

Preparing reports for publication and responding to reviewers' comments[☆]

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1. Introduction

This article is based on a chapter of a new book, *Clinical Epidemiology: How to Do Clinical Practice Research*, which is about designing and conducting practical research in clinical settings. Those most likely to benefit from our suggestions are early in their academic careers (the “you” in the following discussion), though we hope more senior clinician-scientists will also identify some helpful advice.

Publishing the findings of your research in high prestige, peer-reviewed journals is the *sine qua non* of academic success, short of, say, a Nobel Prize. Although it would be nice to believe that the intrinsic merit of your research is the main determinant of whether your article is published in a given journal, many other factors bear on this, including the target audience of the journal, the number of articles published by the journal compared with the number of manuscripts received (“rejection rate”), whether the journal has recently published something on the same topic, whether the findings are “positive” or “negative,” whether the findings are “newsworthy” in the view of the editor, which reviewers assess your article, how well you have written the article, and dumb luck (good or bad). You can do something about most of these factors (Table 1). Sooner or later, you can get virtually any paper accepted by some journal, but this chapter discusses some ways to increase your chances of having your papers accepted sooner rather than later, and by higher prestige journals.

This checklist provides a guide for preparing reports:

- ☒ Choose target journal(s) and write for them
- ☒ Choose a clear message
- ☒ Achieve high quality in your writing
- ☒ Respond to reviewers' comments
- ☒ Deal with the editors

2. Choose target journal(s) and write for them

One of the first decisions you should make in preparing your manuscript is to choose the category of target journal for your publication, and, on occasion, the target journal itself. Depending on their nature and objectives, one journal may greet your article with enthusiasm, whereas another will view that same article with disdain. You should consider several issues in choosing and writing for your target journal.

2.1. Tailoring content to the target journal

As a clinical researcher, most of the articles you write will report on the clinical studies you undertake, and your fellow clinicians will constitute the target audience. On occasion, however, you may be writing a paper with a more methodological focus. Such papers explore issues of optimal study design, methods of measurement, or interpretation of findings.

We can think of three categories of journals in which you will publish your research: general medical journals, subspecialty journals, and methodologically oriented journals. Many articles produced by clinical researchers have the potential for succeeding in more than one category of target journal.

Clinical journals are often interested in papers that focus on methodological issues. By the same token, methodologically oriented journals often welcome what are fundamentally clinical papers with a methodological slant. Although

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Table 1
Determinants of publication

Determinant	What you can do
Interest to target audience	Choose journal read by those interested in your topic
Rejection rate	Choose lower profile journal
Recent publication on the topic	Choose journal that has recently published on your topic
Whether the findings are “positive” or “negative”	If you have a “negative” study, in your covering letter, you may want to remind the editor of the importance of avoiding publication bias
Whether the findings are newsworthy in the view of the editor	Work hard to vividly highlight the importance of your findings
Which reviewers your article is sent to	In your covering letter, you may want to suggest reviewers likely to be sympathetic
How well you have written the article	Note the suggestions in this chapter
Dumb luck	Choose a coauthor known to have extraordinary and unwarranted good luck

the *Journal of Clinical Epidemiology* is a common target journal for methodologically oriented papers, it also deals with a wide range of clinical areas. *Medical Care*, another methodologically oriented journal, focuses on health services research. You may find methodological journals with a particular focus on your area of exploration. For instance, one of us (GG) has conducted many studies in measurement of health-related quality of life (HRQoL), and the journal *Quality of Life Research* is an obvious potential target for these papers. These methodological journals typically have both a smaller and more select readership than even second-tier clinical journals.

You are likely to be submitting an article that might be appropriate to more than one category of journals. You will write every part of your paper differently depending on the target you ultimately choose.

Most journals prescribe the “IMRAD” format for original articles: Introduction, Methods, Results, and Discussion. When writing your introduction, bear in mind that clinical journal audiences will need an explanation of why they should be interested in a methodological topic. For instance, not too long ago we published a paper about a new version of a popular questionnaire for patients with chronic lung disease [1]. We targeted a clinical journal that addresses issues of respiratory disease, *Chest*. Our introduction began with the following sentence: “Health-related quality of life (HRQoL) outcomes are gaining importance in clinical trials of patients with chronic airflow limitation (CAL).”

