

# Physicians' Preferences for Active-controlled versus Placebo-controlled Trials of New Antihypertensive Drugs

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**OBJECTIVE:** To evaluate physicians' preferences for referring patients to, and using information from, active-controlled trials (ACTs) versus placebo-controlled trials (PCTs) of new antihypertensive drugs.

**DESIGN AND SETTING:** Nationwide mailed survey, with telephone contact of nonresponders to assess nonresponse bias.

**PARTICIPANTS:** One thousand two hundred primary care physicians randomly selected from the American Medical Association's Master File. Of 1,154 physicians eligible to respond, 651 (56.4%) returned completed questionnaires.

**MEASUREMENTS AND MAIN RESULTS:** We measured physicians' stated willingness to encourage hypertensive patients to enroll in ACTs and PCTs of new antihypertensive drugs, their views of the relative merits of ACTs versus PCTs, their stated willingness to prescribe new drugs tested in ACTs or PCTs, and their views regarding the overall justifiability of the 2 designs. Physicians were significantly more likely to indicate they would encourage their patients to enroll in ACTs than in PCTs ( $P < .0001$ ). Physicians thought ACTs provided more valuable information for their practices, were more likely to lead to a public health benefit, offered enrolled patients greater opportunity for personal benefit, and were less likely to expose enrolled patients to unnecessary risks (all  $P < .0001$ ). Physicians were more likely to prescribe new drugs that had been compared in ACTs ( $P < .0001$ ), and viewed ACTs as a more justifiable method for testing new antihypertensive drugs ( $P < .0001$ ). There was no evidence of nonresponse bias for these main results.

**CONCLUSIONS:** Although PCTs remain the standard method for testing new antihypertensive drugs, physicians strongly prefer ACTs. Using ACTs to test new antihypertensive drugs may enhance the efficiency of patient recruitment and more strongly influence physicians' prescribing practices.

**KEY WORDS:** clinical trials; placebo-controlled trials; antihypertensive drugs; physicians' preferences; ethics.  
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In evaluating a new antihypertensive drug, should that drug be compared to placebo, or to an alternative drug already known to be effective?<sup>1-5</sup> Placebo-controlled trials (PCTs) have several advantages. By comparing new agents to placebo, they use a standard reference comparison, and provide unambiguous measures of efficacy.<sup>3,6,7</sup> Furthermore, PCTs are presumed to be more efficient because they generally require smaller sample sizes than when active controls are employed.<sup>6,7</sup>

However, physicians may have concerns about letting hypertensive patients receive placebo.<sup>8</sup> Thus, they may refer only a selected group of their patients to PCTs (e.g., patients with the fewest comorbid illnesses, those perceived to have the lowest risks for adverse events off medications, or those who have not responded to standard treatments). Because these patients may not reflect the broader population of those to whom the intervention would be available, such selective enrollment limits the generalizability of the results.<sup>9-13</sup>

By contrast, active-controlled, noninferiority trials<sup>7,14,15</sup> compare new agents to previously established therapy to determine whether they are at least as good as an available alternative. This information may be more valuable<sup>16,17</sup> to clinicians because it can help them choose which among competing alternatives to prescribe (whereas PCTs can show only whether a new agent is better than nothing).<sup>4,9</sup> Additionally, because active-controlled trials (ACTs) do not expose research subjects to placebo in settings where effective therapies exist, physicians might be more willing to refer hypertensive patients to these trials,<sup>8</sup> and patients might be more willing to enroll in them.<sup>18</sup>

Despite the different advantages of the 2 designs, the U.S. Food and Drug Administration requires data from PCTs before approving new antihypertensive drugs.<sup>5,19</sup> To further inform the debate on the scientific and ethical merits of these competing designs,<sup>1-5,20</sup> we studied physicians' views on 3 specific issues: 1) their willingness to refer their hypertensive patients to ACTs versus PCTs of new antihypertensive drugs; 2) the relative influence that information derived from ACTs and PCTs would have on their prescribing practices; and 3) their views of the justifiability of ACTs and PCTs in testing new antihypertensive drugs.

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## METHODS

### Questionnaire Development

This study was approved by the Institutional Review Board of the University of Pennsylvania. We developed the questionnaire by conducting focus groups and personal interviews with 50 physicians at the Hospital of the University of Pennsylvania. We then pilot tested the questionnaire by mailing it to 75 clinicians randomly selected from the American Medical Association's Master File of Physicians.

