Looking at CER from the Pharmaceutical Industry Perspective

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ABSTRACT

BACKGROUND: Comparative effectiveness research (CER) is increasing as an element of health care reform in the United States. By comparing drugs against other drugs or other therapies instead of just to placebo, CER has the potential to improve decisions about the appropriate treatment for patients. But the growth of CER also brings an array of questions and decisions for purchasers and policy makers that will not be easy to answer and which require significant dialogue to fully understand and address.

OBJECTIVE: To describe some of the impact, both positive and negative, that comparative effectiveness research (CER) may have on the pharmaceutical industry.

SUMMARY: As CER data proliferate, questions are being raised about who can access the data, who can discuss it, and in what forums. Regulations place different communication restrictions on the pharmaceutical industry than on other health care stakeholders, which creates a potential inequality. Another CER consideration will be the tendency to apply average results to subgroups or individual patients, even if not every individual experiences the average result. Policy makers should implement CER findings carefully with a goal toward accommodating flexibility. A final impact to consider is whether greater expectations for CER will have a negative or positive effect on incentives for drug innovation. In some cases, CER may increase development costs or decrease market size. In other cases, better targeting of trial populations could result in lower development costs.

CONCLUSION: The rising expectations and growth in CER raise questions about information access, communication restrictions, flexible implementation policies, and incentives for innovation. Members of the pharmaceutical industry should be cognizant of the questions and should be participating in dialogues now to pave the way for future solutions.

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What is already known about this subject

- The amount of and demand for comparative effectiveness research (CER) is increasing.
- Regulations place different communication restrictions on the pharmaceutical industry than on other health care stakeholders.
- CER will affect policy makers’ decision making and drug manufacturers’ development costs.

What this article adds

- This article invites dialogue about the communication restrictions between the pharmaceutical industry and other health care stakeholders, with an eye toward affecting future regulations in a positive way.
- As policy makers expand their use of CER data, they should be cautious in applying average results to subgroups or individual patients.
- CER’s effects on future innovation may be both negative (e.g., increased trial sample sizes, longer-term endpoints, or the risk of unfavorable results) and positive (e.g., reduced sample sizes by identifying target subgroups earlier in development, or real-world data that show increased value for the drug, spurring further development). Therefore, regulators and developers must begin exploring ways to prepare for potential impacts.

Comparative effectiveness research (CER) has the potential to improve decision making by helping those involved to understand who might benefit from what interventions and under what circumstances. It is important, however, to examine additional effects that CER may have on the health care industry so that we are not surprised by potential unintended consequences.

The pharmaceutical industry faces many requests for evidence and continues to strive towards producing the most comprehensive data possible. Today, the U.S. Food and Drug Administration (FDA) requires specific efficacy and safety data as part of the development and regulatory approval process. Payers want manufacturers to provide product dossiers with additional clinical, epidemiologic, and economic information. With CER there will be increasing expectations that clinical trials will have active comparators, evaluate non-surrogate endpoints (morbidity, mortality, hospitalizations), and measure cost. And payers, providers, and patients will want data generated from real-world environments.

This rising evidentiary bar will have implications, of which I will examine 3: (a) who has access to these new sets of data and who gets to talk about them, (b) how we interpret the results so that we don’t confuse the average with the individual, and (c) whether this increase in CER data will have a positive or negative effect on innovation.

Restrictions on Dialogue

Historically, knowledge about a drug and its role in therapy was developed by manufacturers and shared primarily through dialogue between the drug manufacturer and payers, and with providers. In this environment, the manufacturer presents and shares data that were part of registrational trials, and payers might have some data of their own. Now, communication of evidence is changing as more parties participate in CER. In general there will be an ever increasing volume of data available on new technologies through CER and other real world database studies, however there are significant restrictions on how the manufacturer can communicate this information to stakeholders.

One of the regulations pertaining to how the pharmaceutical industry communicates with a payer audience is FDAMA 114. The majority (81%) of pharmaceutical industry experts (out of 517 surveyed) consider the use of FDAMA in their communications to payers when presenting health care economic evidence directors at major pharmaceutical and biotechnology companies) surveyed consider the use of FDAMA in their communications to payers when presenting health care economic information. However, almost as many (75%) also stated they would benefit from additional guidance by the FDA as to how such promotions should be made to payers. A cornerstone of this new CER world will be the development of new databases. Two laws, the American Recovery and Reinvestment Act and the Patient Protection and Affordable Care Act (PPACA),
Looking at CER from the Pharmaceutical Industry Perspective

provided funding to invest in the development of various sources of information. For example, the FDA will have databases from which it will be mining and releasing information. Medicare will be making some of its data available for comparative purposes. Various other public and private databases will be used for CER. All of these information repositories will allow more and more researchers—from manufacturers, academics, the government, health plans, and others—to compare the performance of drugs to each other and to other therapies in ways that previously have not been feasible.

With researchers and others looking at available data, questions arise as to who has the right to access this information, and who has the right to talk about what is found. Historically, it has been very difficult and expensive to access data, and those data were often limited in the populations they contained. But, as more data opportunities become available, there needs to be an open debate about the pros and cons of having this information widely available. The more people who have access to the data and can work with it, the more this issue has relevance. Multiple researchers will be able to analyze the same data and openly discuss different results, methods, or endpoints. Will pharmacy benefit management (PBM) companies or health plans consider supporting these open databases and sharing their own information? Will all parties have similar access rights, or will just selected government personnel or a handful of researchers have that access? Or will access to taxpayer-funded data be generally available? There may be no right answer, but the conversation should begin.

