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STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies

Chapter 6. Maximizing Value

This article is the sixth part of a 15-part series from STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies by Hugo Stephenson, MD, President, Strategic Research & Safety, Quintiles.

Large pharmaceutical companies are frustrated by the lack of impact from Phase IIIB and IV research, especially given the amount of money they spend in this area. To address this problem, brand team members need to understand that the impact and value of a Phase IIIB or IV study is measured not only by the statistical significance of its results but by a combination of factors that include the scientific immediacy of the research to patients and physicians and—even more importantly—the timing of its conduct. A successful strategic research plan involves having what you need to say when you need to say it, and is most effective when you keep goals focused, keep studies simple, and communicate both internally and externally.

Plan Ahead

The culture of the pharmaceutical industry is not conducive to rapid decision-making. The most effective companies recognize that the process of developing a research strategy, creating a protocol, obtaining necessary internal approvals, and securing funding is a long and slow process that can delay a response to a market opportunity or crisis. To address these delays, brand teams develop a research wish list by identifying:

- weaknesses in their existing data that could compromise their ability to differentiate their products effectively,
- opportunities to supplement existing data in support of the value of their product,
- and "safety net" data that could be useful in the event of a product or competitive crisis.

Researchers develop a range of research protocol synopses around this wish list and establish budgets, timeframes, and priorities for each opportunity. To maximize the value of their research investment, they must consider whether multiple objectives can be addressed

Rapid Response Demonstrates Commitment to Safety

In 2002, Johnson & Johnson (J&J) faced growing concern over the safety of their blockbuster treatment for anemia, Eprex (erythropoietin alfa). Regulators were growing concerned by a slow but significant increase in the incidence of Pure Red Cell Aplasia (PRCA), a rare adverse event, among patients receiving Eprex by subcutaneous injection. Although the cause of increasing PRCA was not known at the time, J&J reacted rapidly by initiating an Urgent Safety Restriction (USR) to ensure intravenous administration of the medicine while, at the same time, announcing an extensive epidemiological study of patients receiving erythropoietin treatment. The study's goals were to better understand risk factors for PRCA development, to monitor and confirm the safety of intravenous administration, and to ensure that the USR was effective in reducing Eprex's subcutaneous use. Facing stiff competition from a new erythropoietin drug manufactured by Amgen, J&J's rapid actions not only reaffirmed the company's commitment to safety, but prevented a broader product restriction that could have quickly cost J&J a sizeable part of their $1.1 billion Eprex franchise.[1]

within one study or conversely whether multiple studies could synergistically support an objective.

By proactively developing a portfolio of possible research protocols (not all will be funded) in anticipation of the brand teams needs, companies can react to market changes three to six months faster than their competitors. Having these procedures in place allows a company to kick off pre-approved protocols quickly, improving its chances of producing the right data at the right time.

Know Your Goals

Strategic research is associated with greater latitude in protocol design than registration research and it is also used to answer many different questions than the earlier phase research. These expanded means and goals make it possible for studies to proceed without clearly defined research aims or endpoints, causing many projects to fall flat on value because of a lack of clarity and focus in their original design. Just because it is possible to conduct studies that span a broad range of objectives in Phase IIIB and IV does not mean that you should.

Designing strategic research activities should start with how you want to use the data, when you want to use it, and to whom it needs to be addressed.

The design of a Phase IIIB and IV study is equally influenced by its scientific objectives and by the need for information due to market context. Failure to clearly identify a study's scientific goals and its target audience can result in the execution of inappropriately designed studies and the underachievement of research potential. Many companies

Randomized Studies Do Not Have to Be Complicated

With the benefits of treatment with Angiotensin Converting Enzyme (ACE) inhibitors well established for patients with cardiovascular disease, manufacturers of a newer class of agents known as Angiotensin II Receptor Blockers (ARBs) have long recognized the need to validate the non-inferiority of their products versus ACE inhibitors. The difficulty was the need to conduct RCTs with the tens of thousands of patients to ensure statistical significance.

In 2001 Boehringer Ingelheim embarked on this challenge for their ARB product Mycardis (Telmisartan) through the ONTARGET/TRANSCEND program, which consists of two randomized sub-studies both scheduled to report in 2007. By sharing the same research infrastructure and materials between studies, opting for a very simple visit schedule and focusing data collection efforts on major endpoints and safety, this simple research program was able to win significant investigator interest and exceed its recruitment target of 23,400 patients by over 5,000.[2]

Patients in the research program are screened for ACE inhibitor tolerability—those who pass are enrolled into ONTARGET (which includes ACE, placebo, and Mycardis treatment groups), those who fail are enrolled into TRANSCEND (which only involves placebo and Mycardis treatments). Taking this approach has allowed Boehringer to include patients that would otherwise have been ONTARGET screening failures (up to 20 percent of the study population). By conducting two parallel and relatively simple RCT studies, Boehringer is on track to capture the volume of data they need to prove that their product is as effective as the popular ACE inhibitors in treating patients at high risk of heart disease.

commence “catch all” studies on the basis that valuable data may turn up. Unfortunately, this is almost never the case.

