

DESIGNING TRIALS PAYERS CAN TRUST

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A PAREXEL® Consulting analysis of the reimbursement decisions of three national reimbursement agencies from 2005 to 2014 found that just over a third (39 percent) of submissions to payers were approved.

One reason for this low acceptance rate of already-approved treatments is that pharmaceutical manufacturers are not presenting the data that payers want, demonstrating that a new treatment is more cost-effective than those already on the market.

Drug developers design their trials primarily for regulatory approval. This is reasonable; without regulatory approval their therapies would never reach payers for reimbursement consideration. This leads manufacturers to focus Phase III trials on their new treatment's efficacy versus placebo or established standards of care. However, this is a less demanding hurdle than comparing them with the market-leading therapies commonly used by clinicians and against which payers are likely to compare. Consequently, developers are left trying to assemble the data payers demand after Phase III trials have finished, using the data they have. This often means constructing an indirect case against the payers' preferred comparators. Not surprisingly, this can cause payers to become skeptical about the reliability of the developers' arguments and the value of their treatments.

For example, in the UK, NICE issued a negative final appraisal for Benlysta, a lupus treatment, despite the fact that the drug's developer, GlaxoSmithKline, sought approval for Benlysta only as an add-on therapy for patients with active lupus who were



THE CHALLENGE IS TO DESIGN TRIALS FOR REGULATORY AND COMMERCIAL STAKEHOLDERS.

receiving other medicines, and even offered a discount on the list price. But NICE expressed uncertainties over Benlysta's cost-effectiveness, noting the lack of data comparing the drug with Roche's MabThera, the prevailing treatment.

Even if developers could predict accurately the data they would need to ensure success in every submission, it would be too overwhelming and expensive to collect it all. Therefore, they must collect and model better data, incorporating information from prior submissions for similar therapies and indications,

DESIGNING TRIALS PAYERS CAN TRUST

and use it to design better-targeted trials. This is an achievable goal.

DON'T REPEAT MISTAKES OF OTHERS

The search for better data and economic models begins with avoiding mistakes others have already made. Developers should look at submissions for similar compounds to see where the gaps in the evidence were, factoring those into their trial design.

By reviewing previous reimbursement decisions, developers can identify the sources of payer uncertainty, which can help them to understand what data might be important and to prioritize accordingly. This may result either in the commissioning of further studies or in a change to the trial protocol. It can sometimes be relatively easy to collect the required data from a single trial that will meet the needs of multiple agencies.



EARLY ECONOMIC MODELS MAKE IT POSSIBLE TO ADDRESS KEY ISSUES OR DATA GAPS BEFORE SIGNIFICANT INVESTMENT.

PAREXEL, for instance, has an oncology client planning trials to satisfy two quality-of-life (QoL) measures: one disease-specific focused on pain and one generic based (the EQ-5D). NICE prefers EQ-5D data, which is not very specific concerning pain and therefore not very good at distinguishing severity in this illness. The specific measure, better at distinguishing between levels of illness, cannot be compared across different illnesses. If both measures are collected in the same trial, one could map from the specific to the general (for example, a given range of pain scores mapped to a corresponding range of EQ-5D values). This type of equation could be used to estimate EQ-5D values indirectly if the disease-specific measure is the only one collected in a clinical trial. NICE prefers EQ-5D data to be collected directly, rather than mapped, and other agencies prefer other measures, such as the

Short Form Health Survey, or SF-36. Clearly, what is collected and what is mapped could have a pivotal role in what an agency might approve.

It is therefore important to review prior reimbursement-agency submissions for the specific therapeutic area and determine for each whether mapping has been criticized or accepted, or whether the agency requires directly measured EQ-5D (or SF-36) data. On that basis, a developer can decide what to collect directly and what to map, and put in a plan to explain its strategy to payers and gain their trust at an earlier stage.

For one client, PAREXEL analyzed the relationship of hospitalization for heart failure to mortality, demonstrating a strong correlation between rehospitalization and life span. PAREXEL quantified the number of rehospitalizations that needed to be prevented to have a significant impact on mortality by an intervention. This allows the possibility of using readmissions as a surrogate endpoint in clinical trials, potentially saving time and money in development.

As in the oncology example, patient-reported outcomes (PROs) are becoming increasingly important to securing regulatory approval. They can strengthen the case for a product's therapeutic value, particularly when establishing a label claim. They have also become relevant in overcoming many market-access hurdles, including reimbursement submissions, and in price setting. Therefore, it is important to factor PROs into early-stage planning.

The range of existing and validated PRO instruments is extensive and growing, and if a developer wants to compare symptom outcomes with a competitor's product for the same indication, it may make sense to use the same instrument. However, if a new claim is being made for a treatment compared with a competitor's, it may be wise to develop a new instrument. In either case, collecting this data is time consuming and expensive (especially when developing a new instrument), and should be done as early as possible. This enables a developer to determine what data various stakeholders and decision-makers will

likely most value, and what study design will produce the quality and quantity of data desired. This can all shorten time to market.

Along with improving trial design by taking into account different sources of data, it is also valuable to develop an economic model before Phase III. This makes it possible to determine the potential cost-effectiveness of any compound early enough to address key issues, or fill data gaps, before investing resources in a treatment that has no realistic chance of achieving commercial success.

