Caveats for Scientific Publication in the Modern Marketplace

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The articles of a printed scientific journal are dressed deliberately in the same monotonous house style. This uniformity is expected to minimize a reader’s distraction from the logical sequence of the presented material. It can also obscure the origin, complexity, and significance of the article. Increasingly, a brevity desirable to both the reader and the journal is added to this presentational anonymity. As a result, the publication of clinical trials as printed journal articles is already something of a shorthand. The Editors of printed journals are turning to other media to extend the possibilities of presentation. For example, one journal is converting to a condensed template print publication of research articles, with full papers accessible online (1).

The currently available latitude for authors within each section of an article, whether in print or online, still allows the benefit of their perspective. Ultimately, a progressive publication shorthand might put at risk the capacity for informed scientific skepticism by a forced narrowing of that potential.

With this trend of publication, the caveat emptor of the reader and the caveat venditor of the authors, as buyers and sellers of the packaged “message,” are not becoming less problematic. The buyers include the reader, typically a clinician scientist who may also be a prescriber, pharmacists, and payers. Another interest group consists of the regulatory authorities and guideline agencies. The authors, as vendors, are involved with their career academic institutions, collaborators, funding bodies, and perhaps commercial interests.

To simplify the assessment of clinical trials, in particular, various guidelines to reporting have been developed that give publications a consistent and comprehensive framework, with apparent benefit (2,3). The public registration of trials and a broad consensus on study design, supervision, statistical analysis, and declarations of conflict of interest are widely accepted as partial guarantors of “merchantable quality” (4,5). The scientific article, however, remains far from an adequately assured consumer commodity.

Social anxiety about safety, suspicion of the probity of the pharmaceutical marketplace, and the misconduct/unreliability of investigators have provoked political action designed to extend and strengthen existing practical and presentational conventions (6,7). For prompt access to possibly important messages, U.S. Federal law now mandates a final unreviewed report of “basic results” of registered studies within 12 mo, which short circuits the more sedate, traditional quality assurance of scientific publication (8). Monitoring the authenticity of trial data remains an incomplete area of development.

The regulatory authorities participate bilaterally in the research effort by specifying the performance features necessary to their acceptance of trial evidence and by judging the outcome as a submission for approval. Journal evaluation and presentation, compared with a regulatory submission, allows the authors some scope for their viewpoint in the selection of the material, the pitch of the discussion, and the referenced support for the hypothesis, for good or ill (9). Publication is a performance to the potential scientific and commercial audience, as well as a credential toward regulatory approval.

The demonstrated behavior of Pharma, in wringing every possible advantage out of the scientific nexus, has made the public, journal readership, and Editors wary of studies arising from commercial initiatives (10,11). The conventions of clinical trial procedure and presentation go some way to managing that concern, but it remains difficult to mitigate the commercial special pleading that can occur on publication. The commercial scene is simply too complex for each discretionary element of authorship to be assessed adequately. Pharma may feel that, with such a compromised public reputation, there is nothing important to lose from the equivalent of the sporting “professional foul” (12). However, caveat venditor is betrayed by each spin of content, because of a threat to the reputation of any core message. There is even a special hazard in health care, because the social idealization of caregivers flips rather readily into a demonization of the demonstrably cynical. It serves both caveats for Pharma-based trials to contain even less than usual special pleading for the views of the authors and their sponsors.

In this volume, the work of Pergola et al. (13) is an instructive rehearsal of these issues. The work seems to have been designed from the outset to fill an evidential niche in the dosing of their erythropoiesis-stimulating agent (ESA) at extended intervals (14). Those intervals have been explored widely in current practice and in a variety of studies with their agent, but the absence previously of a thrice-weekly (TIW) treated control group had not allowed the change to the package insert that would make extended interval use consistent with the Food and Drug Administration (FDA)-
approved label (15). The registered protocol (for “Efficacy”) follows the conventions of showing “noninferiority,” and the presentation is focused on fulfilling FDA criteria. This leads arguably to redundancy of presented tabular results regarding safety issues. The FDA preference is for the primary results to be presented for Intention to Treat over Per Protocol statistical analysis, which trumped any preference of the authors. This is a paper arguably more preoccupied with effectiveness in a current U.S. setting than (global) efficacy.

As far as substantiation of the work goes, the details of the renal anemia management algorithms are incomplete where falling hemoglobin (Hb) values are concerned, and an intra-study protocol change of the upper Hb limit for intervention is not mentioned in the text [from an authorial comment at review].

Such fine detail is not material to the FDA element perhaps, because the conventions have been otherwise followed, and the declared noninferiority limit is not breached (16). On the other hand, the characteristics of the dosing regimens and algorithmic control are certainly relevant to the practical application of extended interval ESA use. It may be asked usefully just which quality of noninferiority of the extended intervals has been established. The more rapid rise in Hb of usefully just which quality of noninferiority of the extended application of extended interval ESA use. It may be asked and algorithmic control are certainly relevant to the practical application of extended interval ESA use. It may be asked usefully just which quality of noninferiority of the extended intervals has been established. The more rapid rise in Hb of the frequently dosed group (TIW versus weekly and every 2 wk [Q2W]) is compensated by the algorithmic control system after an interval of 3 to 4 mo, and this is shown twice graphically. It is not surprising that, thereafter, Hb values remain congruent in the groups. The noninferiority of Hb result is guaranteed after this latent control interval by the setting of the intervention thresholds and dose ladder of the algorithms (17). Any difference in the treatment schedules can only be reflected in other attributes of the system—in this case, the mean dose of ESA, which is 35% higher at Q2W.

Although this is of lesser interest to the FDA, the nonregulatory emptores will be concerned by the dose penalty of extended intervals. For them, a subtle diminishment of that apparent inferiority is presented by the authors, perhaps inadvertently, given their intense focus on regulatory submission. The 35% is not mentioned in the abstract. It is described as “modest” twice and is justified extensively (and perhaps legitimately) in clinical and operational terms. It is even made desirable, because there is an authorial emphasis on the more frequent dose changing and noncompliance with guideline advice that were more evident in the TIW group. Those do appear in the abstract. They were probably caused by the weight-related (TIW) rather than fixed (weekly, Q2W) initial ESA dosing and the latency of the algorithmic correction. Those two contingent factors exonerate frequent dosing itself from the innuendo of adding to management difficulties. No explanation of this is to be found in the text. One other potential piece of special pleading is the absence of an emphasis on the application of the study only to otherwise healthy patients with chronic kidney disease. It may be imagined that the progressive transfusion requirements carefully documented with extended interval treatment might have implications for less healthy subjects experiencing intercurrent complications from a lower Hb baseline. That would represent a third form of possible inferiority.

These issues indicate at least some sacrifice of scientific interest for the main task of providing FDA evidence according to convention. That sacrifice has a cost in the failure to attribute the Hb outcome noninferiority to the treatment algorithm. The ESA dose penalty necessary for its achievement is exposed in a way that might be described as “buffered.” Clearly, the conventions of trials do not eliminate the need for caveat emptor exercised in the nonregulatory context. The paper of Pergola et al. points up the duality of objectives that can be provoked by journal publication within the prevailing marketplace, the cost-benefit of authorial freedoms, and perhaps a subtle erosion of clinical science.

Disclosures
None.

References


See related article, “A Randomized Controlled Study of Weekly and Biweekly Dosing of Epoetin Alfa in CKD Patients With Anemia,” on pages 1731–1740.