Keep It Simple

As well as remaining focused on the goals of a Phase IIIB or IV study, it is equally important to minimize the operational complexity of each project. Address different objectives through multiple simple protocols that are coordinated as a program of parallel studies and/or sub studies rather than as a single complex protocol. Every unnecessary protocol complexity places the smooth execution of a study at risk, and every extraneous data point collected increases disclosure risks associated with holding data that may not be exhaustively analyzed.

Protecting the simplicity of a study increases the chance that researchers can control its timing and manage costs, and that the study will successfully address a sponsor’s goals. By running multiple simple studies as a program rather than as one large study, one can individually control the timing of each component and avoid the scenario where all objectives are placed at risk together.

Communicate

A study in a vacuum will generate no noise. To achieve maximum value from a study, one must design it to answer the information needs of the market and ensure that its results are communicated to its target audience. Delivery, performance, and timing of strategic research can make or break a commercial strategy. Historically, many pharmaceutical companies have had difficulty clearly managing the coordination of strategic research between clinical and commercial groups, often designing studies with limited value for the market or missing opportunities to maximize communication with the public.

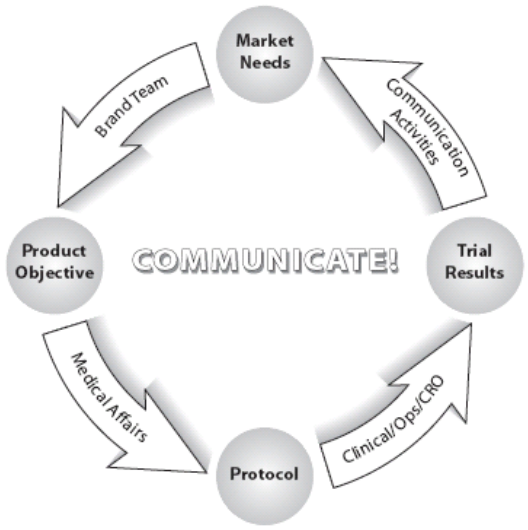

Figure 6. The process of Phase IIIB and IV research must be coordinated so that communication activities at the end of the process are ready to start as soon as study results are completed.

Although clinical research operations are usually charged with designing, executing, and consolidating a study, other stakeholders are also involved in the project. At the beginning, corporate strategists—including representatives from medical affairs, health economics, marketing, sales, and reimbursement—set the key priorities for the product and directions for potential research. At the end, the same group is responsible for maximizing the value of any research conducted. As with any endeavor that involves multiple stages and multiple stakeholders it is important that the study group charge someone with ensuring effective communication and transition of responsibilities between parties.

Equally important as good internal communication is communication with external stakeholders. The most effective sponsors have members of the brand team create draft publication and communication plans in parallel with their protocols. As each study progresses, they refine these plans with additional detail to maximize public relations opportunities through

medical and lay media pickup, and they encourage appropriate use of these results in regulatory negotiations, reimbursement strategies, or the development of marketing plans and materials. A brand team that is isolated from Phase IIIB/IV research planning and execution, and is not prepared to receive study results as they become available, will not be able to work the results effectively into the brand strategy.

Team members must consider a variety of questions. How should results be communicated? Which journals should be targeted for publication? When and how do these journals need to receive manuscripts? How could data be used to maximum effect in continuing medical education programs, newsletters or other sponsored activities? Could sales representatives use interim data to drive field activities? Is corporate public relations involved in the process?

Key opinion leaders play a large role in amplifying research messages. Much time, effort, and money is spent developing them as important leaders for the medical community and press. Some companies actively involve key opinion leaders in their publication planning and communication process, reinforcing the clear messages that were developed during the earlier stages of the research by using these leaders' ability to communicate study results to the media as well as to well-organized seminars and conferences.

Getting the Right Message Through

Publishing a study provides no guarantee that the medical community will notice its results, let alone be satisfied with the objectivity of the research or interpret them in line with a sponsor's expectations. A coordinated communications approach at the time of publication, however, can go a long way to ensuring that good science becomes a good investment. In late 2003, Novartis announced the publication of results from their VALIANT trial—a randomized study of 14,703 patients – that confirmed that its angiotensin II receptor blocker (ARB), Diovan, is as effective as an ACE inhibitor at improving health outcomes when used after a myocardial infarction.[3] The VALIANT study was well timed, positioning DIOVAN as the first ARB to demonstrate therapeutic equivalence with ACE inhibitors and thereby achieving the scientific significance required for publication by the New England Journal of Medicine.

As members of the study's scientific committee, clinical leaders from Harvard and the University of Glasgow provided vocal and public support for the study's results. It clearly bodes well for a product's opportunities when an international scientific leader claims that "even if a newer agent is more expensive, it is welcome news that we now have the option and the alternative, and we should be extending the use to people who are having difficulties with the cheaper, better-used, better-studied, better-known agents."[4]

Conclusion

The key to successful strategic research is understanding what needs to be achieved, then working backwards from this objective toward study design. The objective of registration research is always clear: regulatory approval. Clarifying the objectives of strategic research involves more thought and discipline to balance the needs of different stakeholders. Plan ahead, know your goals, keep the study simple, and make sure you communicate your results in the most effective manner possible. In communicating study results, close attention to the timing of release and the amplification of key messages will help you get the maximum value from your research.

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* Note: All citations to websites listed in this book were verified in May of 2005.