

Can Managed Care Organizations Partner With Manufacturers for Comparative Effectiveness Research?

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Community-based clinical trials of marketed products and services developed to answer real-world questions faced by decision makers have been termed pragmatic or practical clinical trials (PCTs).¹ In 2003, Tunis and colleagues¹ called for PCTs to fill the real-world evidence of treatment effectiveness void. Interest in PCTs is consistent with the recent high-profile policy and political initiatives calling for more comparative effectiveness evidence.²⁻⁵ This interest is in response to the fact that, while the traditional randomized controlled trial (RCT) provides the foundation of what could be effective in real-world community clinical practice, the concern is commonly raised that RCT results may not always be the same as those experienced in community medicine.^{6,7} Most of the recent private proposals⁸⁻¹² and congressional bills¹³⁻¹⁵ envision major public or public-private funding on the order of hundreds of millions, even billions, of dollars. In contrast, none address the opportunity for manufacturers to privately fund such research in what could be termed a private-private partnership with managed care.

A conventional response to insufficient evidence of effectiveness (and cost-effectiveness) is to engage in decision analytic modeling.¹⁶ Such models analytically connect the evidence “dots” from trials, epidemiologic studies, and clinical opinion, as well as assumptions and beliefs about real-world clinical practice patterns, cost structures, and patient variables.^{17,18} Although decision modeling is considered a valuable and accepted method of estimating effectiveness,¹⁹ the demand for credible real-world evidence of empirical effectiveness and cost-effectiveness of healthcare interventions is growing.

Recently, there have been several nationally prominent PCT-focused policy developments. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 requires the Secretary of Health and Human Services to support research concerning “the outcomes, comparative clinical effectiveness, and appropriateness of healthcare items and services (including prescription drugs)...”²⁰

In July 2006, the Centers for Medicare and Medicaid Services issued a guidance document entitled *National Coverage Determinations With Data Collection as a Condition of Coverage: Coverage With Evidence Development*.²¹ This document describes how Medicare is attempting to integrate evidence development policy

Objective: To describe 2 published pragmatic or practical clinical trials (PCTs) as case studies illustrating successful partnerships between managed care organizations (MCOs) and pharmaceutical manufacturers.

Study Design: In today’s environment, there is increasing concern about the comparative effectiveness of medical interventions. Various opinion leaders and stakeholders lament the death of such evidence and are calling for the public and private sectors to invest up to billions of dollars to create better comparative evidence.

Methods: We selected 2 PCTs conducted at different points in the drug life cycle to highlight strengths, limitations, and policy implications. The phase IV study compared fluoxetine hydrochloride vs 2 generic tricyclic antidepressants in selected primary care clinics of a health maintenance organization from 1992 through 1994. The phase IIIb study compared daily budesonide via dry powder inhaler vs triamcinolone acetonide metered-dose inhaler in adult patients with persistent asthma in 25 MCOs from 1995 through 1998.

Results: Both PCTs were successfully sponsored and funded by pharmaceutical manufacturers in collaboration with MCOs and provided potentially useful evidence of real-world effectiveness and evidence of value to healthcare decision makers.

Conclusions: Industry-sponsored PCTs in managed care are feasible when manufacturer and MCO incentives align and can provide real-world evidence of comparative effectiveness and value for money. These trials can be conducted successfully in the phase IIIb and phase IV environments.

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into its national coverage decisions within the following 2 categories: national coverage determinations labeled as “coverage with appropriateness determination” and “coverage with study participation.” A national coverage determination that requires the former indicates that sufficient evidence has been provided to recommend coverage only for patients and services described in the submitted data, which must continue to be collected to ensure appropriateness of treatment. The latter allows coverage for a promising treatment or service with the condition that information be collected within a research setting on its progress to inform future coverage. This new policy was first applied to positron emission tomography for people with suspected Alzheimer’s disease (trial), implantable defibrillators for patients with severe heart disease (registry), long-term home oxygen care (trial), and off-label uses of 4 drugs approved for colorectal cancer (oxaliplatin, irinotecan hydrochloride, bevacizumab, and cetuximab) (trial).²²

