THE AUTHORS REPLY: Auger and Jamieson highlight the importance of pulmonary endarterectomy as a potentially curative treatment for chronic thromboembolic pulmonary hypertension. In CHEST-1, rigorous measures were taken to ensure that only patients with chronic thromboembolic pulmonary hypertension that was adjudicated to be technically inoperable or who had persistent or recurrent pulmonary hypertension after pulmonary endarterectomy were included. An expert committee to assess operability reviewed 51% of cases during screening; local decisions (by a collaborating experienced surgeon, as defined in the study protocol) were permitted in the remaining 49% of cases. We completely agree that the availability of a new specific medication for patients with inoperable chronic thromboembolic pulmonary hypertension should not exclude any patient from this potentially curative surgical therapy.

In response to Egom: direct soluble guanylate cyclase stimulation by riociguat leads to dose-dependent production of cGMP and vasodilatory effects that cannot be further maximized by coadministration of a phosphodiesterase-5 inhibitor.[1] This is the rationale for individual dose adjustment of riociguat (according to a strict protocol) that is limited by the predefined boundaries of systemic systolic blood pressure. Although concomitant administration of a phosphodiesterase-5 inhibitor could in theory result in increased efficacy, this would most likely occur only in patients receiving an insufficient dose of riociguat, which in clinical practice should not happen. Furthermore, PATENT PLUS (Evaluation of the Pharmacodynamic Effect of the Combination of Sildenafil and Riociguat on Blood Pressure and Other Safety Parameters) showed no evidence of a positive risk–benefit assessment when riociguat was combined with a standard dose of sildenafil, predominantly because of the number of discontinuations,[2] and this combination is contraindicated in the prescribing information for riociguat in the United States and Canada.

Oh et al. note that lifelong anticoagulation is mandatory in patients with chronic thromboembolic pulmonary hypertension. All patients received effective oral anticoagulation for 3 months or more before enrollment and throughout CHEST-1, as stipulated in the study protocol.

Finally, the concerns raised by Post were seriously considered when the study was designed in 2006 and 2007. All local ethics committees approved the study, and all patients were informed about the potential risks and benefits of participating. Given the relatively short duration of the study, the fact that predefined criteria for discontinuation were implemented to allow patients to switch to commercially available therapy for pulmonary arterial hypertension if needed, and that medications specifically for pulmonary arterial hypertension are not available in all countries, it was considered justifiable to conduct the study in this way.

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Since publication of their articles, the authors report no further potential conflict of interest.

1. Schermuly RT, Janssen W, Weissmann N, Stasch J-P, Grimminger F, Ghofrani H-A. Riociguat for the treatment of pulmonary hypertension. Expert Opin Investig Drugs 2011;20:567-76.
2. Galiè N, Neuser D, Müller K, at el. A placebo-controlled, double-blind phase II interaction study to evaluate blood pressure following addition of riociguat to patients with symptomatic pulmonary arterial hypertension (PAH) receiving sildenafil (PATENT PLUS). Am J Respir Crit Care Med 2013;187: Suppl:A3530. abstract.

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Randomized Clinical Trials — Removing Obstacles

TO THE EDITOR: Reith et al. (Sept. 12 issue)[1] suggest that clinical trials comparing widely accepted therapies should not be held to the "excessively detailed informed consent" standards of trials involving new therapies. Their justification appears to be as follows: for treatment purposes, patients already accept the risks of well-understood therapies for which evaluative data are

sparse, so why should clinicians and researchers need to adhere to more stringent consent standards when providing those same therapies in a research context?

Clinical research is designed to narrow the scope of clinical uncertainty by identifying unknown risks and benefits and determining which therapy is most effective. Inviting patients (who are already in a vulnerable state) into this realm of uncertainty — no matter how small — without fully acknowledging the implications of their participation is to treat them as passive instruments of medical expertise rather than as people who deserve to exercise control over their lives. That such invitations may take place in the clinical setting without this acknowledgment is not an argument for easing research consent requirements — it is an argument in favor of strengthening clinical consent standards.

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1. Reith C, Landray M, Devereaux PJ, et al. Randomized clinical trials — removing unnecessary obstacles. N Engl J Med 2013; 369:1061-5.

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THE AUTHORS REPLY: The consent process should appropriately inform clinical-trial participants of relevant aspects of the trial, including the reasonably foreseeable risks and alternative available treatments (with their potential benefits and risks).[1] In the context of trials comparing widely accepted treatments, the alternative to participation in the trial is essentially the receipt of routine clinical care. Robust safety and efficacy data to support the use of many treatments commonly used in practice is lacking, yet such treatments are frequently prescribed without discussing this uncertainty with the patient, and hence by extension they are effectively prescribed without informed consent. For example, aspirin is commonly prescribed as primary prevention for patients with diabetes who do not have vascular disease, despite a paucity of reliable knowledge about the risks or benefits of this approach. If trial procedures remain disproportionate to their likely hazards as compared with routine medical care, medical practice will continue to use therapies unknowingly that may be damaging because of the impediments to conducting trials to resolve such uncertainties. These evidence gaps are harmful to individual patients and public health.

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Since publication of their article, the authors report no further potential conflict of interest.

1. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Guideline for good clinical practice E6(R1). June 10, 1996 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf).

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Abusive Prescribing of Controlled Substances

TO THE EDITOR: In their Perspective article, Betses and Brennan (Sept. 12 issue)[1] state that overdose of a controlled substance has become the second-leading cause of accidental death in the United States. They go on to discuss the ethical duty of pharmacists to combat this growing public health problem. To this end, they report on the effort undertaken by their employer, CVS Caremark, to curtail the inappropriate prescribing of narcotics.

However, the senior vice president and chief medical officer of CVS Caremark neglect to mention that in April 2013, their company paid $11 million in fines to settle charges brought by the Drug Enforcement Administration that CVS pharmacies in Oklahoma and elsewhere were violating the Controlled Substances Act by irresponsibly dispensing narcotics.[2]

All the while, CVS has continued to sell the nation's leading avoidable cause of death — tobacco[3] — in nearly every 1 of its 7400 drug stores nationwide. Pharmacists and physicians