Building Flexibility into Your R&D Strategy

Enhancing and Widening Your Asset's Potential

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Successful R&D strategies aren't always able to avoid every wrong turn, but they do steer clear of dead ends. Incorporating optionality into clinical development can enable companies to surmount unanticipated challenges and clinical trial setbacks. This paper will discuss how flexibility in clinical development can be incorporated at various points along an asset's life cycle and how to avoid the kinds of decisions that will irrevocably shunt development programs down a single, narrowly defined path, resulting in all-or-nothing outcomes that kill, delay, or increase the cost of future development.

Many of these tactics are focused on positioning data generation in creative ways that can enhance and widen an asset's value across multiple development paths and ensure compelling positioning across multiple stakeholders.

Nearly every early-stage R&D program will face uncertainty. Here we examine preconceived notions of the R&D process, identify ways of building in flexibility, and maintain a nimble clinical development approach in an always-changing marketplace. This optionality may manifest differently depending on the therapeutic area or targeted patient population, or even based on competitor treatments on the market or in the pipeline. But whether the drug candidate addresses a rare disorder or a mass market population, whether it's a potential monotherapy or combined with an established therapeutic regimen, these concepts still apply.

Building flexibility into development programs can admittedly be a function of available capital, and a luxury some smaller biotech companies can't afford. Nevertheless, it's an important exercise that shouldn't be dismissed entirely because of cost, as streamlined development pathways might not always be the most appropriate – particularly in areas where competition is fierce. Optionality in clinical development can rescue an asset or technology, or simply better position it against future competition.

Debunking the Myths

It isn't necessarily true that there's a clinical lock-down point after which drug development strategies cannot pivot. Simply accelerating through clinical development as rapidly and streamlined as possible along a narrow path that appears to be the most compelling might not always be the most appropriate strategy for your technology or asset, even if it's the least expensive option from the outset. We do not discount the approach of establishing proof of principle in a targeted patient subpopulation – but rather advocate for maintaining flexibility once that has been accomplished.

Although the path toward approval may narrow following Phase 2, incorporating exploratory endpoints and data-gathering into even later-stage clinical studies may be the most prudent strategy. This could mean tracking a set of biomarkers from the outset, and possibly using that data to enrich a trial with a certain subset of patients later. Or it could mean incorporating additional endpoints in early trials that allow you to pivot development as the asset progresses.

Take for example the case of Shire's SHP607, a complex of recombinant human insulin-like growth factor-1 (IGF-1) and IGF binding protein 3 (IGFBP-3), an experimental ex vivo protein replacement therapy. Shire originally tested the candidate as a treatment for retinopathy of prematurity (ROP), a rare eye condition in severely premature infants who lack sufficient endogenous production of the protein. SHP607's Phase 2 study unfortunately failed to meet its primary endpoint in ROP.

But because Shire had designed its trial in such a way as to measure a host of different clinical endpoints and biomarkers to explore the holistic effect the drug candidate was having on the infants in its trial, the company was able to determine that SHP607 had positive impacts on other maladies facing severely premature infants. Demonstrated improvements in endpoints related to severe bronchopulmonary dysplasia (BPD), a condition of pulmonary dysfunction, and a type of brain injury called severe intraventricular hemorrhage (IVH) provided a basis for continuing to advance the program.

Including additional measures in a trial can increase complexity and cost related to early development. But the flexibility intrinsic to the chosen development strategy provided optionality

to a promising clinical program, and sets the company up for the drug candidate's pivotal trials. In September 2017, Shire announced Fast Track designation for the asset as a treatment to prevent chronic lung disease in extremely premature infants.

Widening the Net to Avoid Narrow Victories

Continuing to explore alternative clinical hypotheses, or gathering the data necessary to reposition a compound is a sound strategy that isn't limited to large pharmaceutical companies with larger R&D budgets. What's more, the reasons for maintaining optionality and flexibility within clinical development programs aren't confined to being able to pivot a program after a failed clinical trial.

This flexibility also provides a company with important optionality that might be needed to position a technology or asset in an increasingly crowded landscape. Take for example the less common approaches being pursued by a few companies developing treatments for non-alcoholic steatohepatitis (NASH). While many programs are limiting their pursuit to NASH patients with varying levels of fibrosis, others – such as Galectin Therapeutics – are exploring patients who have become cirrhotic.

This gives the program an opportunity to differentiate itself from most agents in the rich NASH pipeline, and it provides an opportunity to look for clinically-relevant effects on many endpoints. This includes traditional endpoints such as histological assessments of liver health, but also includes alternative markers such as measuring the hepatic venous pressure gradient or the signs and symptoms of decompensation. Overall, the program's design could measure multiple effects in a clinically-significant disease, providing choices when it comes to future positioning with regulators, clinicians, and payers.

