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Comparative Effectiveness Research in the Regulatory Setting

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Abstract

Consumers today have access to more information regarding everyday decisions than ever before. Healthcare is no exception. The US health reform laws signed in March 2010, provided a vehicle for systematically facilitating the application of this trend to the US healthcare system through the creation of an independent, government-funded institute, whose purpose is to advance the understanding of which treatments and approaches to healthcare work best for which patients.

This article discusses the implications of comparative effectiveness research (CER) for governments, industry, healthcare systems, clinicians and patients. Properly developed and applied information derived from CER can help establish the value of medicines, procedures and services, and promote a more quality-focused, cost-effective healthcare system. However, much uncertainty remains that centres on precisely how this information will be used. Recently, many patient groups, physicians and biopharmaceutical companies have raised concerns that CER might have the unintended consequences of restricting access to treatments.

These effects must be weighed carefully when considering whether comparative effectiveness data should become a prerequisite for US FDA submissions. The process of designing and implementing comparative clinical trials at such an early stage in product development poses numerous challenges including dose selection, use of marketed comparators (which may lead to consumer bias and increased patient dropout rates), physician comfort and experience (for medical devices), and endpoint selection, among others, and could delay introduction of new therapies. In addition, 'over-interpretation' of early comparative data could lead to an underappreciation of benefits in patient subgroups and an undervaluation of incremental innovation. Thus, a requirement for premarketing comparative studies could prove not only to create a costly disincentive to invest in developing therapies, but could also have a detrimental impact on their development.

Regardless of how information is provided to patients and healthcare decision-makers, it should be gathered in a manner that does not delay patient access to new technologies nor hamper innovation. The desire to provide consumers with more information regarding choice is well intentioned; however, patient care and satisfaction should always remain the foremost concern when discussing the implementation of new policies in the healthcare field.

1. Comparative Effectiveness Research (CER) in the Regulatory Setting

Many years from now, the defining characteristic of the modern era may be the widespread availability of more and better information and its influence in everyday decision making. Consumers face more choices than ever before and, as a result, are seeking out and demanding information to enable comparison shopping in every aspect of life, including healthcare.

The Affordable Care Act (the US health reform laws signed in March 2010, collectively referring to The Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act of 2010) provided a vehicle for systematically facilitating the application of this trend to the US healthcare system,[1,2] most notably, through the creation of the Patient-Centered Outcomes Research Institute (PCORI), a public-private institute whose purpose is to advance our understanding of which treatments and approaches to healthcare work best for which patients. PCORI builds on the foundation established in the American Recovery and Reinvestment Act of 2009 (ARRA, or the stimulus package), which provided initial funding to help jumpstart US investment in comparative effectiveness research (CER).[3]

Properly developed and applied, information derived from CER can help establish the value of medicines, procedures and services, and promote a more quality-focused, cost-effective healthcare system. However, much uncertainty remains around precisely how this information will be used. Many patient groups, physicians and developers of treatments have raised concerns that CER will be used to restrict access to treatments, some of which may be precisely what particular patients may need. Indeed, many countries, especially in Europe, have required health technology assessments prior to making a decision as to whether to provide public funding for a new medicine or technology.

It is important to consider the unintended consequences of CER requirements. As described in the US and embodied in the legislative authorization for PCORI, CER is the research on new treatments and processes that is performed to develop comparisons of competing approaches or treatments once they are approved by the FDA and available for 'real-world' use.[4] Important questions that arise include: how will CER impact pharmaceutical and device development for US registration; what is its proper role in the regulatory approval process; and how can 'comparison information' be developed and used in a manner that sustains the drive for healthcare innovation that serves tomorrow's healthcare needs?