Had we submitted the paper to “Quality of Life Research,” such an opening would elicit groans, because we would be making a statement that readers (and reviewers) would perceive as completely obvious. Clinical journal readers and reviewers, however, must be reminded (or told for the first time) about the importance of HRQoL measurement.

If you are writing for a general medical vs. a subspecialty medical journal you may need to provide greater explanation of not only methodological, but also clinical issues. For instance, a group of us began the introduction of an article we recently published in the *New England Journal of Medicine* with the following statement: “Mechanical ventilation is the most common form of advanced life support in the intensive care unit (ICU).” [2] Had we been writing for

a critical care journal, such an introduction would be self-evident.

Methods sections, including descriptions of statistical analyses, should be much more detailed in a methods journal. Even in a clinical journal, you need to inform reviewers and other researchers (if not clinical readers) of crucial methodological details, and your paper should provide sufficient information that another investigator could reproduce your study. At the same time, clinical journals will want your methods section to be as compact as possible, and you should oblige them. Methods journals will be more indulgent of, and may even demand, detailed descriptions of your methods.

Publishing a methods paper in advance of the results papers for your study is an excellent way to achieve the economy demanded by high circulation clinical journals. Open access electronic journals, such as BioMed Central (www.biomedcentral.com) provide an excellent service for this purpose. If the details of your methods are published there, then your results papers can refer to them for details—and you will gain an additional publication for your resume. If your study is important, many second-tier clinical journals will also accept methods papers, especially if baseline data are included. For example, the North American Symptomatic Carotid Endarterectomy Trial methods paper was published in *Stroke* [3], the main results paper in the *New England Journal of Medicine* [4]. Publishing the methods paper in a timely way can also publicize the trial, provide collaborators with tangible benefits, and stimulate recruitment.

The same issue of level of detail applies to the results. For instance, our HRQoL measure for patients with chronic lung disease has four domains (dyspnea, fatigue, emotional function, and mastery). One can aggregate the first two domains into a physical function domain, and the last two into an emotional function domain. When writing for a methods journal, we always provide information on all four domains. When writing for a clinical journal, however, we may describe only the aggregated two-domain results.

The discussion is similar to the introduction in that, when submitting to a clinical journal, you may need to address issues of the importance of your methodological work. On the other hand, you might have more scope for exploration of methodological issues in a methods journal.

2.2. Tailoring format to your target journal

Virtually every journal has issues of formatting and presentation to which you must attend. Most of these are relatively trivial (such as section headers or reference citation style), and will occupy you when you are polishing the manuscript for submission. Other issues are more substantial, and you should address them early on. For instance, if you are aiming at a very prestigious journal, your total word count is liable to be much more limited than for a lower profile target. In addition, some journals have special sections that may be particularly suited for your publication, such as “Brief Communications” or “Special Articles.”

2.3. Choosing a journal with a fondness for your topic

Some journal editors and editorial boards are fond of particular topics or areas of inquiry. If a journal has previously published a study in an area closely related to your investigation, it qualifies as a likely target for your submission. On the other hand, a dearth of articles in your area or using your methodology provides a message that you should look elsewhere. The *New England Journal of Medicine*, for instance, publishes very few systematic reviews and meta-analyses, whereas other major general medical journals (*JAMA*, *BMJ*, and *The Lancet*) favor them.

2.4. How high to aim

One question you will confront is how high in the pecking order your paper might climb. Many view five top general medical journals as particularly attractive vehicles for their papers: *New England Journal of Medicine*, *Lancet*, *JAMA*, *BMJ*, and *Annals of Internal Medicine*. Authors often wonder whether it is worth a try at these or other prestigious journals. Even experienced investigators find predicting success (or the lack of it) challenging, and this challenge makes the decision concerning the best target journal more difficult.

For instance, knowing that top journals accept few methodology papers (with the exception of papers that are part of a series negotiated with journal editors), one of us strongly discouraged his coauthors from submitting a discussion of the intention-to-treat principle to the *BMJ* [5]. They ignored the advice and, lo and behold, the *BMJ* accepted the paper (the price being the need to reduce the word count by 50%, with considerable loss of useful discussion). With electronic publication not burdened by space restraints, clinical journals (including the *BMJ*) are offering a partial solution to this problem by parallel paper (short) and electronic (longer) publication.