In the final questionnaire, we first assessed physicians' willingness to encourage their moderately hypertensive patients (blood pressure = 155/95 prior to medication, now with blood pressure = 130/80 on a standard medication) to go off their treatment and enroll in an ACT and in a PCT. Each trial was described as having a 1-month placebo washout phase, followed by a 2-month treatment phase in which patients would be randomized to groups receiving either a new drug or placebo (the PCT), or the same new drug or standard drug (the ACT). Physicians responded using a 5-point scale from "definitely not" to "definitely" to indicate their willingness to encourage the described patients to enroll in each trial.

Second, we asked physicians to directly compare the 2 trial designs with regard to 1) the trials' abilities to provide "useful information for [the physicians'] practices," 2) the likelihood that each trial would "provide knowledge leading to a public health benefit," and the 3) risks and 4) benefits each conferred on enrolled patients. Physicians responded using 5-point scales from "definitely PCT" to "definitely ACT" to indicate which design was more likely to have each of the 4 characteristics.

Third, we described a tradeoff to physicians in which more experimental drugs "in the pipeline" could be tested if physicians were willing to refer their patients to trials in which greater percentages of patients would be randomized to placebo. We told physicians that such a tradeoff existed because, as the percentage of patients assigned to placebo is reduced from 50%, more patients must be enrolled in each individual trial to obtain the same statistical power. We further explained that limited financial resources, as well as limited eligible participants, restricted the total number of trials that could be conducted at one time. Our goal was to force physicians to make an explicit tradeoff between increasing potential benefits to society (in terms of the number of new drugs that could be tested) and reducing potential risks to study participants (in terms of the probability of receiving placebo).

We described 3 sets of trials to physicians, and asked them to rank these sets in the order in which they would wish to refer their hypertensive patients. In Set 1, 10% of patients would be assigned to the placebo group, and 1 new drug would be tested; in Set 2, 30% of patients would be assigned to the placebo group, and 3 new drugs would be tested; in Set 3, 50% of patients would be assigned to the placebo group, and 5 new drugs would be tested.

Fourth, we asked physicians which of 2 drugs they would prescribe for hypertensive patients who could no longer tolerate their present treatment with "Standard Drug X." Drug A was described as having reduced blood pressure by an average of 15 mm/Hg systolic, and 8 mm/Hg diastolic in a large, premarketing PCT in which it was superior to placebo at the  $P < .0001$  level. Drug B was also described as having reduced blood pressure by 15 mm/Hg systolic, and 8 mm/Hg diastolic, but in an ACT in which it was statistically equivalent to Standard Drug X. Physicians stated their prescribing preference on a 5-point scale from "definitely drug A" to "definitely drug B."

Finally, we asked physicians to evaluate the overall "justifiability" of ACTs and PCTs in the development of new antihypertensive drugs using a 5-point scale from "PCTs are much more justifiable" to "ACTs are much more justifiable." Physicians were also asked to explain their preferences with open-ended responses.

### Participants

We mailed the questionnaire and a cover letter to 1,200 general internists and family practitioners randomly selected from the Master File. As part of a separate study of response rates,<sup>21</sup> we randomly assigned physicians to receive either a \$5 or \$10 bill as an incentive (there were no differences in the substantive responses provided by physicians receiving the 2 different incentives). We tracked respondents by numerically coding the questionnaires and return envelopes. We mailed a second questionnaire packet to all physicians who did not respond to the initial mailing within 5 weeks. Physicians returning questionnaires with more than 80% of items completed, up to 6 weeks after the second mailing, were included in the analyses.

To assess the potential for nonresponse bias, one investigator (SDH) placed phone calls to 70 nonresponding physicians, selected from a list of nonresponders by random number generation. Of these, 30 had matching telephone numbers and were available for interview. We compared these physicians' demographic and practice characteristics, as well as their answers to a subset of the original questionnaire items, with those of physicians responding to the mailed questionnaire.

### Statistical Analysis

Given approximately 650 completed responses, we would have 90% power to detect group differences of 5% or greater in mean responses on each of the 5 main outcome measures. Interviewing 30 nonresponders would then provide 80% power to detect differences (nonresponse biases) of 15% to 20% on each of the outcomes measured in both groups.