Manufacturer-Sponsored PCTs in Managed Care

Why do pharmaceutical and device companies not fund comparative PCTs to demonstrate the comparative effectiveness and value of their products? Tunis and colleagues¹ listed the following barriers and challenges: (1) a lack of demand by payers, health plans, and other policy makers for high-quality effectiveness (and cost-effectiveness) evidence (which may be changing); (2) the high cost and long length of time for PCTs to be completed; and (3) the risk of generating evidence that may not support marketing objectives. Policies of the US Food and Drug Administration (FDA) (or lack thereof) may also inhibit these studies. For example, for results of a PCT to be most useful to manufacturers and health plans, studies would optimally be initiated, and at best completed, before a product’s market entry (phase IIIb). However, neither manufacturers nor the FDA have significant experience with PCTs, and there is no FDA guidance to address concerns about safety related to minimizing clinical protocol constraints for a drug being studied in phase IIIb before approval. Notwithstanding these obstacles, the value of timely comparative effectiveness and cost-effectiveness evidence to health plans, manufacturers, physicians, and patients is greatest at the time products enter the market, when it would affect pricing, reimbursement, formulary placement, and initial clinical decisions.

Herein, we describe 2 different successful PCTs within a managed care setting, one among patients with depression and the other among patients with asthma. The depression case study was conducted in a single staff-model health maintenance organization (HMO) from 1992 through 1994 and

compared initial prescribing of fluoxetine hydrochloride (Prozac; Eli Lilly and Company, Indianapolis, Indiana) vs tricyclic antidepressants (TCAs) under usual care conditions.²³ The second PCT was conducted in multiple managed care organizations (MCOs) around the country and compared budesonide administered via dry powder inhaler (Pulmicort Turbuhaler; AstraZeneca, Wilmington, Delaware) vs triamcinolone acetonide administered via pressurized metered-dose inhaler (Azmacort; Aventis Pharmaceuticals, Bridgewater, New Jersey) in adult patients with persistent asthma.^{24,25} Both studies were funded by the respective manufacturers.

REPORT OF CASE STUDIES

PCT Case Study 1 (Fluoxetine vs 2 TCAs)

In the fall of 1983, Eli Lilly and Company submitted a new drug application to the FDA for the antidepressant fluoxetine. The drug was approved by the FDA 4 years later (fall of 1987) and was launched on the US market in January 1988. For the next several years, Prozac (fluoxetine) enjoyed near-celebrity status, including being featured on the cover of *Newsweek* magazine.²⁶ The impetus for the PCT was convergent HMO and manufacturer objectives. The HMO (Group Health Cooperative of Puget Sound, Seattle, Washington) was concerned about the increasing drug cost associated with the growing popularity of branded fluoxetine and its potential for becoming first-line therapy vs generic tricyclics for patients diagnosed as having depression. Consequently, the HMO was considering relegating fluoxetine to second-line therapy. The manufacturer was worried that such a formulary restriction would become standard policy across the country when, in fact, a fair real-world trial could demonstrate that fluoxetine would be better tolerated and better adhered to because of a more favorable adverse effect profile and good value for money. Approximately 4 years after the launch of fluoxetine, the manufacturer approached the HMO and proposed to fund a collaborative PCT, assuming the risk that a fair real-world comparative effectiveness study would show that first-line therapy of branded (expensive) fluoxetine compared with generic (inexpensive) TCAs within a primary care HMO setting for the treatment of mild-to-moderate depression would be cost-effective for the HMO and beneficial to patients.

This phase IV, randomized, real-world, open-label, intent-to-treat trial was conducted within primary care clinics.²³ The objective of the study was to compare the clinical, functional, and economic outcomes of initially prescribing fluoxetine with the outcomes of initially prescribing an older TCA, imipramine hydrochloride or desipramine hydrochloride. The study was specifically designed to evaluate comparative

effectiveness and value within the following usual care conditions: (1) patients were recruited in the normal course of seeking care after their physicians empirically diagnosed them as having depression and decided to prescribe an antidepressant medication, (2) patients who agreed to participate were randomly assigned to fluoxetine or to a TCA, (3) treatment was open label, (4) drug treatment decisions (ie, initial dosage, dosage changes, treatment discontinuation, switch to a different antidepressant, and specialty referral) were made without guidance from a study protocol, and (5) patients filled prescriptions for their antidepressants rather than receive drugs during study visits from study personnel. Patients were enrolled in the study from 1992 through 1994.

