorable tolerability profile, which may be consistent with superior patient acceptance compared to bile acid sequestrants.

[The antecedent is clearly "profile," which is correctly placed immediately before "which."]

While: Has a time connotation. (See also above "since/because.") Substitute "whereas" or "although" if these are the intended meanings.

Who have (wordy) Patients with diabetes (*not the dehumanizing "Diabetics"*) may experience fatigue.

Not:

Patients (*or, worse "Those patients"*) who have diabetes may experience fatigue.

Years' experience: I have 30 years of experience as a medical writer. Hence, I also have the "experience of 30 years" or 30 years' experience (possessive). Check your CV!