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Editorial

Ethics in Publications

"Although this may seem a paradox, all exact science is dominated by the idea of approximation. When a man tells you that he knows the exact truth about anything, you are safe in inferring that he is in inexact man." Bertrand Russell (1872–1970)

Uncertainty is the only certainty in science: nothing is clear-cut. That this is also the case about treatment for major human conditions, including osteoporosis, is an unfortunate reality. Investigations of novel and potentially better treatments are certainly warranted. Because of the high costs of success and failure, basic and clinical scientists are subject to predictable financially related pressures. In this arena, therefore, the reliability of what we do "know" is paramount. Any errors that creep into our knowledge base can delay, distract, and mislead with potentially disastrous consequences. When these occur by honest mistake, it is most unfortunate, and correction of known errors is essential. If they arise and are allowed to stand uncorrected from conscious action, it is indefensible. The importance of this issue relates to the critical marriage between peer review and ethics in the published word. These concepts are of major concern to the editorial team of a scientific journal. The structure of all scientific publication depends on the twin pillars of integrity of the authors and of reviewers. We depend on the honesty of the authors and rely on their assertions that they have had sufficient access to the data to be convinced of its reliability. We depend on honest and forthright review unimpeded by any personal or financial bias for or against what is written.

Failures or delays to report negative studies are as unacceptable as publishing patently false data. Concern about such publication biases has recently lead to the requirement by major medical journals for pharmaceutical companies to register all studies, including listing of primary and secondary endpoints and preplanned analysis, before enrolling their first patient. The *JBMR* has agreed to a similar requirement as set out below. The *JBMR* editorial team strongly supports this improvement in transparency.

Other critical ethical issues that deserve our careful concern as well as informed consent include primarily scientific internal and external validity and the threat from conflict of interest, and statistical issues and validity of endpoints and the fairness in the pursuit of human and animal studies. Other issues include honesty and transparency and appropriate authorship. Each of these issues requires careful consideration by authors, reviewers, and editors.

INFORMED CONSENT

In human studies, investigators have daunting ethical responsibilities as set out in the Declaration of Helsinki. Each participant must be adequately informed of the risks as well as potential benefits of participation. These points are usually set out in the Patient Information and Informed Consent, overseen by any Research Ethics Committee or Institutional Review Board (IRB). However, the availability and lucidity of these patient-directed materials do not override the investigator's primary responsibility to the participant including the duty to ensure that the participants have a clear understanding of what is considered an acceptable risk (e.g., of fracture). In addition to making sure patients understand the risks, investigators must consider that there is the potential to achieve a meaningful outcome. This concept, which is part of the IRB review process, includes the requirement for valid comparators, adequate study size for reasonable power, and clear guidelines on dealing with potential conflict of interest.

VALID COMPARATORS AND SURROGATE ENDPOINTS

Valid comparators are a major concern, especially in osteoporosis studies. Placebo controls give clear information about benefit of an intervention versus no treatment. However, such studies are no longer justifiable in the high-risk group of men or women with osteoporosis and prior fractures, in whom the risk of subsequent fractures is substantial. The alternative of active comparator trials leads to unattainable sample sizes for fracture endpoints. This situation has led to dependence on surrogate endpoints that may be reasonable within drug classes but not between types of agents. The early work with sodium fluoride rang this warning bell early in the osteoporosis field. Although fluoride increased BMD, obvious even on X-ray, placebo-controlled fracture studies showed no fracture reduction. Thus, surrogate endpoints have inherent limitations. Such studies, supported by animal data, may be appropriate for initial proof-of-principle human and dose-finding studies, but are inadequate for new types of agents, in which mechanism of action of effect may not be clear-cut.

ANIMAL STUDIES

Similar issues apply to animal studies (i.e., validity of the scientific question, optimal number of animals used (neither too few nor too many), and scientific validity with meaningful outcomes versus surrogate endpoints). Appropriate species must be used with humane care and treatment and in vitro testing, and alternate models should be fully explored to minimize any suffering and to minimize animal use.

EXTRAPOLATION

Some extrapolation of data from initial studies, from initial time frames, and from initial study subjects is common

and must be justified on a case-by-case basis. However, many years after the use of bisphosphonates is virtually the standard of care, there are still discussions about if it is reasonable to extrapolate findings to all types of osteoporotic fractures and indeed to individuals with health states that would have led to their exclusion from the pivotal randomized controlled trials. Moreover, extrapolation beyond the original study time frame requires great care and should only be made with caution, whereas ongoing data collection allows greater confidence. This is true for both benefits and adverse outcomes. Ongoing studies are still addressing outcomes, such as fracture benefit for bisphosphonates and breast cancer reduction for selective estrogen receptor modulators (SERMs). Similar studies are sadly lacking for some adverse outcomes even when observational data are conflicting as with those related to sex hormone therapy.

STATISTICAL POWER AND PREPLANNED ANALYSES

A major issue in all studies relates to adequate power. Studies that are underpowered can seldom address any question meaningfully. This may represent a waste of investigators' time and funding resources but, where there are real risks to the subjects involved, they are not ethically acceptable. Similarly, animal studies that are underpowered, leading to uninterpretable outcomes, are also unacceptable. Importantly, in human studies, risk may be not only from the test agent per se but also from denial of an alternative effective therapy. A well-designed trial will have the backing of initial animal data and well-defined precalculated, adequate power calculations and predefined endpoints.