An expert advisory panel (including author BRL), recruited by the HMO and chaired by the HMO clinical research psychiatrist (who was the principal clinical investigator and first author of the subsequent publication²³), oversaw and approved the clinical protocol, conduct of the study, and its evaluation. The clinical article²³ reporting the results was completely under the independent control of the investigators (ie, not the manufacturer).

The results of the study²³ were published in 1996, 8 years after fluoxetine was launched in the United States. Patients taking fluoxetine reported fewer adverse effects of treatment. In addition, they were more likely to continue the initial treatment and were more likely to refill prescriptions at rates consistent with minimal dosage recommendations than patients initiating TCA treatment. Health-related quality of life and depression-related cost outcomes were similar across treatment groups (higher drug acquisition costs for fluoxetine were balanced by fewer outpatient visits and lower inpatient costs). These findings formed the foundation for the branded product (Prozac) to be given first-line formulary status at the HMO and had a role in the development of evidence-based clinical guidelines on depression management.²⁷

PCT Case Study 2 (Budesonide Inhaler vs Triamcinolone Acetonide Metered-Dose Inhaler)

This study was a phase IIIb effectiveness and cost trial of budesonide inhalation powder delivered via dry powder inhaler (Pulmicort Turbuhaler) vs triamcinolone acetonide (Azmecort) administered via a pressurized metered-dose inhaler. The drug manufacturer, Astra USA (now AstraZeneca), submitted the original new drug application for the inhaled corticosteroid budesonide in 1994. At that time, inhaled corticosteroids were the standard recommended daily therapy for mild-to-moderate persistent asthma. Asthma was and is a major chronic illness that affects approximately 15 million persons in the United States each year.²⁸ In 1994, the annual

cost of asthma was estimated at \$10.7 billion,²⁹ and there was ample literature demonstrating that many patients' asthma was not well controlled.^{30,31} Given the range of new pharmacotherapeutic agents available for the treatment of asthma, it was becoming increasingly important for patients, providers, and payers to determine which treatments were most effective and cost-effective in real-world settings.³²

After the new drug application submission, the manufacturer approached and recruited multiple MCOs and subsequently funded a multisite, randomized, open-label, phase IIIb, comparative, cost-effectiveness, intent-to-treat trial among patients with asthma (study²⁴ SD-004-9323) comparing Pulmicort Turbuhaler with Azmecort. Although there were multiple inhaled corticosteroids on the market,³³ Azmecort was chosen as the comparator because it was a market leader at the time of the study and was expected by the manufacturer to be the key competitor of Pulmicort Turbuhaler. The manufacturer believed that a fair real-world comparative effectiveness study could potentially demonstrate that budesonide in the then-unique Turbuhaler delivery system would lead to higher patient preference. This higher preference, it was believed, would result in better adherence, leading to improved effectiveness and cost-effectiveness compared with Azmecort in the treatment of adult patients with persistent asthma in a managed care setting; thus, managed care plans would consequently be willing to collaborate to develop such evidence. The main inclusion criteria were male or female patients aged 18 years or older with a history of asthma requiring daily use of an asthma controller medication. The study was designed, to the extent possible in a phase IIIb prelaunch environment, to generalize results to usual care practice as follows: (1) inclusion and exclusion criteria were kept to a minimum so that enrolled patients would better represent the population of patients with asthma currently being treated with an inhaled corticosteroid in MCOs, (2) starting dose and subsequent adjustments were selected at the discretion of the investigator based on clinical judgment, and (3) study-related visits (5 scheduled during the 52-week study period) and procedures were limited to minimize their effect on treatment compliance and study discontinuation. Twenty-five MCOs located throughout the United States participated in this study, a key criterion being the capability to track patient use electronically.