In a recent PAREXEL engagement, an early-stage economic model illustrated that changes in patient utility were a key driver of cost-effectiveness, and that evidence in the literature for utility for patients with the target disease was subject to uncertainty. Following this modeling, the client, in addition to collecting EQ-5D in its Phase III trial, implemented a separate study designed to collect utility data for patients treated with the current standard of care. In this case, better information and better economic modeling reduced uncertainty and strengthened the argument for cost-effectiveness.

DIFFERENT DATA FOR DIFFERENT STAKEHOLDERS

Clients sometimes come to PAREXEL with a drug that has been approved by regulators, and a study designed to gather health economic data to support their reimbursement submissions. These studies might follow patients to understand QoL factors and the costs of hospitalizations, readmissions, emergency room visits, and the like. Determining how many patients need to be followed to provide valid data is often approached via the traditional statistical methods for clinical trials. These methods work when a trial seeks to achieve one outcome to a certain level of statistical significance, as is the case when demonstrating to regulators the efficacy of a compound versus a single outcome. But it does not work well for a trial that seeks to quantify many variables in order to build a comprehensive model.



THE GREATEST SUCCESS IN GAINING PAYER APPROVAL ROUTINELY INCLUDE PAYER-PREFERRED ENDPOINTS IN THEIR TRIALS.

In such cases, the success of the model is determined not by the statistical significance of each individual variable within it; it stands or falls on whether there is enough data to estimate each of the variables well enough for the overall model to be valid.

In practice, applying the right power analysis to such a trial will often result in one with fewer patients or a shorter duration. It also may guide the client toward a more careful patient-recruitment strategy to ensure that the most appropriate data is collected in the most efficient way. Costs, for example, can vary by setting (such as hospital or outpatient clinic) or by country. An observational study is not a clinical trial, and if it is treated as such, costs almost always will be higher and critical data may not be collected.

Indeed, the data needed for reimbursement submissions can frequently be collected during Phase III trials without making the trial larger or more complicated. Phase III trials need to be designed for the primary clinical outcome, but it often is possible to get precise measures of other variables using sub-samples of the patients already enrolled in the trial. Doing so allows manufacturers to investigate more variables without making substantial additional investments—especially when they know the preferred payer endpoints. According to PAREXEL surveys, companies that have the greatest success in gaining payer approval routinely include payer-preferred endpoints in their trials.

FEEDBACK BUILDS SMARTER TRIALS

Adaptive trials provide another way to help facilitate rapid, cost-effective development, especially in the early stages.

DESIGNING TRIALS PAYERS CAN TRUST

An adaptive trial uses data derived from the trial itself to make decisions as the trial progresses. For example, in Phase I, the developer doesn't yet know the variability of response to a compound. If the data coming in indicates that the variability is greater than the initial estimate, the developer can increase the power of the trial when it is still relatively easy to do so.

In Phase II, the same principle can be extended to dose ranging. For example, a developer could run a trial with six arms (each at a different dose), and decide to enrich or terminate different arms depending upon early outcomes. If an arm at a high dose shows unacceptable toxicity, and one at a low dose shows no efficacy, both could be terminated and investment in the remaining arms increased. Decisions such as these must be made by a data board that can see the unblinded data, and made at arm's length on the basis of predetermined criteria.

Adaptive designs are more challenging in Phase III. The added complexity of change introduces statistical uncertainty, and makes the results harder to understand, even if the criteria are written into the protocol, as they must be. For instance, changing the target population during a Phase III trial on the basis of apparent differences in efficacy between subpopulations generally would not be considered confirmatory.

GET THE PAYERS ON YOUR SIDE

A recent PAREXEL survey found that manufacturers are often reluctant to engage with payers on trial design, despite the fact that most countries now have early engagement processes. This is unfortunate. Manufacturers should involve payers in defining key trial features and designing a parallel evidence-generation strategy fully validated by them. They can then use that strategy going forward to manage trials, evidence reviews, and economic modeling. Manufacturers that are most successful in gaining payer approval for their submissions do this. One large pharmaceutical company, for instance, has embraced the idea that payers are customers, and



AS PAYERS RAISE THE BAR ON SUBMISSIONS, DEVELOPERS HAVE TO RESPOND WITH BETTER DATA.

actively engages with them throughout the process. It has found this makes it harder for reimbursement agencies to reject their products.

As payers raise the bar on reimbursement and market access submissions, developers must respond with more and better data and analysis. Key to this is running trials that meet payer as well as regulatory needs, but are still cost-efficient and targeted at proving the endpoint that will ensure regulatory approval. As has been described, there are many tools and techniques developers can use at every stage of the development process to create submissions payers can trust, including evidence reviews, early economic modeling, sophisticated power analysis, adaptive design, and the collection of observational data. Usually the earlier these are planned for, the more efficient and effective development will be. But these are also tools that can be deployed to reinforce a development process that is already under way. You can find in-depth articles about all of these tools and strategies on the PAREXEL commercialization Web page. These can help developers provide the outcomes-focused, objective information payers want, better preparing them for the debates on their products' efficacy, safety, and value.

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You can view more commercialization resources online at:

[Commercialization.PAREXEL.com](https://www.PAREXEL.com)

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