Linking requirements for clinically relevant CER to enhanced access and utilization could provide incentives for developers to invest beyond the threshold required for product registration and address more outcome-based questions. Yet, much important medical innovation occurs incrementally, and its true value is often best observed and understood through a retrospective examination of the cumulative impact over time. Using CER in a way that discounts the cumulative impact of incremental innovation may inadvertently cut off important avenues of research and, over time, stifle the development of beneficial treatments. An example of incremental innovation that might not have survived comparative effectiveness analysis is treatment for childhood leukaemia; yet this incremental development of treatments has, over the course of four decades, improved 5-year survival rates from just 3% in 1965 to 88% by 2007.[5,6]

Patients, payers and providers should all benefit from the findings of properly conducted CER. However, the primary value of CER will often be as a supplement to, and not as a replacement for, placebo-controlled or sham-controlled randomized clinical trials to identify safe and efficacious new medical or device technologies. This review examines the current and future roles of CER in medical innovation in the US.

2. The Current Role of CER

As defined by the US Department of Health and Human Services (HHS), CER "is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions. The purpose of this research is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are more effective for which patients under specific circumstances."[7]

Under this definition, cost is not an intrinsic part of CER. Specifically, CER is not cost-effectiveness research, nor is it cost-minimization or cost-benefit analysis. It is not intended to limit or restrict patient access to new technologies, whether they are medicines, devices or treatment approaches.

Instead, the purpose of CER is to provide healthcare decision makers, and patients and their personal physicians, with more and potentially better information to help choose the best intervention and thereby facilitate the best possible patient outcomes. Developing this type of comparison information promises to help US physicians select better treatments for each patient. The result is a more efficient treatment decision process: patients more quickly identify the course of treatment that is most effective for them, potentially reducing unnecessary healthcare spending throughout the system.

2.1 CER and the Centers for Medicare & Medicaid Services (CMS)

The Affordable Care Act, HHS and its umbrella entities, including the Centers for Medicare & Medicaid Services (CMS), are strictly regulated in how the findings from CER are used in setting coverage and reimbursement decisions. While comparative data disseminated by PCORI may be part of the

package of evidence assembled to support a proposed coverage determination, the process for reviewing and approving that decision must be open and transparent and provide ample opportunity for public comment.

More broadly, the CMS increasingly requires that developers of new medical products and treatment approaches provide comparative data to support a coverage and reimbursement decision for the product or service to be made available under the federal healthcare programmes. Specifically, evaluation by the CMS often includes a review of appropriate outcomes data, such as whether the product provides improved, equivalent or complementary health outcomes compared with the alternative options already covered.

Private insurers often follow the CMS lead on coverage and reimbursement decisions and sometimes develop their own comparison data to support such decisions.

2.2 CER and the US FDA

The FDA is responsible for ''protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, vaccines and other biological products, medical devices, our nation's food supply, cosmetics, dietary supplements, and products that give off radiation.''[8] The FDA is not responsible for assuring that a new technology is superior to existing technology.[9]

In most cases, comparative studies are currently not required as part of the submission package reviewed by the FDA when evaluating potential new treatments and new uses of existing treatments. Exceptions include cases where the sponsor is specifically seeking a superiority claim, or where existing drugs reduce mortality or prevent irreversible morbidity. Of note, some other regulatory authorities, e.g. the European Medicines Agency, are more apt than the FDA to require comparative studies premarketing.

Some authors have recommended including comparative studies in product labelling.[10] Indeed, the ability to promote favourable findings of a comparative study would, in some cases, provide valuable incentives for companies to conduct them. However, the FDA has set a high bar for including comparative studies in labelling, noting that (i) many aspects of study design and conduct may lead to an 'unfair comparison', (ii) allowing comparative claims without a very high standard could lead to conflicting claims from different sponsors regarding the same comparison, and (iii) replication is critically important.

Moreover, comparative studies that can detect or rule out modest but clinically relevant differences can be very difficult and expensive to conduct because they typically require the enrolment of very large numbers of patients. Withholding approval while these large, long-term studies are completed would delay patient access to safe and effective new technologies and treatment options, and would potentially lead to poorer health outcomes.