Generally, if it is appropriate that you seriously think of submitting to a top journal it means that your research has been well-planned, and well-implemented (in other words, you have followed the advice in the book from which this article arose) and on top of that you have

gotten lucky. More often, the internal debate (internal to you or to your investigative team) may be whether to make your first submission to a second-tier journal (perhaps, for instance, the top journal in your subspecialty area) or a less prestigious journal more likely to accept your paper. As we have mentioned, reading tea leaves is often as likely to provide as accurate a prediction regarding journal receptiveness as is any other strategy. The resulting uncertainty makes the choice of target journal more difficult.

In advising junior colleagues, we generally ask them about how patient they are feeling regarding the timing of publication. Almost invariably, the timing of publication is not urgent. On rare occasions when you feel you are competing with other investigators whose own submissions may be imminent, you may aim lower to make rapid acceptance more likely, but this may backfire if the lower journal is slower at processing manuscripts, which is often the case. You may, however, be able to negotiate quick review and accelerated publication if you speak directly with the editor.

Top journals typically respond quickly. A local young investigator who asked for expedited review by *The Lancet* and received his rejection 4 hours later probably holds the record for quick rejection. More typically, if rejection is your fate, you can expect to know within 3 months. Other journals take longer. You may want to check with colleagues about your target journal's track record. Rejections after more than 6 months are becoming less common, but can still happen with some publications.

One benefit of aiming high is that there is a chance that an astute review will help you improve your paper. Our experience is that substantial improvements on the basis of reviewers' comments are unusual, but do happen on occasion. So, if you are feeling patient, and several rejections will not hurt your ego, aim high. If impatience and vulnerability characterize your psychological state, choose a lower status journal more likely to accept your paper on first submission.

3. Choose a clear message

Your work may be quite complex, and a clear conclusion not self-evident. You must keep considering and reconsidering the nature of your results until you have defined a clear message. If your audience is to take away a single point, what is that point to be?

Having decided on your message you need to write your introduction in such a way that readers have no doubt about the importance of your question. The approach should have the same components as a good story. The introduction should raise the reader's curiosity, the results should satisfy that curiosity, and the discussion must show how important the results are.

Not too long ago, we completed an observational study examining the incidence of clinically diagnosed

venous thromboembolism (VTE) in critically ill patients [6]. We found that only 2.4% of patients had clinically diagnosed VTE. Of patients with diagnosed VTE, about half were receiving heparin prophylaxis and half were not. We could have concluded that VTE is infrequent and is not a big problem in patients in the ICU. Alternatively, we could have left it for readers to make their own inferences about the clinical conclusions they should draw. The first approach would have compromised enthusiasm for our ongoing research program in the prevention of VTE. The second would have led to a ho-hum paper that would not likely catch the imagination of reviewers, editors, or readers.

Instead, we chose to focus on the difference between VTE detected in screening studies (around 10%) and clinically detected VTE. That choice allowed us to conclude that VTE was clinically underdiagnosed, and clinicians should raise their diagnostic suspicion. The fact that 50% occurred in those not receiving prophylaxis suggested that clinicians should use strategies to enhance compliance with prophylaxis administration. The fact that 50% occurred in those receiving prophylaxis suggests the need for innovative prophylaxis strategies.

Having made the choice to present the results in this manner, we wrote the introduction accordingly. The key sentence read as follows: “We hypothesized that the rates of deep vein thrombosis and pulmonary embolism suspected clinically and subsequently confirmed radiologically are lower than those suggested by surveillance testing.” The discussion then picks up and echoes the lead-in of the introduction.

Often, you can structure the first sentence of the discussion using the Patient/Intervention or Exposure/Outcome format, but frame as an answer rather than a question. For instance, in this case, “In this multicenter cohort study of patients admitted to an ICU during the year 2000, we found that the prevalence and incidence of definite DVT or PE during admission to a medical-surgical ICU or for eight weeks post-ICU discharge were both approximately 1%.” Later, we highlight the concern about underdiagnosis of VTE: “In the ICU, patients are often unable to communicate symptoms, signs of VTE are non-specific, clinicians are often inattentive to the physical examination of the lower extremities, and there are multiple alternative reasons for changes in hemodynamics and hypoxia in mechanically ventilated patients. All these factors militate against an optimal index of suspicion for VTE in the ICU.”