We used Wilcoxon signed-rank tests for paired, within-subjects comparisons, and Mann-Whitney tests to evaluate preferences for ACTs versus PCTs across subjects. We used  $\chi^2$  tests for trend to evaluate preference differences between responders and nonresponders, and between

groups defined by gender, specialty, years in clinical practice, proportion of professional time spent in patient care, and whether physicians had previously enrolled patients in randomized trials. We used the Friedman test to analyze ranked preferences.<sup>22</sup>

## RESULTS

Six hundred fifty-one physicians completed a mailed questionnaire. Three additional physicians returned incomplete questionnaires, and were counted as nonresponders. The response rate was 56.4% after excluding 46 (3.8%) ineligible respondents (23 bad addresses and 23 deceased or retired physicians). Table 1 describes the respondents.

### Enrollment Preferences

Most respondents (67.1%; 95% confidence interval [95% CI], 63.4% to 70.7%) indicated they would probably or definitely encourage their hypertensive patients to enroll in the ACT, compared with 29.7% (95% CI, 26.2% to 33.3%) who would encourage enrollment in the PCT. Pairwise comparisons revealed that physicians were significantly more willing to encourage enrollment in ACTs than in PCTs ( $P < .0001$ ) (Table 2). Physicians who had previously enrolled or referred patients to hypertension trials ( $P = .006$ ) or to any other randomized trials ( $P = .0001$ ) were more likely to indicate they would encourage their patients to enroll in ACTs than were physicians without prior research participation. There was no association between previous patient enrollment and current willingness to encourage enrollment in PCTs. Gender, specialty, years of clinical practice, and proportion of time spent in direct patient care were not associated with enrollment preferences.

Physicians viewed the ACT as providing more useful information for their personal practices, as contributing more broadly to a public health benefit, as offering

enrolled patients a greater chance for personal benefit, and as being less likely to place subjects at unnecessary risks (all  $P < .0001$ ) (Fig. 1). In open-ended responses, physicians generally offered 2 reasons for preferring ACTs. Some felt that "if the patient has hypertension and is responding to medication, it's unethical to put him in a placebo trial." Others focused on the value of the information provided by the different trial designs. As one said, "I am interested in [the] benefit of newer medications versus old. We have already established that antihypertensives are better than placebo."

When we introduced the tradeoff in which physicians could choose to refer patients to trials with smaller probabilities of placebo assignment, but only at the cost of limiting the number of new drugs that could be tested, physicians still preferred to limit their patients' exposures to placebo. Physicians gave significantly higher preference rankings to sets of trials in which fewer patients would receive placebo, even though referring patients to these trials limited the number of new drugs that could be developed ( $P < .0001$ ) (Fig. 2).

### Prescribing Preferences

Most physicians (55.5%) were neutral in their preferences for prescribing a novel antihypertensive that had been compared against placebo versus a similar agent that had been compared against an active drug. These physicians commonly explained their choice by noting that "because the safety and efficacy of each [drug] appear to be the same, one simply has to choose one." Nevertheless, 31.2% (95% CI, 27.6% to 34.8%) of respondents said they would be more likely to prescribe the drug that had been shown to be equivalent to an active agent, compared with 13.3% (95% CI, 10.7% to 16.0%) of respondents favoring the drug shown to be superior to placebo ( $P < .0001$ ). Physicians who thought ACTs provided more useful information for their practices were significantly more likely to indicate they would prescribe the drug that had been compared in an ACT ( $P < .0001$ ). Physicians typically explained this choice by noting, for example, that the ACT "provides better evidence that the new drug is a reasonable alternative to what the patients were taking."

### Justifiability of ACTs and PCTs

A majority of physicians (67.3%; 95% CI, 63.7% to 71.0%) thought ACTs were more "justifiable" than PCTs as a means of testing new antihypertensive drugs, whereas 10.4% (95% CI, 8.0% to 12.7%) thought PCTs were more justifiable ( $P < .0001$ ).