Full transparency of all planned statistical analyses is essential to ensure reliability of the statistical analyses and adjustment for multiple testing and preplanned versus posthoc analyses. Multiple testing is inherently likely to "reveal" significant associations (i.e., in 1 in 21 comparisons; that is what is meant by $p < 0.05$ and 95% confidence limits). There is nothing fundamentally wrong with posthoc analyses provided they are clearly defined as such. In contrast, failure to reveal and adjust for such comparisons is deceptive and misleading. This point is central to the requirement, as noted above and detailed below, for pharmaceutical companies to register studies before enrollment. However, this issue is just as critical for investigator-driven studies as it is for pharmaceutical company–designed studies. As of January 2006, epidemiological and genetic studies will also be required to state preplanned versus posthoc analyses and how many different comparisons and genetic loci have been analyzed within the data set presented. This sort of transparency of statistical approaches is key to the reliability of scientific advances.

CONFLICT OF INTEREST/ COMPETING INTERESTS

All committed scientists will and should have some "interest" in the scientific question they study. These relate to a "beautiful hypothesis" as well as to recognition, grants, and career advancement. It is critical to ensure separation of potential personal benefit from the scientific content. One of the most obvious is potential financial benefit from a particular outcome. Few are above the siren call of financial recognition for perhaps a lifetime of work and commitment. Hence, even modest potential benefit is now required to be declared for all manuscripts, presentations, etc. Openness and full disclosure are always preferable, and it is better to declare even potential competing interests if in any doubt; failure to do so is unacceptable. This is obviously central to the reliability of, and our trust in, pharmacological studies but is no less relevant to investigator-driven studies. In addition to financial issues, there are less obvious but no less pernicious conflicts that apply to the reviewing of scientific papers. The *Journal* is particularly concerned by this situation and asks that one declare any competing interest if in doubt. The ASBMR now has in place a committee to deal with any suggestions of failure to follow these and related ethical rules.

HONESTY AND TRANSPARENCY

One of the best protections against any appearance of conflict lies in honesty and transparency. Failure to acknowledge related work by others or even related work of one's own can sail dangerously close to the well-recognized problems of plagiarism and publication of fraudulent data. At a different level, duplicate publication is an issue that can distort potential subsequent review of scientific data (e.g., meta-analyses). If detected, it can lead to summary rejection of both papers even at an advanced stage of the review process or their withdrawal. The importance of these issues leads to the authorship criteria that each author must have made a substantial contribution to intellectual content, design, analysis, and/or interpretation of the study, participated in drafting or critically revising the manuscript, and approving the final version and any subsequent revisions. Acknowledgments must be supported by the consent of any person acknowledged. These requirements are particularly challenging for national and international multicenter studies and, while all contributors can be listed separately, the actual author list must meet the above criteria.

CLINICAL TRIAL REGISTRATION

In line with the concern to ensure transparency of clinical trial endpoints and preplanned statistical analyses, any clinical trial–related manuscript submitted to the *JBMR* must have been registered at http://www.clinicaltrials.gov. Trial data may be submitted by sponsors legally responsible for conducting clinical trials, governmental or international agencies conducting or supporting clinical trials, and lead principal investigators who are responsible for conducting and coordinating the overall clinical study. For multisite studies, submission of data should be coordinated among the sites so that clinicaltrials.gov does not receive multiple copies of the same trial. Each trial should follow the World Health Organization standard for minimal registration data set (http://www.icmje.org/clin_trialup.htm#table1). For more information, please see the frequently asked ques-

tions from clinicaltrials.gov (http://prsinfo.clinicaltrials.gov/faq.html or visit http://www.clinicaltrials.gov/). We will expect this information for any studies initiated after appearance of this editorial.

ADVANCEMENT OF SCIENCE

The advancement of clinical and basic science is a central aim of all good science, and it depends on the highest quality human, animal, and basic studies. Sharing of biological reagents and materials (e.g., cell lines, DNA clones, antibodies, therapeutic agents, and the like) is critical to allow reproducing of results. Intellectual property can be protected through reasonable Material Transfer Agreements.

The Editorial team of the *JBMR* and ASBMR itself are focused on the ethical issues that surround publication and scientific presentations because of the critical uncertainty of science and the consequent importance of reliability and scientific validity. The *JBMR*, through the editorial and peer review processes, is focused on ensuring that studies have appropriate informed consent and humane animal use, are scientifically valid with relevant comparators and endpoints, have openness of statistical questions and preplanned analyses, have declaration of potential conflict, have avoidance of unwarranted extrapolations, have appropriate authorship, and have appropriate referencing of our own and others work. Ensuring that these ethical issues are met and ideally surpassed means that components of the ethics of scientific publishing are always evolving. No system will be perfect, so we are always trying to improve. The *JBMR* aims to remain in the forefront of these efforts because of the centrality of these issues to the advancement of science that we all hold dear. This central aim depends on our ability to rely on the validity of scientific data and statistical analyses presented and on presentation of any potential conflicts that might affect how readers evaluate the conclusions. It is key to not stretch the facts by separating belief from data, separating potential from actual, and not overextrapolating the data into inadequately substantiated leaps-of-faith. Attention to these criteria supports our common aim of better understanding, new knowledge and furthering of science.

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