CLINICAL ENDPOINTS: WHAT DO PAYERS AND REGULATORS WANT?

THE REQUIREMENT THAT NEW DRUGS show effectiveness is based on a 1962 amendment to the Federal Food, Drug, and Cosmetic Act. This law requires substantial evidence of effectiveness and specifies that this evidence must be derived from adequate and well-controlled clinical investigations. Clinical benefits that have supported drug approval have included important clinical outcomes – for example, increased survival or symptomatic improvement, but have also included effects on established surrogate endpoints – e.g., blood pressure, tumor markers, and serum cholesterol.

The question that naturally arises is how clinical endpoints should be chosen to optimize the chances for both regulatory and reimbursement success. Fortunately, the answer is largely the same for both: endpoint(s) chosen must either demonstrate a clinically significant improvement over available therapy or a clinically significant therapeutic activity where no available therapy exists. Clinically significant effects can include improved survival, a distinct benefit that is detectable by the patient or family – such as improvement in symptoms or functional capacity, a decrease in healthcare requirements and costs associated with the illness, and/or decreased likelihood of developing a complication that is itself undesirable or harmful. Therefore, a study endpoint should be an objective measure of one or more of these.

Endpoints may be direct – those that directly measure how a patient feels, functions, or survives, and in themselves represent or characterize the clinical outcome of interest; surrogate – a laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint, therapeutically induced changes which are tightly coupled with changes in a clinically meaningful outcome; patient reported – those reflecting the status of the patient's health reported directly by the patient, without interpretation of the patient's response by anyone else; and composite – a single measure of effect, based on a combination of individual endpoints.

While "direct" clinical endpoints are those most commonly associated with the approval of new drugs, each of these types can, alone or in combination, serve as the basis for drug approval. Surrogate endpoints, for example, may be particularly useful in cases where the clinical endpoints occur too infrequently or after too long a period to be adequately studied, yet are nonetheless serious enough that treatment is important; patient reported outcomes are increasingly becoming of interest because they provide direct information on patient-perceived benefits and quality of life, which in many cases are more important than numeric effects of a therapy on disease parameters; and composite endpoints are particularly useful for therapies that can benefit patients in several ways or where component effects are too small or infrequent to show easily measured signals on their own.

Among available choices for clinical endpoints, outcome measures worthy of particularly favorable consideration include, but are not limited to those which are widely accepted as a direct measure of clinical benefit and can be easily and accurately measured; are sensitive to change and specific for the change in the effect under evaluation; measure changes that are the result of therapy and not natural history or other confounding factors; have been used in prior studies as the basis for successful approval of a product; have been shown to be valid and reproducible over time and across observers; and which measure a change that directly reflects improved quality of life and/or better health outcomes – especially as opposed to those measuring changes of debatable clinical value.

For most disease-related outcomes of interest – be they biological, psychological, or social – there are many acceptable endpoints from which to choose that meet the above criteria. It is, however, important to note that it is usually not so much the choice of particular outcome measures (endpoints) that hinders drug approvability or reimbursement, but rather the intended purpose of the endpoints or the manner in which they are used or interpreted. Because all drugs have potential risks, and because we are fortunate to live in an age where there are many effective and generally well tolerated therapies already on the market for many disorders, new product approval and reimbursement decisions require demonstration that the product meet a genuine, clinically significant unmet need (with clinically significant defined as above), and reimbursement decisions require that product pricing be proportional to genuine clinical value. Indeed, in the face of rapidly rising drug costs, pharmacies and payers are responding with new, more restrictive formulary management policies, including exclusion lists. These lists contain drugs that are not eligible for reimbursement, as well as recommended alternatives in the same therapeutic class that are covered. For the majority of these drugs, the manufacturer has failed to conduct comparative clinical or cost-effectiveness studies against existing therapies, the lack of which greatly increases the uncertainty to payers, providers, and patients about a drug's relative value, and decreases the likelihood that a new drug will be reimbursed, prescribed, and commercially successful. The traditional reluctance of manufacturers to conduct head-to-head comparisons of their products against current "standard-of-care" treatments – sometimes because of cost or even for fear of appearing to fall short in some area of efficacy or safety – has become counterproductive in a day and age when reimbursement at a premium to current therapies – and sometimes reimbursement at all – is increasingly requiring demonstration of clinically meaningful product superiority over those therapies.

