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Melding Regulatory, Pharmaceutical Industry, and U.S. Payer Perspectives on Improving Approaches to Heterogeneity of Treatment Effect in Research and Practice

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ABSTRACT

Effective pursuit of the science and management of heterogeneity of treatment effect (HTE) relies on the mutual understanding of the perspectives of, and collaboration among, the various stakeholders in health care. In this article, we compare, contrast, and endeavor to find areas of alignment across the perspectives of three such stakeholders — regulators, the biopharmaceutical and device industry, and U.S. payers. First, we discuss how evidence of HTE is generated and could be improved upon. For pharmaceuticals, much of the initial research is conducted by the pharmaceutical industry, guided by basic science but also delimited by potential markets, regulatory approval requirements, trial size considerations, and payer expectations for evidence of value. Once a drug is marketed, further evidence can be generated via combining trial data, conducting meta-analysis, and analyzing real-world results through observational research designs; we explore how these efforts can benefit from cooperation across these stakeholders. Second, we discuss the equally important utilization of HTE evidence so that physicians and patients have access to and can benefit from the learnings from this research. Research findings must be translated into actionable information and guidelines that can be incorporated into everyday practice. Doing so requires interaction and collaboration among all involved, based on facilitated communication as well as further evaluation research. We provide examples of several cross-sectorial initiatives that are under way in this area. Finally, we explore some economic aspects of HTE research as part of the drug development, marketing, and treatment process. Understanding the economic incentives present is fundamental to aligning those incentives to improve the availability and utilization of HTE evidence. Clear understandings among regulators, pharma, and payers about high-value targets, methods to efficiently generate and communicate information, and value propositions can lead to "win-win" scenarios for patients, individual payers, the health care system overall, and the future of drug development in producing new medicines.

Keywords: collaborative research, heterogeneity of treatment effect, personalized medicine.

Introduction

As our understanding of the pathophysiology and genetics behind disease and its related therapies has expanded, our appreciation for the variations in effectiveness of different treatments in diverse patient populations has also grown. While heterogeneity of treatment effect (HTE) has been an important element of medical decision making for quite some time, the burgeoning area now often referred to as "personalized medicine" is a more recent phenomenon. It is no longer just the realm of academic researchers interested in the basic science, or those most affected in everyday practice—physicians and their patients. All sectors of the health care world, including policy regulators, payers, and the pharmaceutical, biotech, and medical device industry, are taking a major interest in this expanding field. HTE per se includes both treatments specifically defined by diagnosis using genetic or other biomarker information and more traditional approaches using clinical or phenotypic stratifiers such as demographic characteristics, disease severity, comorbidities, previous response to treatment, side-effect tolerance, behavioral characteristics, and patient/caregiver preferences [1–3]. Improved understanding of HTE is a key enabler of the growth of personalized medicine.

For effective progress in generating and applying evidence about HTE to improve patient care, from the underlying science to frontline practice setting, there needs to be agreement about the type of evidence needed, about methods by which it is generated, evaluated, and communicated, and ultimately about how it is put into practice. There also need to be effective and aligned economic incentives to generate and use that evidence across the health care continuum. The three primary sectors mentioned previously—regulators, payers, and the pharmaceutical, biotech, and medical device industry—are key players in generating, interpreting, and applying HTE-related evidence on a

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large scale, and so it is of much interest to understand how each one views these areas. To that end, a session at the May 2011 ISPOR conference was organized, in which each sector's perspectives were represented and discussed [4]. This article is drawn from the presentations and discussion at that session.

This article is organized into three sections—evidence generation, evidence utilization, and economics. The perspectives of each sector are integrated into each section as appropriate. They are followed by a discussion of selected areas for further consideration and a conclusion.

Evidence Generation

Evidence from clinical trial and related sources

Before a new product is approved, incentives to detect HTE are present but, until fairly recently, have been distinctly muted. From a regulatory perspective, it is well known that using the mean outcome effects from clinical studies does not necessarily paint the full picture of the safety and efficacy profile of the drug, and that using subgroup analysis is one way of identifying HTE [5]. In some cases, the manufacturer may know that delineating subgroup effects is an important way to differentiate the product and wish to see such differentiation recognized in product labeling; when genetic differences in diseases and their treatments are scientifically understood, they can be *prima facie* criteria for differentiation (e.g., HER2, K-ras genetic differences in cancer). Payers often would like to reduce the budget impact of a new product by limiting the population to be treated. Approval bodies such as UK's National Institute for Health and Care Excellence and the German Federal Joint Committee (GBA) have prospective criteria for considering subgroup differences in their review because such differences may affect the cost-effectiveness or relative effectiveness of the product [6].