### Nonresponse Bias

There were no differences between responders and initial nonresponders contacted by telephone in their years of clinical practice ( $P = .76$ ), their willingness to encourage patients to enroll in PCTs ( $P = .33$ ), or their relative

Table 1. Characteristics of Respondents

Gender, % male	74.6
Years of medical practice*	19 (13 to 27.5)
Medical specialty, %	
General internal medicine	39.3
Family practice	49.8
Medical subspecialty	3.5
Other	7.4
H/wk in direct patient care*	40 (30 to 50)
Percentage of professional time spent on*	
Direct patient care	95 (80 to 100)
Administrative duties	10 (5 to 15)
Teaching	5 (3 to 10)
Research	0 (0 to 10)
Previously referred/enrolled patients in:	
Hypertension research, %	34.1
Other research, %	58.4

\* Median (interquartile range).

**Table 2. Physicians' Willingness to Encourage Hypertensive Patients to Enroll in an Active-controlled Trial (ACT) or Placebo-controlled Trial (PCT)**

Willingness to Encourage Enrollment in an ACT	Willingness to Encourage Enrollment in a PCT					Total
	Definitely Not	Probably Not	Not Sure	Probably	Definitely	
Definitely not	27	2	1	2	0	32
Probably not	12	61	3	13	5	94
Not sure	8	41	30	7	0	86
Probably	35	147	33	108	3	326
Definitely	15	30	8	31	22	106
Total	97	281	75	161	30	644

*Italicized numbers along the table's diagonal represent physicians who were equally willing to encourage enrollment in either trial. Physicians represented by numbers below the diagonal were more willing to encourage enrollment in the ACT. Physicians represented by numbers above the diagonal were more willing to encourage enrollment in the PCT. Physicians were more likely to encourage enrollment in the ACT (P < .0001 by Wilcoxon signed-rank test for matched pairs). Excluded from the table are 7 physicians who did not answer one or both questions.*

willingness to encourage enrollment in ACTs versus PCTs (P = .15). Nonresponders reported spending more hours per week in direct patient care than did responders (mean difference = 7.7 hours; 95% CI, 1.1 to 14.2; P = .02), and were less likely to encourage their patients to enroll in ACTs (P = .007).

**DISCUSSION**

This study suggests that primary care physicians consistently and strongly favor testing novel antihypertensive drugs via active-controlled, noninferiority trials, rather than via placebo-controlled trials. Most physicians indicated they were more willing to refer their patients for enrollment in ACTs, were more likely to prescribe a drug that had been tested in an ACT, and that they considered ACTs a more justifiable means of testing new antihypertensive drugs. Indeed, physicians preferred to refer their hypertensive patients to trials with reduced probabilities of placebo assignment even when confronted with the plausible tradeoff that doing so would reduce the number of new drugs that could be evaluated.

Similar concerns among physicians about whether trial participation is in their patients' best interests have been reported in trials of cancer treatment and prevention.<sup>23-28</sup> In such trials, physicians' unwillingness to enter their patients severely limited the efficiency of patient recruitment, threatening the trials' statistical power to answer their primary research questions, and limiting the generalizability of the results.<sup>29</sup>

For trials of new antihypertensive drugs, we had hypothesized that physicians would be more willing to refer their patients to ACTs. However, we also predicted that they would want to know an agent's absolute efficacy, obtainable only through PCTs,<sup>19</sup> prior to prescribing a new drug. Such a finding would have created a dilemma by suggesting that recruitment to ACTs may be more efficient, but that the knowledge gained through PCTs would be more clinically valuable. Instead, we found that most physicians focused on the reported efficacy of the new agent, regardless of the comparator used in a trial, and that

many actually preferred to prescribe the drug compared against an active alternative.

There are three important implications of these findings. First, the presumed efficiency of requiring smaller sample sizes may not be a reason to favor PCTs. Although more patients must be enrolled in ACTs, the likely gains in recruitment rate due to increased participation of patients and their physicians in ACTs may offset this advantage of PCTs. Second, although ACTs require several assumptions in order to document efficacy,<sup>6,7</sup> such trials may produce more generalizable results, and thus better predict effectiveness, if they encourage enrollment of a more representative sample of patients.<sup>9-13</sup> Third, because evidence from ACTs may lead more physicians to adopt the intervention, such trials may better achieve the ultimate goal of research: to improve the well-being of patients.