Where companies often go astray in obtaining desired approvals and pricing is therefore not so much in failing to use potentially approvable endpoints, but in using or explaining endpoints in a way that can bias or exaggerate drug effect; choosing endpoints that highlight a desired promotional claim over unambiguously demonstrating clinically significant effects that positively impact the lives of patients or healthcare utilization; or failing to conduct the increasingly required head-to-head trials to demonstrate

unequivocally to payers, providers, and patients why this new product should be purchased, prescribed, and taken over currently available products. Two other common errors include failure to incorporate regulatory input on study design in the manner regulators intended, and not limiting the study objectives and endpoints to those few which are essential to address the particular study goals – for example, including extraneous or detracting endpoints that confound interpretation of study results or statistically compromise endpoint(s) of greatest interest.

Also, companies must realize that if they do not choose the established, validated clinical endpoints recommended by regulatory agencies, they will substantially increase their workload as they must now convince the regulators, prior to beginning their adequate and well-controlled clinical study, that their proposed clinical endpoints are indeed valid measures of a clinically significant outcome. Attempts to simultaneously validate proposed novel clinical endpoints together with the conduct of an adequate and well controlled study have a very low chance of success in our experience.

In summary, to meet regulatory and payer requirements for approval, a product must foremost provide measurable and meaningful clinical benefit, which can then be demonstrated via a number of validated and reproducible endpoints that reflect decreased suffering, improved quality of life, and/or decreased subsequent health care utilization. The outcomes must then be interpreted and presented in an unbiased fashion and in true partnership with regulatory agencies; and for payer approval, the product must also show a clear risk-benefit advantage over existing therapies of magnitude sufficient to justify the cost to patient and payer, with pricing that is not out of proportion to that benefit.

Finally, we also strongly recommend that applicants meet with the FDA before submitting protocols intended to support marketing applications, and do so in the spirit of a true partnership with serious consideration of all FDA input. The FDA will ensure that these meetings include a multidisciplinary FDA team of medical therapeutic specialists, statisticians, clinical pharmacologists, and often external expert consultants. Applicants can also submit protocols after these meetings and request a special protocol assessment that provides confirmation of the acceptability of endpoints and protocol design to support drug marketing applications. With the above considerations in mind, delivering what payers and regulators want – or, more accurately, need – can be a relatively straightforward and rewarding task that, in the end, greatly benefits patients and drug developers alike.

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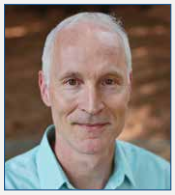

Dr. Modell is a board-certified psychiatrist with over 30 years of experience in clinical research, including 20 years in teaching, patient care, and research in academic medicine, and 15 years of experience in clinical drug development (proof of concept through market support), medical affairs, successful NDA filings, medical governance, drug safety, compliance, and management within the pharmaceutical and CRO industries. His specialties and expertise include neuroscience, psychopharmacology, drug development, clinical research, medical governance, and clinical diagnosis and treatment.

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In the past two years, Dr. Shoemaker has been responsible for four successful marketing applications including two in eCTD format. Dr. Shoemaker has significant experience interacting with the Divisions of Analgesia, Anesthetics, and Rheumatology Products (DAARP) and Gastrointestinal Products (DGP) at FDA and has obtained marketing approval for products in the US, Canada and the EU. He works closely with medical, biostatistics, clinical operations, and medical writing team members to ensure Rho's effort reflects the advantages of his nearly 20 years marketing application experience.

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