OPTIMISING TIME-TO-MARKET FOR INNOVATIVE CELL THERAPY TRIALS

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Across the biopharmaceutical industry, many have expressed concern about the protracted timelines for drug development, which on average are getting longer when most stakeholders insist the time-to-market (TTM) needs to be shorter. Nowhere is this clearer than with new modalities, particularly cell therapies that are often personalised and manufactured starting from a patient's own cells.

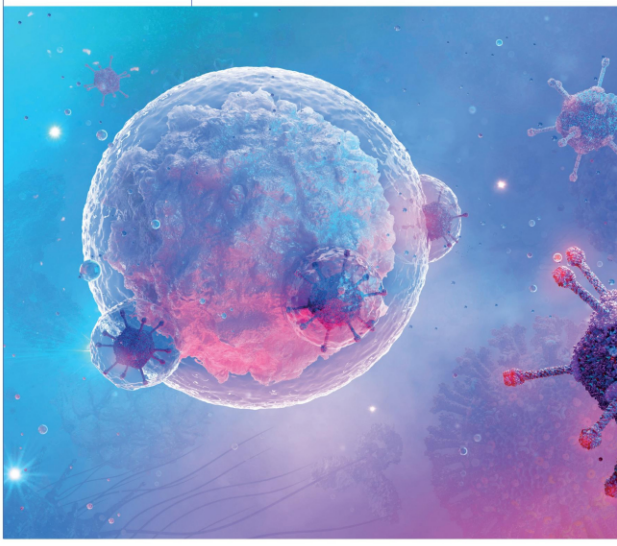
Stakeholders see many advantages to reduced timelines. For one, it may enable a company to be first to market and establish a beachhead. Investors push TTM optimisation for a higher return on investment, higher net present values, and higher market cap. Plus, it can be beneficial for patients in urgent need of innovative therapies for severe diseases, thereby garnering regulatory support as well. However, trading quality for speed is not an option in healthcare for ethical and regulatory reasons. In the cell therapy space specifically, developers, manufacturers, and regulators are still learning best practices as we move toward standardisation.

There are efforts underway to optimise several stages of development but some approaches that impact other therapies do not meet the specialised needs of cell therapies. For example, advances that can abbreviate the discovery stages like high-throughput and in silico screening may not be as impactful on advanced therapies. Additionally, the field has struggled to develop animal models with greater relevance to outcomes in humans, meaning that we are unlikely to see dramatic TTM gains based on advances impacting early-stage development any time soon. This puts greater emphasis on innovating the clinical phase, already the longest part of development.

ACCELERATING CLINICAL DEVELOPMENT

Unfortunately, the duration of clinical trials continues to increase, primarily due to ever-extending patient recruitment periods. The reasons for this are related to the substantial size of the cohort, increasingly complex protocols, limited resources of hospital centres, and the concentration of clinical trials in the same indications among the same expert recruitment sites.

The introduction of new trial designs could change this paradigm, such as those incorporating adaptive design and innovative non-parametric statistical methods (e.g., generalised pairwise comparison). Regulators have been increasingly open to the use of surrogate endpoints that are predictive of clinical outcomes,



like biomarkers and imaging. Surrogate endpoints are especially critical in chronic diseases, where it can take years to tell directly if a therapy has truly altered progression. This is part of our approach at CellProthera, where we are working to advance cell-based therapy into late-stage trials to prevent heart failure in patients following acute myocardial infarction. Severe heart attacks often lead to chronic heart failure and a life expectancy of only 50% after five years, but the use of surrogate endpoints, if sufficiently predictive of the underlying disease, would allow for earlier market authorisation.

The use of real-world evidence as an external control group, although still requiring consensus and standardisation, is also gaining ground and can reduce recruitment duration. Between their openness to such novel approaches, a growing collaborative spirit, and the multiple accelerated development pathways offered by regulators like the U.S. FDA and the European Medicines Agency, agencies have become critical partners for expediting clinical trials

Another aspect of clinical development ripe for acceleration is chemistry, manufacturing, and controls (CMC) activities, which must be conducted to make a product ready for phase 3. Here, prior experience helps to reduce the process characterisation workload and shortens both time frames and investment. CMC changes – to improve on cost or speed, for example – are still possible post-approval, allowing a degree of flexibility in the clinical phase that can make fast-to-market approaches easier to implement.

Additional efforts to accelerate TTM involve reducing the workload on hospital centres and the burden on patients. Everything that can be done outside the hospital should be carried out at home, or at least in a facility closer to the patient. New advances in telemedicine, AI, and wearables are making this transition easier. When in-person interactions are required, the integration of more patient-accessible recruitment centres can facilitate recruitment later, especially since sponsors tend to tighten patient inclusion criteria to maximise the chances of treatment success.

OPTIMISING INNOVATIVE CELL THERAPY TRIALS

The challenges faced for trials of cell therapies require exploiting all the above for clinical acceleration. Approved cell-based therapies have demonstrated unique efficacy and even curative potential, making this one of the fastest-growing areas in biopharma. However, the space is far from standardised, with few examples' successful pathways through the clinic.

As such, innovative technologies are being tested and implemented at a high rate, ranging from ways to edit and modify genes to manufacturing advances related to automation platforms. Yet, finding clinicians with the right expertise can be difficult. One solution is to add production facilities and manufacturing slots, which can give these expert sites more flexibility by allowing extra time to schedule hospital procedures.

This also helps address the issue of overburdened hospitals as recruitment sites. Through the nature of cell therapy manufacturing, we are effectively transferring part of the CMC workload from the trial sponsor to the sites. Asking them to add responsibilities like collecting patients' cells or perform final conditioning are not standard practice for trial sites, and many are understaffed with high turnover rates, meaning cell therapy trials automatically carry extra risk with heightened potential for slow recruitment.

In some cases, it may not be possible to identify qualified research teams at sites with lower turnover rates, and even additional training may be an imperfect solution as bust investigators often lack availability. For this reason, it becomes crucial to alleviate the burden on physical sites by reducing required exams to the minimum and performing as much of the trial as possible closer to the patient – meaning satellite sites when necessary and at-home interactions when possible. This has the added benefit of lowering the burden on patients themselves, which can boost recruitment and retainment.

Accelerating clinical trials cannot compromise quality, and the complexity of cell-based therapy trials makes this balance more delicate. One way to strengthen quality is to add rigor in the patient selection process, based on stringent criteria. For us, this means taking steps like waiting a brief period after heart attack to make sure we do not include patients who recover spontaneously without treatment. While this can add some time to the trial, we feel it is a necessary step to ensure results are robust.

Another quality risk is when variability from one patient's or donor's cells to the next contributes to differences in starting material that result in doses that are out of specification, preventing their administration. Here, developing robust methods and implementing automation as appropriate can both shorten the manufacturing process and minimise process variability. We decided early on to develop our own automated equipment to ensure process robustness across several decentralised production sites.

Especially in the bespoke world of cellular therapies, it should be no surprise that we lack a simple, one-size-fits-all solution to accelerating TTM through optimising the clinical phase. However, innovation clearly is not limited to the therapies themselves – creative solutions can help the field bring better therapies to more patients, faster.