Even so, given the current health policy climate, in which the value of new medical technologies and products is subject to heightened scrutiny, the FDA has become increasingly interested in initiatives to determine how to use clinical trial data to perform CER. These include, for example, the Partnership for Applied Comparative Effectiveness Science (PACES), an ongoing FDA initiative that was funded by ARRA.[11,12] The first step in this project is to use the 'Janus' repository to consolidate and standardize the vast collection of clinical study data at the FDA. The next steps are to host public scientific workshops to discuss the best practices for analysing data across multiple studies and to conduct comparative effectiveness analyses of the data in Janus.

2.3 Parallel Review by the FDA and the CMS

Many companies already conduct comparative studies, often after the pivotal trials for FDA submission have demonstrated the safety and efficacy of the product. However, this serial timing is one factor that can lead to delays between initial product approval by the FDA and a coverage and reimbursement decision by the CMS.

Both the FDA and the CMS have expressed concerns about this delay. Both agencies ''believe they should address the growing need to improve public health by speeding consumer access to and spurring the development of new, affordable, reliable, safer, and more effective medical products and services.''[13] Accordingly, on 25 June 2010, the FDA and the CMS entered into a Memorandum of Understanding (MOU) for the purpose of promoting collaboration and enhancing knowledge and efficiency by providing for the sharing of information and expertise between the two agencies.[14]

Under this MOU, the FDA and the CMS are investigating ''establishing a process for overlapping evaluations of premarket, FDA-regulate medical products when the product sponsor and both agencies agree to such parallel review.''[13] The objective they have articulated is that such a process would reduce the time between FDA marketing approval or clearance decisions and CMS national coverage determinations.

In order to initiate parallel review, it is likely that companies would need to provide data beyond the typical data submission required by the FDA, which would potentially include comparative data. This is because the two agencies serve different

functions and, as such, look for different kinds of information. The FDA is concerned with the safety and efficacy of a medical product, while the CMS must think more broadly to determine what items and services to cover, how they should be paid for, and how much to pay.

Many issues related to such a process remain unresolved at this time. For example, will companies who choose not to participate in the 'voluntary' process face additional scrutiny or hurdles from the FDA? What role would the CMS play in clinical trial design and articulating endpoints? Would only sponsors be able to select a parallel review process, or would the agencies and other third-parties be permitted to petition for parallel review?

How these questions are resolved, and the resulting process, will determine whether parallel review facilitates medical innovation by speeding the development process, or presents new challenges and potential barriers to market approval and a positive coverage determination.

3. Operationalizing CER in the Drug Development Process

While comparative information is not legally mandated and cannot be required by the FDA (except as noted in section 2.2), there are sometimes instances when patient access to new technologies may be hastened by clinical trials that are specifically designed to yield comparative information.

However, it is often the case for new medical products that significant operational challenges impede the ability of companies to develop comparative data prior to FDA marketing approval. Additionally, limited product knowledge prior to approval makes it difficult to ensure that comparisons will be fair.

3.1 Dose/Regimen Selection

Sponsors usually do not know the dose that will be marketed at the time of phase 3 clinical trial design and execution; developing comparative data prior to approval would therefore require studying more than one dose, making for a complex and costly trial. When the comparator has more than one approved dose, the operational complexities multiply and, assuming that some doses are both more effective and more toxic in all or some patients, ensuring a fair comparison before the dose response of the new medicine is known can be challenging or even impossible.

3.2 Blinding

The FDA's evidentiary gold standard involves double-blinded clinical trials: neither the patients nor the investigators know the specific treatment administered. This becomes complicated, however, when using a marketed comparator. Marketed drugs and devices are recognizable. Unless the marketed comparator is somehow blinded or repackaged there is likely to be bias in the assessment of outcomes. If repackaging is performed in order to allow blinding, assuring that the physical changes to the product do not affect absorption in a clinically meaningful way is complex and can be subject to challenge.[15]

3.3 Randomization, Crossover and Dropouts

If a comparative study is performed when only one of the products has been proven safe and effective and has been approved, patients who are not fully satisfied with their response may be more likely to dropout (to ensure they are receiving the proven, approved therapy) than if the study is performed after both products have been proved safe and effective.