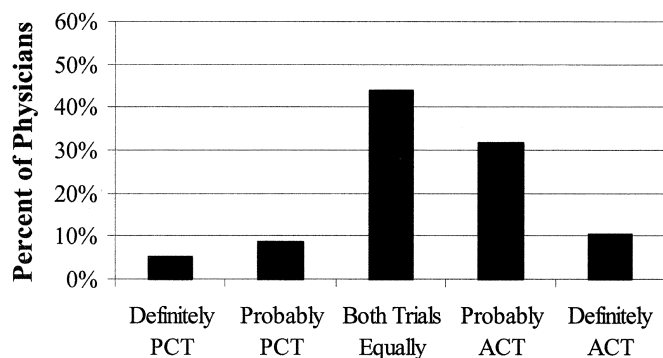
A remaining difficulty with ACTs regards which of the many available antihypertensive drugs to use for comparison. This issue is of growing importance, since many new but similar drugs are being developed for indications for which there are already many effective agents. Although clinicians may wish to know how a new drug compares with all available alternatives, such trials are not feasible.<sup>9</sup> Our results suggest that comparing new drugs to a single agent that physicians are already experienced in using may be an efficient and valuable testing strategy.

This study is subject to potential limitations. We directly investigated the possibility of nonresponse bias by comparing responses to the mailed questionnaire with those obtained in follow-up phone interviews of nonresponders. This comparison revealed that responders and nonresponders were similar in their relative preferences for ACTs over PCTs. As expected, nonresponders spent more hours per week in direct patient care, but this characteristic was not related to any of the main outcome measures.

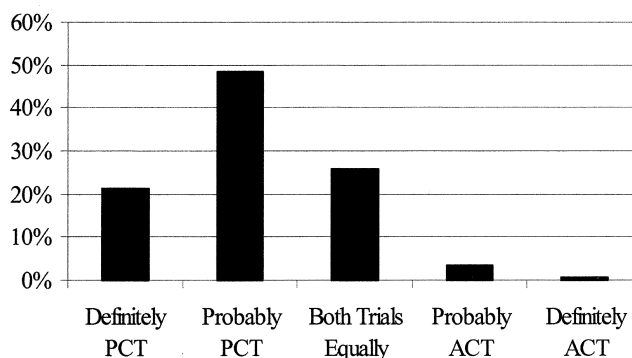
Second, we assessed clinicians' stated willingness to refer their patients to trials, and stated preferences for prescribing drugs, rather than their actual behaviors. Physicians' responses to clinical vignettes have previously been shown to validly predict their actual clinical practices.<sup>30</sup> In the research setting, prospective research



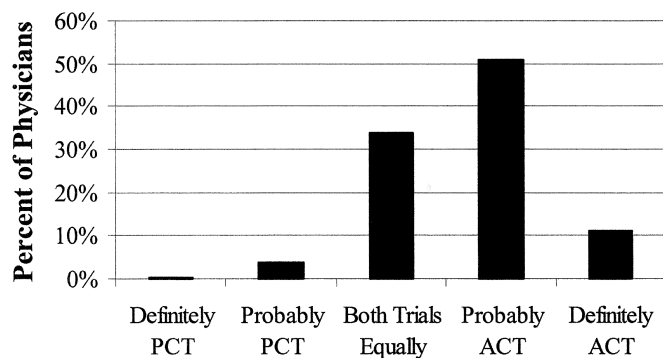
**A. Provide Useful Information for My Practice**



