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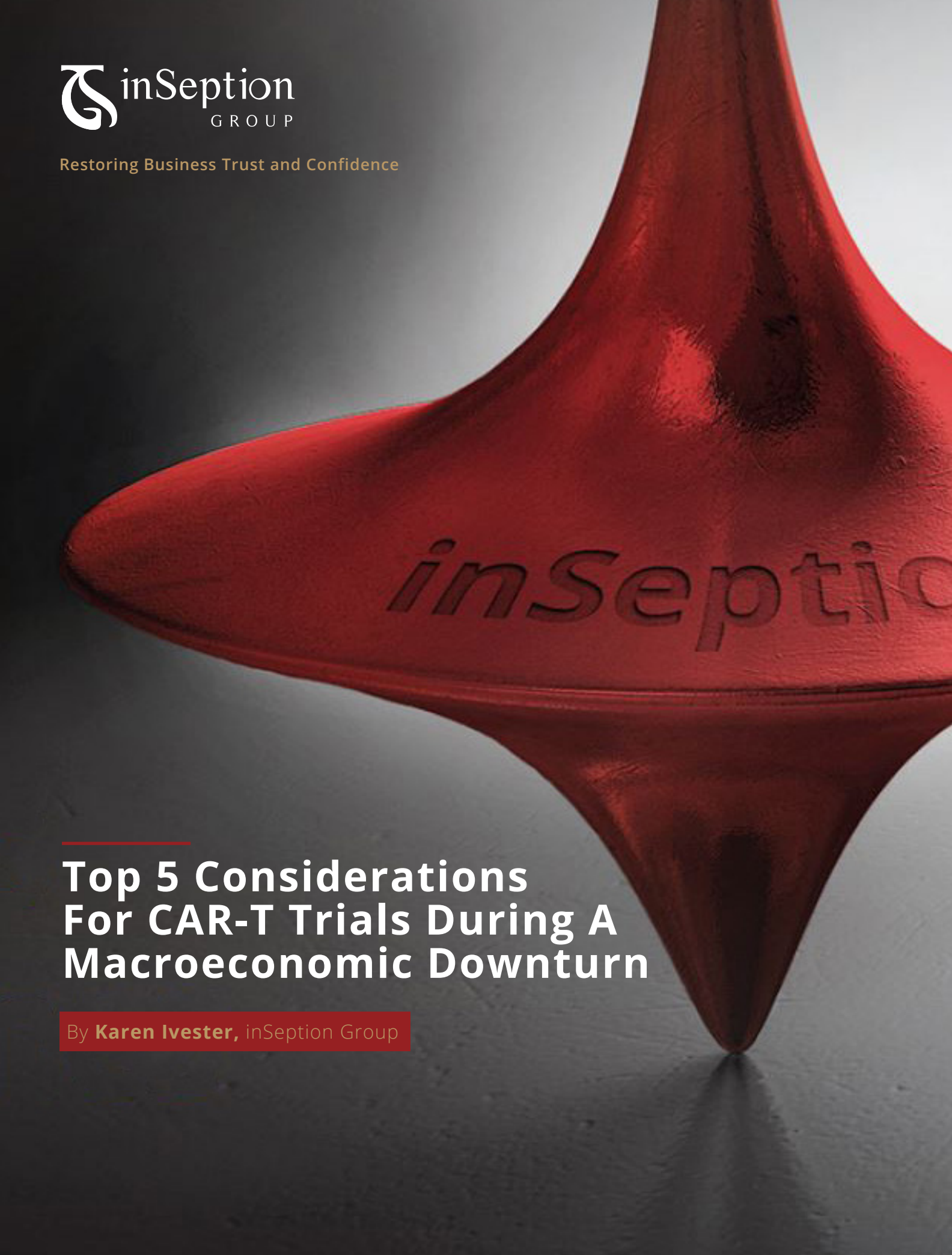

Top 5 Considerations For CAR-T Trials During A Macroeconomic Downturn

By **Karen Ivester,** inSeption Group

Economic downturns, while threatening and unwelcome, offer opportunities to improve operations through technology, training, and hiring. In some situations, organizations can benefit by claiming a manufacturing slot a failing project has vacated, advancing its own timeline.