One could argue that any result would have allowed us to emphasize the importance of VTE in the ICU. That is exactly the point. Whether event rates are high or low, and whether events occurred in patients with or without prophylaxis, we could have found a clinical problem in urgent need of remedy. Maximizing your chances of acceptance in the journal of your choice requires finding a compelling clinical message, and structuring introduction and discussion to highlight that message.

Table 2

Examples of passive and active voice

Passive voice	Active voice
Patients were asked to provide...	<i>Patients provided...</i>
Second, longitudinal validity is not influenced by standardization.	<i>Second, standardization does not influence longitudinal validity.</i>
Material for this series has been taken from the Users' Guides to the Medical Literature.	<i>The User's Guides to the Medical Literature provided much of the material in this series.</i>
More than 40 candidate HIV vaccines have been tested in Phase I and II clinical trials.	<i>Phase I and II clinical trials have tested more than 40 candidate HIV vaccines.</i>

4. Achieve high quality in your writing

Basic writing skills are necessary for success in publishing your work. All the examples used in this section come from drafts of manuscripts in which we believe that we improved on initial wording.

4.1. Use the active voice

Writing in the passive voice represents a long-standing medical tradition. That tradition persists despite the fact that the passive voice makes writing more awkward and difficult to understand, adds extra words, and robs the work of some of its force. Today's books about the quality of writing from a variety of nonmedical fields, as well as courses on writing conducted by the top medical journals, all recommend use of active voice.

Table 2 illustrates the use of passive and active voice.

Moving from passive to active voice creates special challenges in methods sections. In general, move away from “this was done” and “that was done” to “we did this,” and “we did that.” The repeated use of “we” can, however, get repetitive and perhaps egotistical sounding. A number of strategies can help deal with this problem. Consider

All studies were assessed independently by two appraisers for validity and content.	<i>Two appraisers independently reviewed all studies for validity and content.</i>
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Here, we have specified the role of the investigators as “appraisers” to avoid use of “we.”

Studies using surveys were considered qualitative surveys if questions were asked in an open-ended manner and quantitative surveys if questions were asked in a structured manner.	<i>Qualitative surveys asked questions in an open-ended manner and quantitative surveys asked questions in a structured manner.</i>
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Here, instead of changing the original construction to “we considered surveys to be qualitative if...” we personify the surveys and they, therefore, become the subject of the sentence.

Moving away from the passive voice is a challenge for some investigators. We suggest two strategies. First, in every sentence, consider who is the agent, who performed the action. Put that agent first in the sentence. Second, conduct one edit of your paper in which your only goal is to change passive to active voice.

4.2. Delete unnecessary words

Medical writers tend to use unnecessary words. Deleting these words makes your writing easier to read, and more forceful. Journal articles are also subject to stringent space limits. In general, use as few adjectives and adverbs as possible. You are often more convincing when you leave it for the reader to decide that your treatment effect is *very* large, your competitor’s paper has *serious* flaws, or the imprecision of an estimate leaves an effect *extremely* uncertain. And never decide, on the reader’s behalf, what is *interesting*. Consider the examples in Table 3 of using unnecessary words.

The last example in Table 3, aside from pointing out the gratuitous “There are...,” illustrates another common mistake, the misplaced modifying clause.

4.3. Avoid use of the verb “to be”

Using the verb “to be” often has the same effect as use of the passive voice. It robs your writing of vigor and energy. Consider Table 4.

Here, we have changed from “to be” to a more active verb, and also eliminated unnecessary words. Young investigators can experience the goal of decreasing use of the verb “to be” as even more challenging than moving from passive to active voice. Once again, carrying out an edit of the paper in which the only goal is to move from “to be” to more active verbs may be helpful.