Phase 1 Flexibility

Early clinical development offers multiple pathways to optionality. In oncology, Phase 1 "basket trials" that test a therapeutic candidate in a variety of tumor types offer a clear opportunity to maintain flexibility – and occasionally even gather enough efficacy data in a particular tumor that allows a company to file for regulatory approval.

While companies like Roche are well versed in this strategy, it remains an expensive proposition for smaller biotech companies. But there are certain cases in which biotechs too have the opportunity to think creatively and build flexibility into early clinical trial designs, including in a single trial containing patients with different diseases in the same or different therapeutic areas that feature the same target or mechanism.

One example is ILTOO Pharma, developing IL-2 based therapies for autoimmune disorders. In addition to a more 'classic' systemic lupus erythematosus development program (now in the Phase 2 LUPIL-2 trial), the company is conducting the TRANSREG Phase 2 study that includes patients across 14 autoimmune or inflammatory diseases. The trial measures regulatory T cell

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responses but also includes disease-specific biological and radiological criteria. Such flexibility should provide the company with significant options as it moves forward in clinical development.

Other industry examples – such as the exploration of TNT009 by True North (acquired by Bioverativ) in multiple complement-mediated orphan diseases through a single Phase 1b trial – should reinforce this trend.

Similarly, early development for diseases with multiple patient subgroups could include a more diverse patient population. For example, a clinical trial for a drug that is potentially disease modifying, but a company is only convinced it'll demonstrate efficacy in earlier-stage patients where the disease's progress is more likely to be arrested, might include some later-stage patients as well, or prodromal patients with a particular biomarker. Expanding a trial's exploration into additional subgroups to investigate whether an effect is observable can avoid pigeonholing a candidate throughout the rest of its clinical development.

Measuring more than efficacy

This flexibility isn't limited to creatively defined patient populations or efficacy endpoints. Digital technologies are allowing biopharmas to become more savvy at measuring quality of life and health-economic endpoints. Adding these health-economic outcomes measurements to clinical trials, particularly in Phase 2, will also create optionality for biopharma companies. These endpoints can include length of hospital stays, impacts on costs or use of other resources – for example other drugs that treat symptoms of a disease – or whether a therapy allows patients to be treated at home or as outpatients in the first place, rather than in a hospital.

In the area of sickle cell disease, for example, the monoclonal antibody crizanlizumab from Selexys Pharmaceuticals was shown to reduce the length of hospital stays caused by painful sickle cell crisis events by 42% compared to placebo in the drug's Phase 2 clinical trial. That study's results – crizanlizumab also met its primary endpoint of reduction of sickle cell-related pain crises – led Novartis to exercise its option to buy Selexys for up to $665 million at the end of 2016. Other biopharmas developing drugs for sickle cell are

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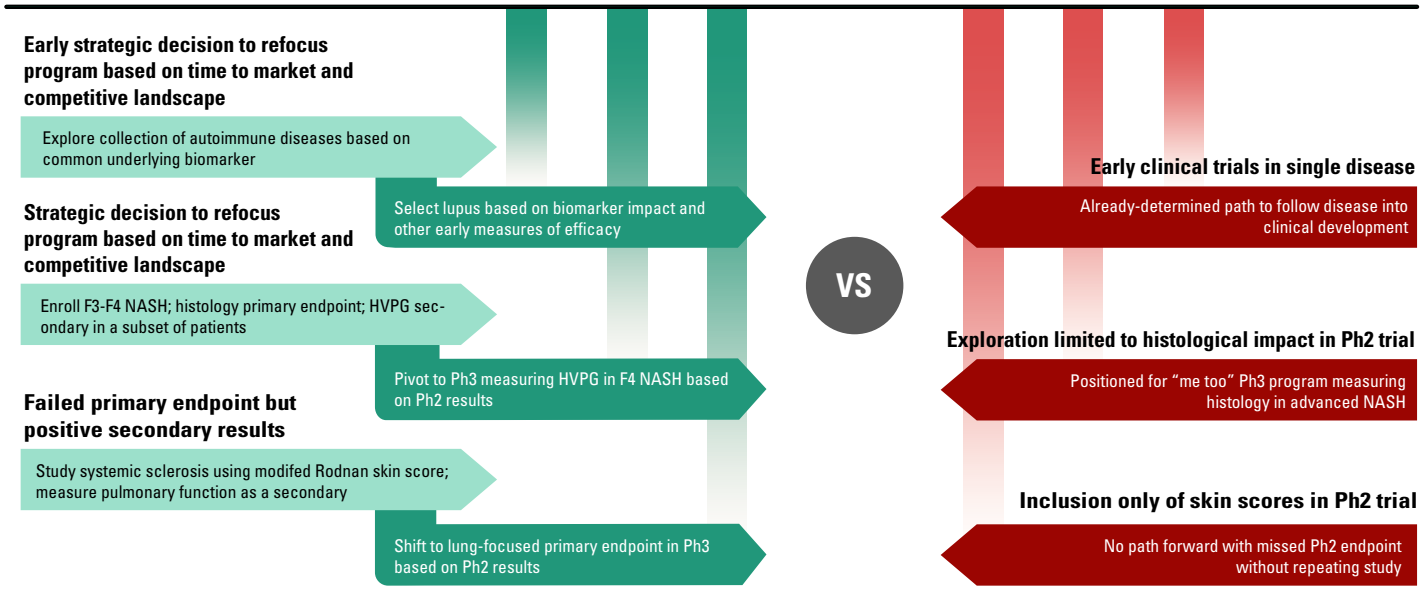