Top 5 Considerations For CAR-T Trials During A Macroeconomic Downturn

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In a macroeconomic downturn, the cost of staffing a clinical trial, procuring reagents, and stocking single-use supplies — among numerous other expenses — can range from inconvenient to disastrous. Trials examining CAR-T cell therapies, which require specialized expertise and materials, are among the hardest-hit. However, five key strategies can help organizations planning or executing CAR-T cell therapy trials to not only endure macroeconomic hardship, but to emerge more efficient and well-prepared on the other side.

1. INSULATE PERSONNEL TO PREVENT LONG-TERM STAGNATION

"Prepare early" applies to nearly all aspects of clinical trials, but that commonality makes it no less critical. The alternative is to react to situations, even though going into "survival mode" easily leads to mistakes or short-term decisions that impact long-term strategy. Approaches to manage many of these challenges can be planned and/or implemented in advance of a macroeconomic downturn.

For example, assays for a CAR-T cell therapy trial should be plotted out up to a year in advance: who will perform those assays and what will the lead times be for each specialty lab? This also ensures the labs can stock sufficient reagents and identify backup vendors to ensure they are available when needed. Particularly in cell therapy trials, early identification and engagement of CDMOs or in-house CMC and manufacturing support are important. But experienced personnel are the lifeblood of an organization, and early preparation should include plans to retain those individuals during a downturn.

Consider that a typical defensive reaction during economic hardship might involve deep cuts or layoffs, rather than focusing on proactive operational improvements that could prevent such cuts. As a whole, this industry suffers significant shortages of qualified specialist personnel within biopharmaceutical companies, within service providers who outsource staff and/or execute clinical operations delivery, and within sites performing autologous cell therapy clinical research.

Losing even one such individual contributes to the long-term stagnation of a company. Think of a company that survived through layoffs emerging from another recent economic downturn around 2016: it made little progress during that time, but as it tries to ramp up operations again, it no longer has access to those individuals with critical expertise — and not many such specialists exist when weighed against how many companies currently are exploring CAR-T

(or any type of cell therapy, for that matter). In short, a company needs those experts to strategically pull it out of a macroeconomic downturn.

One way that COVID-19 altered trial dynamics was restricting the number of personnel allowed on-site which, in turn, impacted trial timelines (e.g., maximum volume of procedures personnel could complete were limited). As CROs and pharmaceutical companies began to struggle with expertise, they created academies to teach clinical and project management concepts, as well as cell and gene therapy courses, to their employees. Large pharmaceutical companies and CROs recruited people who had been clinical research coordinators or site research nurses, and typically they could pay those experts more. Thus, to retain their personnel in these roles, sites now must offer compensation competitive with what the CROs are offering.

Nearly all organizations — biopharma, large pharma, mid-size pharma, outsourcing groups — use or have used IQVIA GrantPlan[1] to determine what to pay the sites, coordinators, and physicians per visit/per procedure. But currently, many personnel-related costs have doubled or tripled, and GrantPlan has not caught up in many cases. Thus, biopharma companies coming into cell and gene therapy, using their own budgets or creating budgets using GrantPlan, often produce unrealistic spend forecasts based on noncompetitive wages. Sponsors must recognize that, post-COVID, sites will need increased rates in their site budgets to retain site research nurses, coordinators, and other necessary personnel.

So, the thought process comes full circle to "we'll teach our personnel," but that requires individuals seasoned enough to combine project management and collaboration across multiple vendors and different bioassay labs, etc. Indication-specific expertise, particularly in hematology and oncology (i.e., areas where the majority of cell and gene therapy approvals have occurred so far), is vital to fast, effective ramp-up coming out of a downturn. Layoffs and cuts in lieu of operational improvements undermine such efforts.