Following informed consent, participants were randomly assigned in a 2:1 ratio to receive budesonide dry powder inhaler or triamcinolone acetonide administered via a pressurized metered-dose inhaler. The 2:1 ratio design was chosen for the purpose of obtaining safety and efficacy information about budesonide, as it was not yet approved for sale in the United

States at the time of study initiation. The study enrolled 945 patients between July 1995 and January 1997, with the last patient completing the study in January 1998. Pulmicort Turbuhaler was approved by the FDA in June 1997 and was launched in July 1998 on the US market.

The clinical protocol for the study was prepared by the manufacturer in collaboration with the outside academic principal clinical investigator. The outside clinical investigator maintained scientific control of the trial and subsequent reporting of the clinical results.^{24,25}

Results indicated that initiating treatment with budesonide treatment was more effective than triamcinolone acetonide in terms of symptom-free days, health-related quality of life, daytime and nighttime asthma symptom severity, breakthrough bronchodilator use, forced expiratory volume in 1 second ($P < .001$ for all), and patient satisfaction.^{24,25} The mean annual total asthma-specific costs (including the study drug) were slightly higher for the budesonide inhalation powder group, although they did not reach statistical significance ($P = .06$). Higher study drug costs for the budesonide inhalation powder group were offset by lower costs for other asthma healthcare use, which included emergency department visits and other expenses.

DISCUSSION

A national dialogue is taking place today about increasing real-world evidence regarding what works in healthcare. Intuitively, one would think that there would be a market demand for such information. In addition, because healthcare decision makers must meet bottom-line requirements in an increasingly resource-constrained world, one might expect that within MCO environments there would be a growing demand for evidence that healthcare products and services deliver good value for scarce dollars. To some degree, the latter seems to be happening. For instance, the Academy of Managed Care Pharmacy Format for Formulary Submissions¹⁷ is believed to be used by an increasing number of health plans, covering more than 100 million lives (R.N. Fry, BSPHarm, written communication, 2005). However, the Format for Formulary Submissions and other similar processes, such as that found at the National Institute for Clinical Excellence¹⁸ in the United Kingdom, do nothing to generate new empirical evidence of effectiveness or cost-effectiveness.

Many major policy stakeholders—including Congress, managed care, the Centers for Medicare and Medicaid Services, the Institute of Medicine, and others—are beginning to look to PCTs to contribute needed real-world evidence. Attaching coverage decision making to evidence

development, as the Centers for Medicare and Medicaid Services is doing, may well garner increasing attention in clinical, industry, managed care, and regulatory circles. The same can be said of the more recent calls⁸⁻¹⁵ for a significant national investment in comparative effectiveness research, noted earlier. However, this interest is in an early stage and likely will remain such until there is more policy development and experience by all stakeholders. The 2 PCT examples described herein may provide some useful insight as to the potential role for private market forces to foster a collaborative relationship between manufacturer and MCO stakeholders to develop efficient and useful scientifically valid real-world comparative effectiveness and cost-effectiveness evidence.

The depression and asthma PCTs provide encouragement that the PCT concept may be viable for the pharmaceutical and managed care industries. They demonstrate the importance and potential usefulness of addressing “real-world effectiveness and cost-effectiveness” evidence separately from RCT-generated “efficacy” evidence. For instance, in both cases, the available RCT evidence comparing product only with placebo provided no direct evidence that the new drugs were more efficacious than relevant clinical comparators, yet each manufacturer believed and was willing to fund and take the risk that their product provided important clinically related advantages that a fair market test would uncover. Each manufacturer also believed that, despite a higher product price, the study would demonstrate that their drug would bring good value for money to managed care and to patients. During the process, the manufacturers and MCOs demonstrated that they could successfully partner to address pressing real-world comparative clinical and economic issues using a scientific outcomes research process by relaxing traditional protocol constraints to maximize studying real-world conditions.