Table 3
Deleting unnecessary words

Fat phrases	Leaner phrases
The patient tells you that he is a self-employed house-painter...	<i>The patient is a self-employed house-painter</i>
The process of evidence-based practice involves acquiring the skills of accessing the highest quality information...	<i>Evidence-based practice involves accessing the highest quality information...</i>
The 26 eligible studies that matched inclusion criteria used several methods of data collection. Five studies used semistructured qualitative interviews...	<i>Of 26 eligible studies, 5 used semistructured qualitative interviews...</i>
There are many factors that may influence an outcome aside from the intervention being tested.	<i>Many factors, aside from the intervention being tested, may influence an outcome.</i>

Table 4
Banishing the verb “to be”

“To be”	Not “to be”
It is challenging for health care personnel to be up-to-date	<i>Health care personnel face challenges in staying up-to-date</i>
There are several strengths of this study, including...	<i>Strengths of this study include...</i>
There is evidence...	<i>Evidence suggests...</i>

4.4. Keep your paragraphs short

Almost 20 years ago, one of us began to write articles concerning health policy, or health politics, for newspapers. Doing a good job necessitated looking carefully at high-quality newspaper journalism. One revelation was the length of paragraphs used in newspaper writing. If you have never noticed, have a careful look: most paragraphs are one or two sentences long, and a paragraph more than three sentences long is very unusual.

One of us was, for several years, writing a health policy column every two weeks. Newspapers demand a strict words count of 800 or less, and the articles generally finished with word counts of between 798 and 800. The discipline of writing for a general audience, and newspaper readers at that, is extremely instructive, and can improve medical writing. Newspaper-style writing is extremely revealing in demonstrating just how many unnecessary words—extra words that decrease rather than increase the forcefulness of the message—you can delete. In addition, newspaper writing reinforces the need to use the active voice, and highlights the merit of short paragraphs—how keeping to one idea generally enhances clarity.

If you wish to use a rule of thumb, keep your paragraphs to five or less sentences. Clarity is a priority and you can seldom justify paragraphs of greater length.

You must commit to editing and reediting your own writing. Achieving optimal style and clarity also involves ample use of colleagues, including coinvestigators, mentors, and students. For example, at least seven people have reviewed and commented on this article. This is a “scratch my back” business and it follows that you should always try to respond to others when they ask for your help.

5. Respond to reviewers’ comments

Journals will seldom accept your paper as you submitted it. Most often, you will face a number of reviewers’ criticisms to which you must respond. How you respond may be critical to whether the journal will publish your paper or whether you will have to start the submission process elsewhere from scratch. The following may help you deal with what some find a particularly onerous task.

- The optimal structure of the response is to state the reviewer’s comment, make any introductory statement you need, and then use italics or some other easily seen

convention to reproduce the change you have made in your manuscript in response to the reviewers' criticism. It is essential that the editor be able to easily follow how you have responded to each of the reviewers' comments. For instance

Comment: "We would prefer that you delete from the Interpretation of the Abstract the clause 'in both higher mortality rates.' While true, this interpretation relates to a previous study."

Response: We have deleted this clause from the Interpretation of the Abstract and the sentence now reads as follows:

Private for-profit hospitals result in higher payments for care than private not-for-profit hospitals.

Following this format will be easiest if you have an electronic copy of the reviewers' comments, so that you can integrate your replies within the comments. An increasing number of journals provide reviews in electronic form to facilitate this. If they do not, you can easily make an electronic version with Adobe Acrobat, and use "cut and paste" to make a word processed document. You can also help the editor to follow your changes by providing a "red-lined" version of the revised manuscript, using the "track changes" feature in word processing programs, along with a "clean" version.

- Unless the reviewers' suggestion will make the paper substantially worse, go along with it. It's seldom worth fighting with the reviewer. We happily make changes that we do not believe improve a paper, as long as they do not result in a poorer product. Even if the original is superior, if the suggested change is marginally less attractive, we are ready to go ahead. Only if the quality drops substantially will we resist.
- If the reviewer really screws up, say so directly but courteously. For whatever reason (haste, ignorance, enmity), reviewers can make mistakes or request changes that do not make sense for the study that you have done or the data you have collected. If so, politely indicate the mistaken or unreasonable nature of the request.
- You are likely to be outraged on occasion that the reviewer has not taken the time to read your paper thoroughly. On occasion, reviewers will manifest this neglect by suggesting a "change" that is already in your paper. Do not point out the reviewer's negligence. Think whether what you have written needs to be clearer or better located. If so, make the change. If you feel, however, that what you have written is fine, say that in the revised manuscript you have "emphasized" the issue the reviewer has raised.
- If you have an excuse to flatter the reviewer, do so. If the reviewer's point is remotely sensible, let the reviewer know that he or she has made an astute observation. Always end off by thanking reviewers for their

helpful comments that have improved the quality of the paper (well, at least they will not have made it much worse). Facetiousness aside, you will find that reviewers' comments sometimes help you strengthen your manuscript.

