Impact of Mandatory Registration of Clinical Trials on Small Medical Journals: Scenario on Emerging Bias

To the Editor: Evidence-based medicine depends on systematic reviews of clinical trials. In many instances, authors of systematic reviews are not able to retrieve all the relevant studies done because, for example, of "publication bias" and unpublished research results, which may have been suppressed because the results were not favorable to the treatment under trial. Such selective reporting of trials may jeopardize the body of evidence and, thereby, the external validity of the systematic reviews.

To overcome parts of these problems, the International Committee of Medical Journal Editors (ICMJE) has announced a statement on clinical trial registration (1). According to this statement, any clinical trial should be registered before its beginning in a database, so that researchers can be aware of its progress and results at different stages of the study. This important action was taken to make conducting and reporting of clinical trials more transparent. By registering as many trials as possible we would, hopefully, be confident that almost all trials –those with positive as well as those with negative results – relevant to our field of interest could be readily retrievable and considered for systematic reviews, hence reducing the likelihood of publication bias. This objective, however, has been followed for a long time and this statement is not the only proposal for clinical trial registration (2-5).

Although the registration of trials sounds good, let us explore the impact of this statement on small medical journals through a hypothetical scenario. Adherence to this policy will not harm mainstream journals with thousands of submissions per year. However, many editors of small journals, particularly those published in developing countries, are already short of submission of good or even modest, though acceptable, manuscripts, so that their journals often do not get published on time. Adhering to the ICMJE statement means that the editors of medical journals must ask for the registration status of each submitted clinical trial as a pre-requisite for peer-review and publication of the work. If these editors find the trial not registered, no matter what the manuscript says, according to the policy, they have to reject it; they may lose some of the few good manuscripts for lack of registration. The authors of these rejected manuscripts, however, will certainly look for another journal to publish their works.

Many researchers working in developing countries, who face several problems (eg, bureaucracy) in running their research, are unlikely to comply with registering their works and its associated complexities (6). Many of them may not even become aware of this statement unless one of their manuscripts was rejected for such reason.

On the other hand those editors who have not already endorsed the statement will face an increasing submission rate due to the shift of the clinical trials rejected by domestic and international medical journals for the lack of registration. This may be treated as an opportunity and will help these editors to absorb more authors and manuscripts, to get published on time, and perhaps to improve the scientific quality of their journals. Although these unregistered trials might be of lower quality than registered ones published in high-caliber journals, lack of registration does not necessarily mean so – registration, per se, does not ensure the quality of a trial. Thus, while adherence to this policy might be a threat to some small journals, it might be an opportunity for others that do not endorse the statement of clinical trial registration. The editors of small journal who have adhered to the statement and suffered its consequences, to save their journals, may no longer abide with the policy and in practice, soon break it. Alas, many of the authors will have switched to another journal and will not be back. That is why I believe only a few editors of small medical journals will endorse the statement and abide the policy.

On the other hand, all the regulations established so far for the conduct of clinical trials (eg, randomization, blinding, and concealment) have been set to abolish bi-

ases, hence to produce results with good external validity. Nonetheless, the recent ICMJE statement on trial registration neither abolishes any bias in the conduct of the research, nor increases the quality of the data produced. It was just established to increase the clarity of the work and to abolish the publication bias. If even all editors of medical journals endorse the ICMJE statement on trial registration, any clinical trial that has not been registered for any reason, even if it is methodologically sound, will not be given the fair chance of peer-review and will not be published. This selective reporting, in turn, introduces another type of bias – let us call it "trial registration bias" – that may jeopardize the body of evidence and the external validity of the systematic reviews as well.

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In Reply: We share the concern of Dr Habibzadeh for the registration of trials from small and developing countries. However, we think that the present editorial policy of trial registration is a great opportunity for editors in such communities to educate authors and to promote the practice of trial registration. Journal editors, as respected professionals and researchers in their own community (1), can be a crucial factor in raising the awareness and understanding the rationale for the registration of clinical trials. They may be the source of information for all interested in conducting and publishing results of clinical trials. They can also actively promote registration by alerting institutional review boards or ethical committees at hospitals and academic and research institutions. Because all research involving human subjects has to be approved by such legal bodies, information about trial registration would then reach all trials in the phase of planning.

We do not think that adherence to registration policy will decrease the number of articles in small journals. First, many clinical trials in smaller and developing communities are a part of larger multicenter trials or conducted by large pharmaceutical companies, which should be well aware of the ICMJE registration policy as they are most interested in publishing the results about their new pharmaceutical products of devices. In fact, researchers from the smaller research communities should make sure that the pharmaceutical company approaching them for a possible trial has already registered or plans to register the trial before the enrolment of the first participant. Second, we believe that trial registration can benefit independent research from small and developing countries because registration would make such studies visible to the global scientific community and, in fact, contribute to the protection of their intellectual rights.

The registration of trials has gained its momentum with the deadline set by the ICMJE, as is clearly visible from the dynamics of registrations at the largest database, *ClinicalTrials.gov* (2,3). For us, the editors in a small country and even smaller medical scientific community, who have actively tried to increase the awareness of trial registration, it was gratifying to learn that there were 77 trial registered from Croatia at the *ClinicalTrials.gov*. Small countries may have more problems in choosing where to register, as their national or even regional trial registration databases (4) may not satisfy all requirements of the ICMJE (5).

We also cannot agree that the registration of trials does not abolish biases in conducting clinical re-

search. It abolishes perhaps the bias very relevant for the medical community – the publication bias. Publication of trial results is the public presentation of the research, so it is imperative for the published presentation to reflect accurately the trial protocol. Medical journals are the main medium for public presentation of clinical trials, and their mandatory registration ensures that we can check the results in a submitted manuscript against the proposed trial protocol and thus ensure that the presentation is honest, transparent, and accurate.

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