2. ACT EARLY TO ASSESS DEBT FINANCIAL MANAGEMENT

An alternative way for affected companies to decrease expenses is to proactively secure a better debt situation, allowing the company to retain valuable long-term personnel resources and outsource when additional support is needed (e.g., during peak periods and times of greater customer demand). Companies may look at increasing royalties or they may choose to reduce debt by shedding assets. A private equity-funded company with access to earlier issues of equity is in a better position to proactively manage debt for all its obligations.

Again, acting early is key to reducing debt without impacting core operations. Organizations must consider how their pipelines will be prioritized and utilized. They may have enough funding to get through preclinical and start-up of clinical activities, but ramping up introduces additional costs like paying the site(s) and/or the CDMO. If manufacturing in-house, reagent acquisition and hiring subject matter experts who understand the upstream cell process development must be considered.

Sometimes, holding onto resources during a macroeconomic downturn means looking at the product portfolio with an eye toward foresight and optimization (i.e., prioritizing projects that are not rare disease or slow enrolling). For example, cancer and leukemia incidence increases as a population ages. While cell therapies are the focus here, any trial that impacts the global growing and aging population, where demand for innovation is greater, should enroll more quickly. Focus on the company's most strategic resources to maximize growth-driving opportunities by prioritizing such trials.

Notably, biopharma companies with only one asset may have no choice but to keep moving forward with that asset. But, for the sake of their long-term growth, they must strive to keep key SMEs, outsource some of the project, and anticipate the time where they may need to ramp up

quickly. Taking a reactive approach of massive layoffs is both costly and damaging to morale: productivity suffers if a team sees everyone around them being laid off, and outgoing workers will be difficult to entice back, resulting in stagnation of the company long-term. Additionally, layoffs decrease the organization's ability to manage any new investments or to act opportunistically. By contrast, engaged people will move projects forward — buy-in among the core operational team is conducive to working at full capacity.

A more effective approach consists of building teams to withstand economic downturns. Then, if the company needs to cut resourcing costs, it can consider some reductions in work hours, partially paid leaves, or even short-term furloughs (depending on local labor regulations). These strategies will help manage cash flow while allowing the company to increase sales and net income. And, by keeping the workforce more aligned and invested, ramping back up as you are able to support higher levels of resources will be faster. It also introduces the possibility of resource sharing.

Specifically, a company asks, "Which projects add the most value, and can resources from a lower-value asset be shared?" Perhaps a slow-enrolling trial can spare part-time work from one of its resources (e.g., partial assignment to a faster-enrolling trial). That said, it is critical that these decisions are determined by frontline personnel. Allowing the people closest to a project, and most familiar with their colleagues' skillsets, to plot a course of action typically is much more effective than the C-suite making decisions based solely on bottom-line numbers (e.g., looking at the company's top earners and cutting them for a lump-sum cost reduction). In fact, employers may find they have a greater need for higher-skilled employees.

Again, early planning is prudent to anticipate and overcome obstacles. And, when devising solutions, utilize decentralized decision-making by gathering input from employees at all levels — not just leaders with decision-making authority.

3. EMBRACE DECENTRALIZED STRATEGIES AND DECISION-MAKING

CAR-T cell therapy challenges relevant to decentralized trial elements mirror those of many other trials, but such issues can be more common due to the complicated nature of cell therapies. Consider that the average remote care provider might not have the expertise to perform a required task, or the testing might require an investigator to sign off on it.

Again, early planning is prudent to anticipate and overcome obstacles. And, when devising solutions, utilize decentralized decision-making by gathering input from employees at all levels — not just leaders with decision-making authority — and strive to understand and respect their expertise in the applicable area. Individuals in the C-suite or others who are not close enough to ground level may be pushing a protocol whose implications (for patients, sites, and other key stakeholders) they do not fully appreciate.