Neither study specifically addressed safety, so we do not have empirical evidence with these examples as to that important issue. However, there is no particular reason why PCTs could not, or should not, be used to develop safety insights. The PCT vehicle might be closer to a registry or spontaneous reporting vehicle than an RCT because a PCT is designed to be real-world applicable. For instance, a PCT may be useful in picking up drug–drug interactions, overdosing, or other inappropriate use or administration, none of which would likely be the focus of a typical RCT as developed for registration.

The fluoxetine example was particularly instructive in that the HMO had a real-world cost–clinical policy dilemma at the time and had initiated a process to determine whether this new expensive antidepressant should be first- or second-line therapy. In the absence of the subsequent PCT, the outcome of this clinical policy review was to restrict fluoxetine to second-line

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therapy. Of course, this was a huge threat to the manufacturer and likely would limit product accessibility to patients.

The fluoxetine study was naturalistic yet ensured an initial unbiased selection of product via the random assignment process, which is the major bias concern of nonrandomized observational studies. Most important, the study question was only derivatively related to the drugs because of the fact that, although patients were initially randomized to study group to ensure unbiased assignment, there was no “control” of the resulting clinical process. Patients and physicians behaved as they normally would in the real “open-label” clinical world. Therefore, the research question pertained more to deciding to initiate therapy in a particular way (ie, one drug vs another) rather than isolating the chemical and physiologic effects of the drug. At the end of the day, the findings could (and, we believe, should) be couched in terms of the effectiveness and cost-effectiveness of the decision to initiate therapy with fluoxetine rather than the effectiveness and cost-effectiveness of the drug per se (although presumably the findings are related to the drug’s chemical properties). This is an important distinction between a true PCT and a true RCT. In the case of a PCT as described herein, the comparative effectiveness, safety, and economic consequences may be driven as much by patterns of care, including patient acceptability, as they are by chemical entity of the drug. A typical RCT specifically attempts to control those real-world variables to isolate the drug’s chemically and biologically induced potential. This issue is the crux of the difference between the 2 trial methods and is the reason they are so complementary.

The fluoxetine study was viewed by the manufacturer as a good investment in that it not only directly informed the aforementioned first-line formulary decision but also formed the basis for a multiyear promotional campaign that touted the drug’s value and patient acceptance. Although beginning the study following market approval provided the ability to be so naturalistic, this timing carried a huge downside: study results were published 8 years after approval, and valuable time was lost to all stakeholders. From the manufacturer’s standpoint, although the study accomplished its objective to support a first-line treatment policy, the findings could also be (and likely were) interpreted as a class effect, benefiting competitor products that began to crowd the second-generation antidepressant market. Therefore, a manufacturer might not reap all the benefits from its investment and risk taking.

The case study of budesonide inhalation powder among patients with asthma differed in several key aspects compared with the fluoxetine depression case study. Most significant, the study was initiated during the period between the new drug application filing and the FDA approval to market

(phase IIIb). This permitted the study to be completed before launch, which provided the manufacturer, MCOs, and physicians the opportunity to better evaluate the potential real-world effect the product may have once it was marketed. Therefore, formulary decision making and clinical practice guidelines could be more informed at the point when initial decisions would have to be made.

The downside with starting in phase IIIb was that a true naturalistic design could not be achieved for several reasons. First, study drugs had to be provided by the manufacturer, which compromised natural prescription processes, including patients’ out-of-pocket expenses. Second, because the drug was not yet approved by the FDA, there were protocol requirements to monitor safety, which somewhat compromised natural clinical patterns. These included requiring some (albeit minimal) protocol-induced visits and not allowing real-world switching patterns. Third, physicians and patients in the study were not yet familiar with Pulmicort Turbuhaler, including the dosing regimen and directions for use, which may have biased the study results toward Azmacort, with which they were familiar.

The budesonide case study was also unique in that it collected patient-level resource use and cost data from 25 MCO sites (recall that the fluoxetine depression case study collected these data from a centralized database within a single MCO). To improve data quality (a key issue given the heterogeneity of these many sites), the study team had to develop a detailed MCO user’s manual to assist with converting “local” resource use and cost electronic coding schemes to a standardized format.

