



recovery and reinvestment

TAMMY BISHOP, Vice President, U.S. Business Development, Pharmarama, shares how President Obama's stimulus plan presents a unique opportunity for pharma with investigational compounds in clinical development

The economic stimulus plan approved by President Obama in February presents a significant opportunity for the pharmaceutical industry. This opportunity is reflected in the \$1.1 billion designated under The American Recovery and Reinvestment Act (ARRA) for comparative effectiveness research (CER), a sweeping federal initiative focused on improving the quality and cost-effectiveness of the nation's healthcare system.

Responsibility for coordinating the government's investment is in the hands of the Federal Coordinating Council for Comparative Effectiveness Research, which this summer issued a report defining the scope of the program and providing recommendations for research conducted with the stimulus funds.

Against the backdrop of a still-challenging global economy and soaring healthcare costs, the Council's recommendations send a clear signal to pharma companies: public funding for clinical development will be available to those sponsors that provide qualitative and quantitative data about the effectiveness of their investigational drugs, not just in comparison with placebo, but against an established standard of care.

REAL-WORLD SETTINGS

In framing the definition of CER, the Council began with a straightforward premise: U.S. patients want to take responsibility for their own healthcare, but the complexity and disjointedness of the information available online and elsewhere create significant impediments. Compounding the problem, the scant availability of data comparing various treatment options for a particular condition creates information gaps for the physicians themselves.

To address these gaps, the Council defined CER as "the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in 'real world' settings." The goal of the research, the Council

said, is to "improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances."

RANDOMIZED CLINICAL TRIALS

The strategic framework for the government's CER investment includes areas such as data infrastructure, human and scientific capital, and information dissemination tools. In addition, randomized clinical trials — specifically those involving comparator arms — are expected to be a key component of the federal comparative research effectiveness program.¹

In recent years, globalization of the clinical development process — and the economy in general — has created an increasing emphasis on the need for research directly comparing new and existing treatments. The European Medicines Agency, for example, has adopted a standard emphasizing the use of comparator evaluation when an established pharmacological alternative is available.² With a growing number of countries now requiring comparative information about investigational medicines, pharma companies are designing studies that seek to meet the safety and efficacy requirements of various countries at the same time.³

In the U.S., however, private sector funded comparator studies have been the exception rather than the rule. While investigational compounds must be deemed safe and effective by the U.S. Food and Drug Administration (FDA) before they can be marketed, under most circumstances a head-to-head comparison with an established treatment is not a prerequisite to regulatory approval. Such comparator trials are required only when manufacturers seek to market their drugs as superior to an existing treatment or in situations in which ethics dictate that trial participants not receive a placebo.⁴

To qualify for funding under the government's

CER program, according to the Council, "trials would need comparator arms other than placebo and be representative of populations seen in 'real world' practice."

Without question, the emphasis on CER presents trade-offs for pharma companies. On the positive side, they have the opportunity to benefit because their products will be compared not only with standard-of-care drugs but also with medical devices and procedures, thereby potentially increasing the market opportunity. At the same time, comparisons with less expensive off-patent medicines could jeopardize sales if these older drugs prove more effective in head-to-head studies.⁵

PRIORITY PATIENTS GROUPS

In addition to devoting more resources to comparator data, the CER program places importance on studies that include priority populations such as the elderly, racial and ethnic minorities and the disabled. Policymakers say these groups are not only underrepresented in medical research, but also have disparate disease prevalence, progression and health outcomes.

The Council also stressed the need to complement the trend in medicine to develop personalized medicine — the ability to customize a drug and dose based on individual patient and disease characteristics. One of the advantages of large comparative effectiveness studies is the power to investigate effects at the subgroup level that often cannot be determined in a randomized trial.

In designing and proposing clinical studies for grant consideration, trial sponsors must focus on "effectiveness" rather than "efficacy." In the typical drug trial for FDA approval, researchers determine whether an investigational medicine is efficacious in ideal conditions using an ideal cohort of patients. A disconnect with "effectiveness" exists because, ultimately, the medicines

must be taken in real-world settings influenced by a range of social, emotional, economic and environmental factors. Simply put, just because a drug works under ideal conditions doesn't mean it will work under usual conditions.

The Council noted that phase III and phase IV studies could be beneficial in generating evidence on comparative effectiveness in addition to other scientific and methodological aspects of CER. This should be of particular importance to companies seeking to market new drugs in the U.S., as late stage studies that evaluate comparative clinical and cost effectiveness will be used to create prescribing guidelines and influence decisions on drug reimbursement.⁶

SOURCING COMPARATOR DRUGS

For the pharmaceutical industry, the swelling drumbeat of interest among policymakers, healthcare professionals, insurers and consumers in CER suggests that comparator drugs may be incorporated more frequently into clinical trial protocols evaluating investigational compounds. But doing so presents a unique set of issues for trial sponsors. Sourcing and procuring comparators is a complex, time consuming process that requires a significant level of expertise and strategic planning.