Important factors, however, work against extensive or exploratory HTE analysis during this preapproval period. Lacking a clear scientific or genetic basis for differentiation, regulatory authorities (e.g., Food and Drug Administration [FDA] and European Medicines Agency) may be skeptical of such claims and prefer to see a product evaluated in the broader population in which it may be used. Manufacturers are more generally inclined to have their products available to larger patient populations unless there are compelling reasons that they need to be limited. In a practical sense, HTE detection often needs large overall sample sizes, but the more patients are included, the more expensive and longer trials become, and analysis of HTE can make submissions more complex both to create and to review. Neither regulatory bodies nor manufacturers are anxious to delay the availability of an effective new product to patients without a good a priori reason that HTE is likely to be present, and so such analysis is often not part of a preagreed development or regulatory review plan. Nevertheless, many manufacturers are now actively investigating HTE potential in early research and development, via genomewide association studies, predictive modeling, and other methods, as a basis for subsequent development planning. In fact, more than 50% of manufacturers have incorporated pharmacogenomics or pharmacogenetic diagnostics into their clinical development programs [7].

Once a product has gone through FDA review and is marketed, the potential to detect HTE improves both due to data availability on product usage and due to the methods that can be applied, especially if different sectors are willing to collaborate in data access and analytic efforts. As more randomized controlled trials (RCTs) are performed, either by the sponsor or by independent researchers, under certain circumstances individual patient data from those trials can be pooled for analyses [8].

While analysis of individual patient data allows for the most detailed analysis of HTE and other comparative effectiveness research questions, access to such data may be quite limited, and the programming and analysis effort is substantial. A more broadly available and classic approach is meta-analysis, and given the increasing number of online journals as well as the results posted on clinicaltrials.gov, the extent of trial results available for meta-analyses is expanding rapidly. Reporting of subgroup results, however, is still quite variable. Uniform guidelines for reporting subgroup results, perhaps defined within disease area, would be helpful, as would guidelines and utilities for interinvestigator cooperation in making unpublished subgroup results available for meta-analyses.

Of course, real-world evidence also begins to accumulate as utilization of the product grows following marketing approval. Such data become a valuable but more analytically challenging source of information on HTE, as discussed in more detail later. Given these different approaches, systematic evidence reviews, such as those sponsored by the Agency for Healthcare Research and Quality, can begin to parse the extant research and refine any conclusions about HTE. The more good quality research is available—a situation that could be enhanced by clear standards for HTE research, whether with RCT or real-world data—the more comprehensive and definitive these reviews can be.

Evidence from real-world data

Real-world evidence demands about the safety, effectiveness, and value associated with biopharmaceutical interventions and devices change as they enter the marketplace. Initially payers, physicians, and other health care providers (HCPs) as well as patients must rely on the evidence of safety and efficacy from the pivotal clinical trials that are available at the time of product launch. Once a product is on the market, however, real-world evidence about the product begins to accumulate rapidly in administrative claims databases, electronic medical record (EMR) systems, and disease and product registries. Real-world data are of great interest to payers, physicians, and manufacturers because it reflect the experiences of patient populations who are treated in actual clinical practice rather than the narrowly defined patient populations studied in clinical trials. Real-world data enable the analysis of variation in medication adherence on health outcomes and health care costs, the analysis of variation in physician treatment patterns, the observation of patient experiences on new treatments as they come on the market, treatment effectiveness in patient groups typically not eligible for clinical trials such as those with multiple comorbid conditions and hence multiple comedications, and many other questions that remain unanswered by RCT.

Databases capturing real-world evidence of health care treatments, outcomes, and utilization enable analysis of large patient populations at relatively low cost and without the delays associated with primary data collection. However, there are well-recognized challenges and limitations with the analysis of these types of observational data that can lead to erroneous conclusions. As data systems evolve and become more integrated, some of these issues will be corrected, as controlling for confounders will be facilitated by the increasing availability of integrated clinical data. For example, the lack of clinical severity measures in medical claims data could be addressed by linking medical claims data with EMRs. In turn, this would address the general lack of health care utilization data across treatment sites typical of most EMR systems. There are several reasons to expect data systems to continue to evolve rapidly over the next several years. For example, in the United States, the Health Information Technology for Economic and Clinical Health Act (February 17, 2009) contained significant economic incentives for providers to adopt meaningful use of EMR systems (as well as penalties if they do not). This is leading to rapid growth in the use of EMRs, which will enhance the technical ability to link EMRs and medical claims data. Similarly, experimentation with new care delivery models