EDITORIALS

Salvation by Registration

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Robert Motzer was not happy when he learned that his manuscript about the treatment of renal cancer with sunitinib could not be considered for publication by the *Journal*. His paper was rejected not on the basis of the science it reported or of the *Journal*'s editorial priorities, but because of the study's inadequate registration in the ClinicalTrials.gov database.

Members of the *Journal*'s staff routinely check the database registration of trials that are being considered for publication. The registration provided by Dr. Motzer — NCT00083889 in ClinicalTrials.gov — failed to meet the standards established by the International Committee of Medical Journal Editors (ICMJE).[1] This registration had been filed by Pfizer, the study's sponsor. On August 26, 2005, the sponsor had entered the following in the outcome-measures field: "Primary (Secondary) outcome information was omitted due to [its] commercial sensitivity and will be revealed at a later date." Since this entry regarding the study's outcome was clearly not informative, the decision was made, on this basis alone, not to consider the manuscript further.

Given that the article appears in this issue of the *Journal*,[2] there is clearly more to this story. Shortly after Motzer was informed that his manuscript could not be considered, the *Journal* learned that one of his coauthors had registered the trial through one of the cancer centers, rather than through Pfizer. This June 2005 registration in ClinicalTrials.gov, NCT00098657, included an informative entry in each of the fields required by the ICMJE. Thanks to this second registration, the manuscript met the requirements to be considered for publication.

In the past year, Pfizer has changed its posture on the registration of clinical trials. None of the database entries for the 115 trials that Pfizer has registered since the beginning of 2006 are missing information in either the intervention or the outcome-measures field, though there are still a few Pfizer records created before 2006 that are missing some of this information. Pfizer is not alone: since the start of 2006, other pharmaceutical companies have also improved the way they register trials. As of December 1, 2006, of the 2983 pharmaceutical-industry registrations filed in ClinicalTrials.gov in the past year, 8% were missing information on outcome measures (down from 26% of the 5355 industry registrations entered before January 1, 2006), and none were missing the name of the intervention. (A small number of trials that were registered before 2006 were still missing intervention names.) Although more can be done, this improvement in registration quality is to be praised.

In the current case, the author's inadvertent duplicate registration allowed the article to be published in an ICMJE-compliant journal, but a better approach for authors in the future would be to coordinate with study sponsors to ensure that a single, informative registration record is provided. Multisite studies, including those conducted in multiple countries, should also be registered under one record. Ensuring that registration is completed properly requires close cooperation among investigators, sponsors, and other study officials.

Investigators can contact the registry database if they are not certain whether their study has already been registered. Inadvertent duplication creates difficulties for the registry and the research community by making it impossible to determine how many and which studies are being conducted, thereby partially undermining the purpose of registration. (Once duplicates are found, ClinicalTrials.gov suppresses one record and cross-references both NCT numbers.)

We urge investigators, including those who receive funding from the National Institutes of Health or other nonindustry sources, to ensure that the studies they conduct are registered with complete information and to check the registration records for accuracy. Specific information about how to register a study in ClinicalTrials.gov can be found at http://prsinfo.clinicaltrials.gov and is described in a recent article.[3] Investigators should avoid participating in trials if they are not confident that an accurate and complete record of the trial will be maintained in an acceptable trials registry.

The sunitinib study is a case in which the willingness of one of the investigators to disclose key information about the protocol allowed a study to be considered for publication by one of the many medical journals that adhere to the ICMJE trials-registration policy. The message should be clear to all investigators participating in clinical trials: before you enroll a patient in a study, be sure that there is a full and appropriate registration of the trial in a public database approved by the ICMJE (www.icmje.org). It could salvage a study report that otherwise would not be published.

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From ClinicalTrials.gov, National Library of Medicine, National Institutes of Health, Bethesda, MD (D.A.Z.).

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Renal-Cell Carcinoma — Molecular Pathways and Therapies

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Renal-cell carcinoma is among the most resistant of tumors to therapy. Until 2005, only a single treatment, high-dose interleukin-2, had been approved by the Food and Drug Administration (FDA) for the treatment of this disease. The approval was based on durable complete responses in 5% of patients with metastatic disease,[1] but high-dose therapy with interleukin-2 is quite toxic, and in most patients its benefit is unclear.

In this issue of the *Journal*, Motzer et al.[2] and Escudier et al.[3] report on the results of phase 3 trials of two oral, small-molecule kinase inhibitors, sunitinib malate and sorafenib, respectively. Both drugs were found to improve progression-free survival in patients with metastatic clear-cell renal-cell carcinoma (a histologic type that accounts for about 75% of all renal-cell tumors). Neither sunitinib nor sorafenib had a significant effect on overall survival, but a final analysis of survival has not yet been reported. An important point in evaluating these trials is that both sunitinib and sorafenib caused clinically significant toxic effects. The two drugs are now approved by the FDA for use in advanced renal-cell carcinoma.

A biologic rationale exists for treating clear-cell renal-cell carcinoma with sunitinib or sorafenib. In at least 60% of these tumors, the von Hippel–Lindau tumor-suppressor gene (*VHL*) is inactivated. The VHL protein is a critical component of a cellular pathway that couples changes in oxygen availability to gene expression through the regulation of a transcription factor called the hypoxia-inducible factor (HIF).[4] HIF is a heterodimeric (HIFα/β) transcription factor that regulates a program of gene expression engaged in facilitating adaptation to tissue hypoxia. The VHL protein is involved in the degradation of the HIFα subunit, specifically when oxygen is abundant, thereby coupling oxygen needs to HIF activity. Unlike normal cells, cells deficient in VHL inappropriately accumulate HIFα under conditions of normal oxygen tension and have increased expression of HIF-regulated genes, including genes encoding angiogenic factors (Fig. 1). The up-regulation of HIF in VHL-deficient cells plays a critical role in tumorigenesis. Indeed, the ability of VHL-deficient renal carcinoma cells to form tumors in xenograft models can be reduced significantly by inactivation of HIF.[5,6]

The observation that inactivation of VHL results in increased HIF activity and thereby increased expression of vascular endothelial growth factor A (VEGF), platelet-derived growth factor β (PDGFβ), and transforming growth factor α (TGF-α) provided the rationale for targeting these