A pharma company embarking on a CER-focused study should begin by formulating a detailed sourcing strategy that takes into account the unique operational, financial and regulatory risks inherent in conducting a comparator trial. An effective sourcing strategy should address areas including supply logistics, documentation and the regulatory requirements of the countries in which the study is being conducted.

As a starting point, sponsors should adopt a rigorous protocol driven process for obtaining a reliable supply of the comparator. Among the key issues to consider are the sponsor's requirements for volumes, dosage strengths, delivery dates, sizes and packaging. Since drugs often are sourced from multiple foreign territories, it is important for sponsors to keep in mind the potential for regional variations in strength, dosage form and packaging type that may affect a drug's suitability for comparison.

A critical part of any sourcing strategy is finding the precise comparator when you need

it. Unfortunately, sponsors often overestimate the availability of a particular comparator. Obtaining a sufficient supply of the drug with an extended shelf life will eliminate potential problems if a company is conducting a lengthy trial involving a large number of patients or multiple cohorts. With estimates of the cost for delays in a pivotal clinical trials ranging from \$600,000 to \$1 million a day, any disruption in supply can be expensive for the sponsor, not to mention damaging to the integrity of the study itself.

According to the Organization for Economic Cooperation and Development, global counterfeiting and piracy of pharmaceutical products costs the industry close to \$40 billion annually. Therefore, proper documentation also is vital to properly managing trial risk. As a result, sponsors always should maintain a comprehensive paper trail that includes a drug pedigree. The pedigree is a statement of origin that traces the drug from the point of manufacture and contains information about all transactions the product undergoes until it reaches the end-user.

An important question for trial sponsors is whether to source the drug directly or outsource the responsibility to a specialist firm. One of the most significant drawbacks to direct sourcing is the loss of anonymity — a drug manufacturer will immediately know which competitor is using its drug in a clinical study. In addition, direct sourcing is a lengthy process that can result in valuable time lost in validating one or more manufacturers and negotiating price and contract terms.

Partnering with a dedicated specialist can eliminate many of the hurdles sponsors face when they attempt to obtain drug directly. This relationship enables the sponsor to maintain the competitive advantage of anonymity and provides an assured, traceable supply from a single point of contact. Perhaps, most importantly, a specialist possesses a comprehensive knowledge of the regulatory landscape and comparator market. This is particularly critical for trials conducted in multiple countries, since each country often has its own regulatory compliance standards and requirements when it comes to comparators.

The specialist's real-time visibility into future supply enables the sponsor to manage its costs and time efficiently while focusing its energies

on running the trial. A specialist also can effectively manage unique supply chain logistics such as physical security for high-value or controlled drugs, cold-chain control, import/export documentation or customs issues.

As part of its sourcing strategy, a sponsor would benefit by analyzing issues such as the market environment, competitive demand for the particular comparator, product availability and options to procure a sufficient supply or alternatives if a sufficient supply proves unavailable. In today's competitive drug-development environment, costs and time can compromise a clinical trial. Therefore, proper planning is integral to avoiding operational and financial risks and improving the chances for success.

CONCLUSION

With the basic framework for the federal comparative effectiveness research initiative created, policy makers and healthcare professionals are beginning to wrangle over how to best prioritize the \$1.1 billion package. While clinical research will likely only account for a fraction of the initial investment, the government's focus on CER validates the important role that the drug discovery and development process has to play in creating more effective therapies for patients. In developing their near-term clinical trial strategies, pharma companies would benefit by using the guidelines developed by the Federal Coordinating Council for Comparative Effectiveness Research and subsequent CER documents as a roadmap to create a more efficient path to market. **FP**

- 1 Luce BR, Kramer JM, Goodman SN, et al. Rethinking Randomized Clinical Trials for Comparative Effectiveness Research: The Need for Transformational Change. *Ann Intern Med* 2009 Jun 30.
- 2 Institute of Medicine. 2007. Learning What Works Best: The Nations Need for Evidence on Comparative Effectiveness in Health Care. <http://www.iom.edu/ebm-effectiveness>.
- 3 National Health Policy Forum. 2008. Exploring Comparative Effectiveness: Activities of NIH, FDA, and AHRQ to Advance Evidence-Based Health.
- 4 Congressional Budget Office. 2007. Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role. <http://www.cbo.gov>
- 5 Selker H. Comparative Effectiveness Research: Medical Practice, Payments, and Politics: the Need to Retain Standards of Medical Research. *J Gen Intern Med* 24(6):776-8
- 6 Tufts Center for the Study of Drug Development Outlook 2008. <http://scdd.tufts.edu/InfoServices/OutlookPDFs/OutlookPDFs/Outlook2008.pdf>



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