Another aspect of communication relates to who can communicate CER findings. Currently, the pharmaceutical industry can speak to physicians and pharmacists about their drugs as long as the conversation addresses using the drug for on-label indications. They can describe the indications and products as long as the conversation addresses using the drug for on-label indications. They can describe the indications and

What are the solutions? Should the communication restrictions on the pharmaceutical industry be loosened when their products are studied by others? Should there be a uniform set of communication standards that apply to all? There are no clear answers, but conversations about them should begin.

Applying Average Outcomes to Individual Patients

Every day, peer-reviewed publications or communication from the National Institutes of Health or the Agency for Healthcare Research and Quality detail the latest results of new clinical studies or systematic reviews. In the future, it will be overwhelming to try to keep up with the new data from the hundreds of studies that will be generated every year. To simplify information overload, the inclination is to remember the bottom line—is A better than B? Although we know logically that individual patients respond differently, we may focus upon the average result. But the reality, of course, is that the average is a composite and may not apply to each individual.

As Kravitz et al. (2004) point out, heterogeneity of treatment has many meanings.8 Inter-study heterogeneity entails comparison of results among several studies. Did those separate studies lead to very similar or very different results? Perhaps the population differed in each study and accounts for the different results. A second type of heterogeneity (inter-patient) relates to typical comparisons of A versus B where the data show that some patients did well and others did not. Rose’s 1985 epidemiology paper is a well-known source on this topic.7 The issue of heterogeneity of treatment has current relevance as the draft of the Essential Health Benefits (a component of the PPACA) requires that only a single agent be available in each drug class.9

Perhaps the most clinical- or policy-relevant type of heterogeneity relates to how patients’ individual responses may differ from the study average.

Let’s examine a hypothetical example where patients on average do better on the “blue pill” than on the “red pill,” an example similar to one recently used by President Obama in a national broadcast.8 But individual patients may do better on the red pill than the blue pill for many reasons, including biologic or demographic distinctions or patient preferences. Policy makers reading an article about a study may note that the average result shows blue is better than red, and develop policies stating that everyone with a particular condition should receive the blue pill. The problem, of course, is that developing such a policy does not account for those individuals for whom the red pill works better. How can decision makers in managed care and PBMs work around this problem?

One commonly discussed theme is subgroup analysis. For example, in this same hypothetical study, we may discover that younger people respond differently than older people. We could falsely assume that the heterogeneity is now resolved and recommend that all younger people receive the blue pill, and all older people receive the red pill.8 Unfortunately, the
Looking at CER from the Pharmaceutical Industry Perspective

How Will the Growth of CER Impact Innovation?

The growing demand for CER will impact the pharmaceutical industry in many ways, and its effect on innovation may be difficult to predict. In a CER environment, the costs of drug development may rise. For example, if the marketplace requires active comparators instead of placebo, the sample size required to show statistical differences will increase. A larger sample size entails greater cost. Second, demands for long-term clinical rather than short-term surrogate endpoints will increase study duration and attendant costs. Third, CER entails exploration of response in patient subgroups. To achieve adequate power, sample sizes will need to be larger. If particular subgroups show greatest benefit and lesser harm, then patients gain from this new knowledge, but the market size and revenue to offset development costs may fall.

Another potential consequence is that certain drugs may not be pursued for clinical development. If a drug comes to market for indication A, but its clinical effectiveness is not shown to greatly differ from the alternative, payers may decide not to reimburse it or to place this new drug in a higher tier. If that happens, the manufacturer may not continue drug development—and risk—of testing it for indication B, where the drug might have performed better than any other drug available. And if a drug never makes it to the market, its descendant, derivative drugs will not be discovered. This is an important issue as a premium price cannot be obtained for a truly innovative product if the incremental steps to its development are not met. However the payer is not willing to pay for incremental developments. If this is the case then these costs get absorbed into the overall development of the innovative product, as recently described by Mansley, et al.11

On the other hand, CER could have a positive effect on innovation. For example, a manufacturer may identify a patient subgroup with biologic or genetic tests, perhaps, before starting clinical trials. In that case, the trials may show clear-cut success, and the clinical trial could be small, keeping costs low. In addition, as a manufacturer develops CER spanning multiple outcomes, including long-term real-world data, productivity improvement, and quality of life, perhaps the research will find even more value.

The increasing expectations of CER present many challenges. Patients and other health care decision makers want this information, and it is correct and beneficial to ask for it. However, it is important to recognize that there are consequences that may affect the viability of bringing drugs to market in both negative and positive ways. As Berger and Grainger (2010) point out, it is clear that there will be ongoing debate on how the pharmaceutical industry should incorporate CER into drug development.12 Organizations will need to consider how they will balance the impact of CER’s impact on innovation against the benefits of CER evidence.

The National Pharmaceutical Council has begun modeling projects to evaluate some of the impacts CER may have on the future of the pharmaceutical industry, but it is too soon to share data or make any predictions. It is not too soon, however, to consider the questions and begin the necessary dialogue toward solutions. And it is likely that there will be solutions, because the value of CER is not, in this author’s opinion, in question. It is how to manage the impacts of CER that requires our attention. One possible example might be to offer different durations of patent life depending on whether a manufacturer conducts placebo trials or the longer and more expensive (and more desirable) comparative trials.

Conclusions

It is important for the pharmaceutical industry to participate in the dialogue on the way CER is conducted, interpreted, and implemented. Many other countries are further along than the
Looking at CER from the Pharmaceutical Industry Perspective

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