Another consideration with industry-sponsored PCTs is the FDA’s role in regulating information dissemination resulting from such studies, particularly given the internal–external validity tradeoffs that inevitably occur. For instance, to the extent that a PCT is initially randomized but is open labeled and not controlled (allowing for crossovers, variable dosing, and adherence patterns), the study results would likely be as much a factor of the decision to initiate a particular therapy as it is the therapy itself. In such cases, the FDA could require promotional statements, for instance, to address the effectiveness or cost-effectiveness of the prescribing decision rather than the drug per se. Needless to say, should the manufacturer not be pleased with the results of the study, the promotional issue may be moot because it would be unlikely that the results of the study would be used to promote the product (as would be true with any form of study). However, because the study would have been conducted in partnership with managed care, whatever results are obtained would (or should) be publicly available. In fact, one could imagine a best PCT prac-

tice partnership that included an a priori agreement on the dissemination of the results regardless of findings.

We noted earlier that a potential inhibiting factor for manufacturers to sponsor PCTs is the lack of FDA guidance relative to design and ultimate use of results in promotional activities. Guidance is critically needed when considering initiating a PCT in phase IIIb. We encourage the FDA to take a broad, creative, market-focused view to this end, perhaps taking a page from its forward-looking innovative Critical Path Initiative.³⁴ For instance, the PCT concept would seem to be a perfect candidate for exploring the application of Bayesian adaptive trial methods.^{34,35}

Important but unresolved issues within the national comparative effectiveness research debate include costs, funding mechanisms, and who is to bear the costs. The most recent proposals envision congressional appropriations, perhaps establishing a dedicated trust fund and levying fees on private insurers.⁸⁻¹⁵ The private sector manufacturer–MCO partnership presented herein requires no federal funding, public levies from MCOs, or any new organizational structure (such as a new “institute” or “center”), nor does it require a public priority setting process, all of which is being envisioned by the various proponents of the national–federal approach. The private sector approach is a form of market vertical integration with direct costs primarily funded by the manufacturer, indirectly supported in kind by the MCO community to develop mutually useful evidence. If done smartly, costs should in the main be vastly lower for PCTs than for traditional RCTs, although they would be variable depending on the design, study size, number of sites, and other factors. However, smart designs minimize and almost eliminate protocol-induced costs; most data can be collected passively via existing administrative systems and data elements kept to a minimum. For marketed products, the manufacturer would not be required to supply a free drug (for instance, a true PCT wants to study the effect of patient cost-sharing, etc). Novel innovative research methods could be used to build new evidence on what is already known, continually adapted to real-world findings and terminated as soon as the sponsor or decision maker is satisfied with the evidence.

STUDY LIMITATIONS

By design, PCTs are not controlled and are open label. Therefore, all the biases that occur in real-life medical care (placebo effect, inappropriate prescribing, adherence patterns, halo effect of switching to the latest innovation, etc) likely occur. Studying the effect of these real-world biases is, in many ways, the point of the PCT; nevertheless, they are biases and

require careful analysis and caution in interpreting findings. The “messy” nature of this real-world research design can also be a limitation, again associated with lack of control. Because of the many uncontrolled variables, it is difficult or impossible to infer causality, except perhaps to the initial prescribing decision. Another limitation pertains to timing. The real-world effect is most validly evaluated only after the healthcare market has had time to learn about the use, usefulness, and acceptability of the drugs of interest. However, that requires time to elapse after the introduction of a drug; therefore, by the time the PCT is initiated, conducted, and reported, many key decisions such as formulary placement and clinical guidelines would have already taken place. For example, the depression case study was published 8 years after the launch of fluoxetine. On the plus side, it reflected real-world practice patterns as an ideal PCT is designed to do. The asthma case study, on the other hand, was launched in phase IIIb, with results available at drug launch (ideal timing in that regard). However, because the Pulmicort Turbuhaler product was not on the market at the study start date, the study could not be designed as purely naturalistic, requiring some controls to satisfy legitimate FDA concerns.