3.4 Target Population

Clinical trials are often designed with a homogeneous population in order to maximize sensitivity; this is key to development. However, heterogeneous populations are typically more desirable in clinical trials that are designed to assess actual use. Certain subpopulations may favour one treatment over another; for example, if they are less susceptible to an adverse effect or if they have less severe disease.

Further complicating attempts to conduct a comparison study premarketing is that the population for which the product will be labelled is not yet known. As a result, the comparison study may include some patients for whom the product is not ultimately indicated and may not be adequately powered for meaningful comparison within the ultimate label.

In some cases, the developer of a novel therapy may choose, based on drug properties or market considerations, to target a population that is not exactly the same as the labelled population for the likely comparator. A comparative study could then involve a population deemed suboptimal for the new drug or a population that is off label for the comparator (not feasible).

3.5 Investigator Selection

In the case of some medical devices, a device that works well and feels comfortable in the hands of one surgeon may feel clumsy in another's, potentially leading to different patient outcomes. In addition, physicians may still be on a learning curve for using the new product and a study performed too early may underestimate its comparative value.

3.6 Choice of Endpoints

Therapies are often evaluated against several endpoints. It is not unusual that one comparator will perform better on some outcomes, while the second comparator will do better on others. Premarket studies to support regulatory approval typically have a single primary endpoint, thereby controlling type 1 error, measuring an outcome acceptable to regulators. To be meaningful to a variety of end users including payers, patients and providers, the selection of a primary endpoint in comparative research might, in fact, be quite different from regulatory requirements, making it a challenge to address the comparative data needs of both regulators and end users under premarket conditions. For example, when assessing the primary efficacy endpoint of an analgesic, pain relief might be key for a regulatory agency but, for a payer, it might be the patient's degree of functionality or productivity. For these reasons, a principal task for PCORI is to discuss appropriate designs and methods of comparative research, including study endpoints that relate to the interests of the patient.

3.7 Timing

The size and complexity of clinical trials appropriately accommodating the concerns identified in section 3 often means the execution of the trials themselves will be a lengthy process. This timing can have a severely deleterious effect on product lifecycles and, therefore, on incentives for innovation. Extended trials raise questions about patent life and data exclusivity and, given current rules, would have an impact on the pursuit of some innovative treatments. For medical devices, in particular, product lifecycles can be as short as 18 months. Adequately designed and controlled comparative trials for these products may be too large or may take too long compared with the product lifecycle, and/or be too expensive compared with the anticipated revenue stream, to justify further development of such products if such comparative information is required. By the time a comparative study of a medical device is completed (the longer term safety and effectiveness profile of medical devices typically take longer to develop), the next generation device may have overtaken the device under study. Similarly, for a medicine, the most relevant comparator may not have been available during the time when the registrational comparative trial was undertaken.

3.8 Interpretation of CER Studies

The interpretation of comparative studies is also often a concern. The over-interpretation of comparative findings – the extrapolation of results for population averages to individuals who differ from the average – can lead to underestimation of the value of new therapies and may thereby discourage investments in research and development, potentially impairing future medical progress.

A main objective of the PACES initiative and of comparative effectiveness in general, is to ''better understand what interventions work best for individuals and subgroups within populations.''[11] However, misinterpreting or misapplying the results from CER may have precisely the opposite effect. Indeed, the growing interest in personalized medicine is based significantly on observations that the best treatment for individuals and subgroups may be different from that for larger populations. If the outcomes for the large groups needed to demonstrate (or rule out) differences in CER are misapplied to clinically distinct subgroups, then optimal therapy may be undermined.

CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) was a landmark comparative study of four newer 'second-generation' antipsychotic drugs and two older 'first-generation' antipsychotics.[16] The study concluded that the efficacy of the conventional antipsychotics was similar to that of the second-generation antipsychotics. However, CATIE was designed to test superiority and was not sufficiently sized to determine equivalence within clinically relevant limits. Furthermore, the study design allowed nonresponding patients to switch to another antipsychotic, and many patients who did not respond to a first-generation drug responded after switching to a second-generation antipsychotic. If the overall findings of CATIE had been used to limit access to costlier, second generation drugs, the resultant savings on the drug bill would potentially be countered by a large 'loss of health' disbursed throughout the health system.[17]

Another landmark study, ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), compared the blood-pressure lowering effects of the main classes of antihypertensive agents and concluded, ''thiazide-type diuretics are superior [to calcium-channel blockers or ACE inhibitors] in preventing one or more major forms of [cardiovascular disease] and are less expensive. They should be preferred for first-step antihypertensive therapy.''[18] However, adopting a policy of initiating antihypertensive treatment with thiazide-type diuretics in all patients based on these findings, would ignore the numerous co-morbid conditions in hypertension that are compelling indications for initiating treatment with another agent or with multiple agents, simultaneously.[19]

These are just two high-profile examples that demonstrate the importance of not only the appropriate design and conduct

of comparative research, but also the appropriate interpretation and application of the results to ensure that an individual patient receives the intervention that is best for that patient, and not just best for a large population.

While early availability of comparative information would be of substantial value, there are many challenges outlined herein, both operational and inferential, that would, in most cases, make comparative research more appropriate for the post-approval space. However, to the extent that the FDA chooses to require or encourage more comparative information prior to approval, conversation should be held with all stakeholders, including sponsors, so that there is a chance for input into a reasonable process for determining when and how to request such information.

Furthermore, concurrent with any initiatives to facilitate the development of comparative information should be transparent guidelines and processes detailing how such data are most appropriately used by both payers and sponsors. Unless product developers can use the results of comparative studies required by payers to provide information to patients and physicians, there will be reluctance to invest heavily in these studies.

4. Looking to the Future: Structuring CER to Ensure a Robust Innovation Climate

In both the 2009 stimulus package and the subsequent health reform laws in 2010, congressional policymakers provided a basic framework for more systematically developing and publicizing comparative data about how different treatments work in different patients. However, as the saying goes, the devil is in the detail, and regulators and stakeholders from across the healthcare sector are still hammering them out. Efforts are specifically underway to standardize the CER methodology promulgated at PCORI, and to investigate possible synergies between the FDA and the CMS for approval and coverage, respectively, using comparative information.

With the exception of when sponsors choose to use active control trials to assess superiority or noninferiority, or when existing drugs reduce mortality or prevent irreversible morbidity, comparative information is not a part of the FDA's approval process and nor should it be. The FDA's mission is to protect the public health by assuring the safety and efficacy of medical products. Often the best way to assess the safety and efficacy of a new product is through placebo controlled trials. Due to the operational and inferential limitations of early (i.e. pre-approval) comparative trials, that timing would be suboptimal for many new products. Requiring comparison data at this early stage in the product lifecycle would not only create a costly disincentive to invest in developing new therapies, but misleading results of such studies could have an inadvertently detrimental impact on the development of beneficial new treatments and cures in the long run.

In the coming years, consumers and other stakeholders in the healthcare system will increasingly demand comparative information to facilitate making evidence-based decisions about their health and healthcare. Including comparative effectiveness information in medical product labelling may be appropriate but should not be a requirement. Regardless of where and how this information is developed and provided to healthcare decision makers, it should be done in a manner that does not delay patient access to safe and effective new medical technologies, nor hamper innovation. Further, comparative effectiveness information will likely be even more useful if gathered when a new treatment is in more general use, post-FDA approval.

At the end of the day, in virtually every aspect of life, consumers want both information and choice. The desire to provide consumers with more information about current choices is well intentioned. Such data can be of value and there should be consideration of when and how to increase such data (e.g. loosening up the requirements for inclusion of data in labelling could create a powerful incentive for the generation of such data in some cases). However, in many cases, the premarketing stage is too early to perform comparative studies. Requirements for such data could impede the entry or availability of valuable new choices. Health and lives are at stake.

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