measuring patients' consumption of drugs to treat the pain caused by sickle cell attacks. Reductions in opioid use and hospital stays are likely to resonate with patients, physicians, and payers.

Quality of life scales help to explore a therapy's impact beyond clinical results. Including multiple means of measuring a drug candidate's impact on quality of life in Phase 2 clinical trials can help a drug developer know which means of measurement is most appropriate for Phase 3 – or indicate that something entirely new could be developed. Pain-related indications such as lupus, neuropathic pain, sickle cell disease or fibromyalgia provide an opportunity to explore patient-reported outcomes (PROs). For example, AbbVie's Eligolix released positive data for its Phase2b, which used the pace of decreased heavy menstrual bleeding as its endpoint for uterine fibroids, an often painful disease.

Late-stage Development

By the time a drug candidate is in Phase 3, most flexibility can be gained by including a variety of key secondary endpoints to measure, or establishing the possibility of an interim analysis to look at relevant clinical measures that could result in an accelerated approval or an early trial stoppage. Companies should also be evaluating biomarkers that might have clinical utility or allow for some future product differentiation. Any means of bolstering a dataset that a competitor may lack will be an asset – such as a pre-specified subgroup analysis that may result in potentially differential labeling. Multiple endpoints may give companies flexibility – even within the context of a single trial.

In the case of Intercept Pharmaceuticals' obeticholic acid for the potential blockbuster market NASH, the company included two co-primary endpoints in its Phase 3 trial – resolution of NASH based on the measurement of a panoply of histological elements that constitute fibrosis (the so called NAFLD activity score) and reversal in fibrosis. Mid-trial, the company agreed with the FDA to modify its endpoint: a positive outcome on either metric would count as a positive responder (instead of needing both).

Based on the company's Phase 2 data, it might have included just the NAFLD activity score, and its trial would have been less likely to succeed. But adding in the composite endpoint gave the company flexibility to discuss a trial modification with the FDA, and effectively give it an extra shot on goal.

Other companies are pursuing similar strategies in the clinic as they explore efficacy in systemic sclerosis, measuring effects on the skin via the modified Rodnan skin score as well as potential efficacy in the pulmonary components of the disease via measures such as forced vital capacity. Depending on the efficacy signals observed, these Phase 2 designs provide optionality for companies as they contemplate Phase 3 designs.

Beyond the Clinic

Even after a product is approved by regulators, flexibility can be incorporated to improve pricing and market access conditions. These issues tend to arise late for most companies – once they know how their product stacks up to the competition and what value it provides to patients and payers.

Creatively thinking beyond classic efficacy measures itself opens up new options for a company. Patient registries may enable companies to track additional quality-of-life data to bolster pricing arguments or provide ideas for additional clinical hypotheses. Companies with marketed products are often pleasantly surprised to see what they're actually able to measure or generate from a data standpoint, and the value that data creates.

Aim for Agility

These strategies to avoid bulldozing down a single path are available at all points along the value chain, and the few discussed here are not all encompassing. Incorporating flexibility into R&D can salvage a failed program, or bolster the prospects of even the most successful clinical asset. Building optionality into clinical trials can pay dividends far down the road with key constituencies such as regulators and reimbursement authorities.

In the maze of clinical development decision-making, wrong turns might be inevitable. But it's often possible, with the right planning, to avoid the dead ends.

About ClearView Healthcare Partners

Founded in 2007, ClearView Healthcare Partners is a global strategy consulting firm serving the life sciences sector. The firm combines international industry knowledge and deep scientific expertise across a range of therapeutic areas with an extensive network of external stakeholders to deliver practical and actionable recommendations to our clients' most complex challenges. The firm's projects include cross-functional support at the corporate, franchise, and product levels for pharmaceutical, biotech, medtech and digital, and diagnostics companies worldwide.

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