The fact that these studies occurred several years ago also limits the usefulness of the comparative findings because of changes in therapy that have occurred in the intervening years. Therefore, these studies serve primarily as models of novel design rather than as outcomes studies for the reader. The results from more contemporary comparisons would be more relevant to report.

There is also the concern expressed that bias may have an undue role in manufacturer-sponsored studies. Of course, bias has an explicit role in the study question. Manufacturers would only be expected to fund and take the resulting risk for bets they expect to win. Therefore, one should expect results to be positive more often than not. However, as is well known and reported, this is true for all manufacturer-sponsored studies, including traditional RCTs.³⁶⁻³⁸ To help minimize potential opportunities for bias, MCOs should have an active partnership role throughout the study process, beginning especially in formulating the design and in choosing a relevant comparator. In the depression case study, the MCO had a dominant role throughout the process, whereas the MCOs had a much more passive role in the asthma case study.

Finally, we note that our article is limited to only 2 case studies representing the private PCT partnership. The studies were selected in large part because we believe that each illustrates different ways in which a partnership can be successful but also because we had key roles (BRL participated in the depression study) in both studies and gained some insight from the 2 experiences. Although we have made no systematic attempt to sur-

vey the literature for other examples, our general familiarity with the literature and our experience suggest that there are few other examples; nevertheless, others undoubtedly exist (we are aware of at least 1 study³⁹). Our point is to highlight what we believe to be an important yet largely unfilled opportunity to develop comparative effectiveness evidence via the private sector, which endeavors to fulfill market objectives with the view that, if both the manufacturer and managed care objectives can be simultaneously met, then the effort likely would result in a net social good. However, there are many reasons not to be overly optimistic that such partnerships will flourish, not the least of which is an environment of general distrust as to motives on both sides. In fact, this distrust is a reason why it is important to encourage the partnerships that we discuss herein.

CONCLUSIONS

Pragmatic or practical clinical trials are feasible when manufacturers partner with MCOs and can provide real-world evidence of effectiveness and value for money. This evidence can be useful to real-world decision making. To foster more of these valuable innovative investments in evidence, several changes need to take place.

Foremost, we recommend that the FDA, pharmaceutical manufacturers, MCOs, and other health plan organizations initiate a process to address needs and opportunities and to establish guidelines and agreements relative to conducting PCTs safely. The discussion should focus on using research results in responsible and useful marketing activities. This will help to alleviate the uncertainty that pervades perceptions about FDA policies toward safety, research design, and promotional policies. Each stakeholder needs to relax preconditions for progress to be made.

We believe that it is important for the FDA to consider the major gatekeeping role it has in the pharmaceutical industry's reporting and communication of any evidence that would come from a PCT. As discussed at some length herein, these trials are not typical RCT explanatory trials but, via random assignment, convey valid information that the market should find useful. Without regulatory acceptance and clarity, manufacturers will likely not have the incentive to fund such efforts, and health plans may lack the confidence and trust to enter into such agreements.

Managed care organizations need to be candid as to their evidentiary needs and desires. Do they truly want good value for money? Are they willing to make decisions based on such evi-

Take-away Points

In today's environment, there is increasing concern about the comparative effectiveness of medical interventions. Many stakeholders lament the dearth of such evidence and are calling for the public and private sectors to invest up to billions of dollars to create better comparative evidence.

- Using 2 case studies, this article examines the benefits of manufacturers and managed care organizations partnering in pragmatic or practical clinical trials (PCTs) to generate real-world evidence.
- Industry-sponsored PCTs in managed care are feasible when manufacturer and managed care organization incentives align and can provide real-world evidence of comparative effectiveness and value for money.

dence? Are they willing and ready to participate with manufacturers to generate such evidence? These questions pertain as well to the Centers for Medicare and Medicaid Services and its new Part D drug plan surrogates (although mainly the Medicare Advantage Prescription Drugs would have the broad healthcare incentive to likely be a candidate for such partnerships).

Manufacturers need to be willing to invest in new ways to meet market demands for real-world effectiveness and cost-effectiveness evidence such as those described herein. This will entail new creative partnerships with their client payers and the willingness to take risks that their products truly deliver real-world value as they often profess to believe.

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