6. Deal with the editors

The best way to "deal with" editors is to give them exactly what they want: well written, concise papers appropriate for their target audience. But often the match between your work and the journal's mission is less than optimal.

On occasion, you may save yourself time, energy, and aggravation, and increase your chance of acceptance, by calling the editor before you submit. "I have a manuscript and I'm wondering whether you might be interested," you say, "I thought I'd run it by you before sending it to you for review." If the answer is no, you have indeed saved both yours and the editor time and energy. If the answer is yes, you may increase the chances of thoughtful editorial review, and thereby the chances of publication.

On occasion, editors exercise poor judgment in rejecting papers. You may be the victim of such an error. If the reviewers have been positive, and if you feel you can deal with their criticisms, do not hesitate to make a special appeal even if you have received an outright rejection. A colleague secured ultimate acceptance of a rejected manuscript through this artfully worded letter.

Dear Editor:

We have received your letter indicating that your journal was not able to accept our manuscript for publication. We noted the reviewer's comments; we found them to be thoughtful and appropriate, and we feel that attention to their concerns will substantially improve our report. As well, we noted that each of the three reviewers provided positive reviews. Many of the suggested changes involved providing additional details on definitions, which we agree are needed and which we can easily remedy. The more substantial revision suggested was to perform additional statistical analyses. Our data collection was quite detailed, and we would be very willing to re-code our data accordingly and conduct the suggested multi-variable regression analyses.

We certainly respect the editorial board's decision concerning our manuscript, and we recognize that your journal receives many more submissions than they can accept; however, we also share Reviewer B's view that our manuscript reports on "an important topic for the practicing physician that does not always receive the attention it deserves." We also feel strongly that your journal would provide the best exposure to practicing pediatricians. Once we complete the revisions suggested by the reviewers would it be

possible to re-submit our manuscript to your journal for reconsideration?

If you have carried out meritorious work that you believe is worthy of publication, do not get discouraged by initial rejection. Peer review is often arbitrary, cursory, gratuitously nasty, or just plain dumb. Nevertheless, reviewers may give insightful assessments and detailed comments and you should carefully consider their advice. In particular, take note if two or more reviewers offer the same criticism—even if they are not right, other reviewers are likely to share their response.

We have, on occasion, finally gained acceptance by the third or fourth journal to which we submitted. You have worked hard to produce your research. Revise, reformat, and resubmit until you receive a positive response. Nowadays, with a proliferation of electronic journals (most notably Biomed Central <http://www.biomedcentral.com> and Public Library of Science <http://www.plos.org>) your likelihood of success is greater than ever.

7. Conclusion

Publishing your articles in top journals involves science, good writing, gamesmanship, and human relations.

Suggestions in this article should promote both your success and your enjoyment of the process.

References

- [1] Schünemann HJ, Griffith L, Jaeschke R, Goldstein R, Stbbing D, Austin P, et al. A comparison of the original chronic respiratory questionnaire (CRQ) with a standardised CRQ version. *Chest* 2003;124:1421–9.
- [2] Cook DJ, Rocker G, Marshall J, Sjøkvist P, Dodek P, Griffith LE, et al. The Level of Care Investigators and the Canadian Critical Care trials Group. Withdrawal of mechanical ventilation in anticipation of death in the intensive care unit. *N Engl J Med* 2003;349:1123–32.
- [3] North American Symptomatic Carotid Endarterectomy Trial (NAS-CET) Steering Committee. North American Symptomatic Carotid Endarterectomy Trial: Methods, patient characteristics, and progress. *Stroke* 1991;22:711–20.
- [4] North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Engl J Med* 1991;325:445–53.
- [5] Fergusson D, Aaron S, Guyatt GH, Hebert P. Post-randomization exclusion of patients enrolled in clinical trials: the intention-to-treat principle does not necessitate that all patients be analyzed. *BMJ* 2002;325:652–4.
- [6] Patel R, Cook DJ, Meade MO, Griffith L, Mehta S, Rocker G, et al, for the Canadian Critical Care Trials Group. Burden of Illness: Thrombo-Embolism in Critical Care (BITEC) Study. Burden of illness in venous thromboembolism in critical care: a multicenter observational study. *J Crit Care* 2005;20:341–7.