Prospective Registration of Marker Evaluation Studies: Time to Act

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In 2005, the International Committee of Medical Journal Editors (ICMJE) initiated a policy requiring investigators to deposit essential information about trial design into an accepted clinical trials registry before the onset of patient enrollment. This policy was aimed at ensuring that information about the existence and design of trials was publicly available from the start, a requirement that would stimulate the dissemination of information among clinicians, researchers, and patients. Registration would also help to assure trial participants that the information that accrues as a result of their altruism becomes part of the public record. In addition, prospective trial registration would facilitate transparency and completeness of the reporting of clinical trials and, ultimately, strengthen the validity and value of the scientific evidence base.

ICMJE member journals made prior registration a requirement before starting the peer-review process of a submitted trial report. Because of that policy, which has been adopted by many other journals, trial registration became an immediate and major success, and the number of entries into the registries has grown considerably. The WHO Registry Network currently includes 13 primary registries (as of September 2011), which all meet common criteria for content and quality control, and are operated by nonprofit organizations. The WHO International Clinical Trial Registry Platform Search Portal provides a single point of access to a searchable database containing trial registration data sets of all registries in the WHO Registry Network (http://who.int/ictrp/search/en/). This portal has been developed to make it easier for users of registries to search for ongoing and completed clinical trials. Prospective registration of clinical trials is now seen to increase confidence in the results of randomized controlled trials and in the scientific community that generates them (1, 2).

The ICMJE initiative initially targeted registration of clinical trials of therapeutic interventions. In comparison, registration of observational studies has received somewhat less attention, although interest is growing (3, 4). At a meeting in London in September 2009, a diverse group of experts in the field discussed the topic. Afterwards, 2 major scientific journals announced that they would actively encourage researchers to register observational studies in a manner similar to what has become a requirement for clinical trials (4, 5). Some of these clinical trial registries already include observational studies, and the average number of observational studies registered per year has grown consistently over time. Observational studies now represent about 15% of all studies registered (6).

This renewed interest in the registration of all studies, not just randomized trials, rekindled the discussion about the need for prospective registration of diagnostic-accuracy studies or, more generally, biomarker evaluation studies. Should all biomarker studies also be registered before they start collecting data?

Before one can recommend or even require registration of biomarker studies as the solution, we should examine the problems registration can be expected to solve. Depositing essential information in these registries may help in reducing publication bias and in preventing selective reporting, both of which are widely recognized problems in the biomedical literature. Researchers and journal editors may handle positive or favorable results differently from negative or inconclusive findings. Unfavorable results are less likely to be included in a report, to be submitted to a journal, and to be considered for publication. Publication bias jeopardizes the validity of all attempts at metaanalysis: The published evidence may not offer a fair representation of the existing evidence.

The extent of publication bias and selective reporting in clinical trials was most clearly assessed with a cohort of trials approved by ethics review boards (7). Although we do not know of similar exercises for biomarker studies, we can expect comparable mechanisms for selective and incomplete reporting in marker studies.

Ionnanidis and Panagiotou recently demonstrated that frequently cited biomarker studies report effect sizes that were often higher than effect sizes reported for subsequent larger studies of the same biomarker and were more extreme than summary estimates reported in a meta-analysis of that biomarker. One of the
mechanisms they refer to was a general interest in publishing major discoveries, which can lead to selective reporting due to chasing significance (8).

Prospective registration of clinical trials was instigated by the concern that important research findings regarding the efficacy and safety of interventions were withheld from the public (9). Although biomarkers differ from pharmaceuticals—unlike most drugs, markers have few side effects—similar concerns apply. Faulty clinical decision making based on inflated estimates of marker performance could put patients at risk by leading to faulty diagnoses, by subjecting patients to the side effects of treatment that they do not need, or by withholding effective management for their condition.

Much of the ethical rationale for the prospective registration of clinical trials also applies to the registration of biomarker studies, or to all studies involving humans (10). Every study that directly acquires data from human participants requires the ethical obligation to participants and the public to achieve transparency in the reporting of study results.

There are several other reasons in favor of prospective registration. Many biomarker studies have major methodologic shortcomings (11). Prior documentation of the study design in a registry can improve the quality of the research. Other reasons are identifying knowledge gaps, facilitating collaboration in research, and avoiding redundant studies.

So, in summary, the case for the prospective registration of biomarker studies appears to be clear. Yet before making a general recommendation, we should critically examine the conditions necessary for the registration of biomarker studies. Merely obtaining a trial registry number will not be sufficient.

To be useful to registry users, registries of biomarker studies should prepare a list of essential items to be included for marker studies. Professionals from academia and industry could sit down and develop the list of essential items to be included.

At present, registered trials use a 20-item format in the WHO Trial Registration Data Set. These items reflect the minimum amount of trial characteristics that must appear in a registry to make it scientifically informative. Agreement was reached on the minimum data set required at the time of trial registration during a 3-day meeting in Geneva (2005) with various representatives of major stakeholders, including academic researchers, governments, pharmaceutical industries, journal editors, ethicists, and registry owners (12).

A comparable set of registration data for biomarker studies does not currently exist. Individual registries can choose to register biomarker studies if they wish, but there is no obligation to do so. A basic search in the WHO Search Portal of the International Clinical Trials Registry Platform retrieved 1953 biomarker studies from trials (accessed September 2011), but these records reflect a very broad variety of registered information.

We believe that the minimum data set for biomarker studies should include a unique trial identifier, contact information, a definition of the marker, the clinical context and the relevant outcomes, main results, criteria for the expected marker performance, and the targeted study size. These items would fit more or less to key areas of registered “20 items” trial entries.

André and colleagues recently proposed the development of a separate, dedicated registry of marker evaluation studies. This registry would have the disadvantage of making searches more problematic, would entail a duplication of efforts, and could disconnect marker evaluation studies embedded in clinical trials—an area with clear potential for growth, given the interest in predictive markers, companion diagnostics, and personalized medicine (13).

More authors have lamented the poor state of biomarker research. Poste has pointed out “the dismal patchwork of fragmented research on disease-associated biomarkers” and argued that it should be replaced by a coordinated “big science” approach (14). After the unraveling of the human genome, research into biomarkers has not yet delivered on its promise. Society invites researchers to be complete and transparent in reporting the results of research involving human participants. Biomarker studies are no exception. Prospective registration of key elements of study designs could help us all to achieve this goal and could improve the effectiveness of studies evaluating biomarkers and medical tests.

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Opinions

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