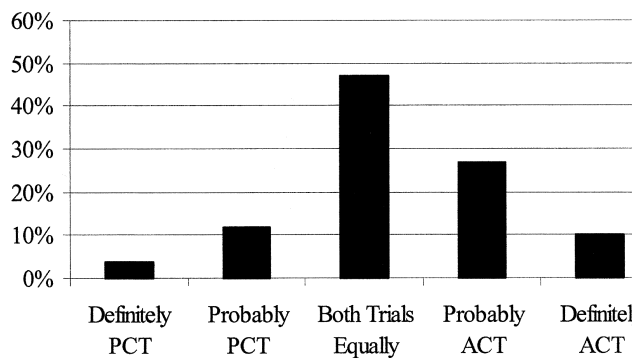
**B. Put Patients at Unnecessary Risk**



**C. Offer Patients a Greater Chance for Personal Benefit from Participating**



**D. Yield Knowledge Leading to a Public Health Benefit**



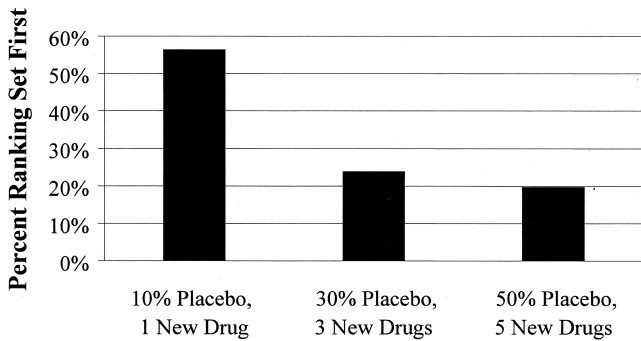
**FIGURE 1.** Physicians' views of the comparative merits of ACTs and PCTs. Physicians were asked to indicate, by circling one of the 5 available choices, whether they thought active-controlled trials (ACTs) or placebo-controlled trials (PCTs) of novel antihypertensive drugs were more likely to have each of the 4 characteristics indicated in panels A-D. Each of the 4 distributions differs significantly ( $P < .0001$ ) from that expected under the null hypothesis that physicians would regard the 2 designs equally.

participants' stated willingness to participate in a trial is the single best predictor of subsequent enrollment.<sup>13</sup> Nonetheless, similar evaluations of the validity of physicians' stated preferences for enrolling patients in research are needed to extend the present results.

Third, we specifically assessed physicians' preferences for referring patients who were already well controlled on, although not always tolerating, standard medications. We considered such patients in our vignettes because they reflect the characteristics of the overwhelming majority of patients recruited for antihypertensive drug trials.

Although physicians may have different preferences when considering patients with newly diagnosed hypertension who are not yet being treated, such patients are rarely recruited because they are difficult to identify during the typically brief period between diagnosis and the initiation of treatment.

Fourth, these results regarding physicians' preferences for ACTs over PCTs may not be generalizable across all drug classes. Indeed, they likely apply only to drug classes in which 1) effective therapies are available outside of a trial, 2) PCTs remain a common method for evaluating



**FIGURE 2.** Physicians' willingness to limit the number of new drugs tested in order to decrease placebo use in trials. The ordinate shows the percentage of physicians ranking each trial set as the most preferred one to refer their patients to.

new agents, and 3) there are risks, either perceived or documented, to foregoing active medication for a few months. Nonetheless, these conditions exist for several commonly prescribed drug classes, including antihyperlipidemic agents, oral hypoglycemic agents, and antidepressant agents. We have documented physicians' intolerance for PCTs of antihypertensive agents, and might expect even less tolerance for PCTs of oral hypoglycemic<sup>31</sup> and antidepressant<sup>32,33</sup> agents.

Finally, the reported preferences in this study represent the views of a sample of physicians representative of the U.S. primary care physicians, so the results may not reflect the views of other groups of physicians. For example, although many physicians in our sample had referred their patients to clinical trials, very few spent time directly involved in research. It is conceivable that physicians who spend more time conducting research might have different views. We intentionally chose to study primary care providers because these physicians provide the primary source for the majority of patients recruited for trials of new antihypertensive drugs.

## Conclusion

If clinicians perceive that trials do not address questions relevant to their practices, they may not be influenced by the results.<sup>34,35</sup> This may explain, for example, why physicians' management of hypertensive patients generally does not reflect current guidelines derived from randomized trials.<sup>36</sup> Although head-to-head comparisons of approved antihypertensive agents have recently been reported,<sup>37,38</sup> such trials are rare, and are presently only conducted several years after drug marketing. With the development of so many new drugs with mechanisms of action and therapeutic indications that are virtually identical to existing agents, there are many risks for industry in conducting such comparative studies. It may be far easier to wage aggressive marketing campaigns than to attempt to prove margins of relative efficacy that are likely to be small.

We suggest that regulatory bodies, such as the U.S. Food and Drug Administration, give renewed consideration to ACTs as a means of testing new antihypertensive drugs. We also suggest that the results of our study may inform the corresponding debates regarding placebo use in trials of new antihyperlipidemic, oral hypoglycemic, and antidepressant agents. Current regulatory insistence on PCTs may not only put enrolled patients at unnecessary risk, but may also limit the degree to which research is incorporated into clinical practice.

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