For example, determine when 100 percent monitoring is absolutely necessary, versus when just examining critical variables will fulfill trial requirements and be in the best interest of patients. Did the organization have the foresight to utilize an EDC system where it can assign those variables? Often, monitors are left

in the dark when discussion arises about backing off 100 percent monitoring because they cannot readily discern which variables are most important.

4. INVEST IN OPERATIONAL IMPROVEMENTS VS. DEFENSIVE REACTIONS

A common misconception holds that operational improvements always trickle from the top down. In reality, such improvements can and often do begin at the project level, particularly within cell and gene therapy. One example is EDC integration with cold chain logistics: if errors are present, users can learn ways to improve the system's performance on the fly and, in turn, that knowledge can be carried across the platform or the company's portfolio of studies.

Additionally, focus on your teams' morale. Hold town halls, for example, to address what's coming up for them and to keep them engaged. Ask them to be proactive and open to bringing their ideas, questions, concerns, and mistakes to management — carefully ensuring an environment of psychological safety without fear of punishment or humiliation. Encouraging people to propose ideas, raise concerns, and brainstorm together generates countless opportunities to improve specific trials and overall operations, because the people closest to the trial know where its issues lie and likely have the expertise to find solutions.

Even a department director, while still very close to work performed on the project, oversees several direct reports. Unless that director knows each individual and their CV intimately (nearly impossible in a large organization), that person cannot know the extent of each individual's capabilities. And, when managers and executives are not aware of their personnel's abilities, they may unnecessarily hire someone with overlapping expertise. Ensuring close communication and raising awareness of company resourcing needs is of critical importance during economic downturns.

Thus, it is imperative to maintain meaningful professional growth among personnel. Carefully consider who you attract and retain, as well as how much you can unlock the talent in each person by providing them with fulfilling and interesting activities and opportunities. Not only is this critical during a downturn, when that in-house expertise is so valuable, but it impacts operations positively overall. By re-energizing teams, you are also emphasizing the long-term resiliency of the life sciences industry to potential candidates.

5. FUND EFFICIENCY INITIATIVES AND BUILD THE SUPPLY CHAIN NOW

During a time when massive layoffs are occurring at other biopharma companies, an organization with the money and foresight to hire those individuals can pull off a coup as opportunity costs may be lower. Companies often blindly cut the people making the most money, with the most experience and expertise — creating an opportunity for competitors to hire higher-skilled employees. Further, skillful application of technology by these individuals during a downturn can help a company automate redundant tasks, increasing its agility and promoting additional cost savings.

Moreover, some efficiency initiatives are inexpensive as well as prudent: updating SOPs, turning resources from a slow-enrolling trial to a higher-enrolling trial, etc. The same applies to using this time to assess and build the supply chain by identifying and locating any weaknesses. This includes checking inventory levels and exploring backup vendors for everything the project demands, from filters and reagents to vector suppliers, shippers, and manufacturing slots. This exercise also includes examining vendor capabilities; between new market entrants and organizations that get acquired, merge, or fold, a lot of movement is taking place in the industry.

FINAL THOUGHTS

Economic downturns, while threatening and unwelcome, offer opportunities to improve operations through technology, training, and hiring. In some situations, organizations can benefit by claiming a manufacturing slot a failing project has vacated, advancing its own timeline.

It can be easy, instead, to turtle up and act defensively. Life sciences company management can get caught up looking at the problems and challenges of tomorrow (e.g., an ongoing submission) without fully considering any given action's effect on the organization's entire portfolio of assets. This simply cannot happen within autologous therapies because each trial may have patients at the other end who may be wait-listed or staring down their last hope.

To learn more about the execution of CAR-T cell therapy clinical trials and thriving (versus surviving) through an economic downturn, contact the author and visit inseptiongroup.com.

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REFERENCES

1. https://sp.grantplan.com/Next/login

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Karen Ivester, RN, MA, is the Executive Director, Operations, Cell & Gene Therapy Programs at inSeption Group. She has greater than 25 years' experience in the life sciences industry. Karen has 23 years' oncology experience (across multiple hematology and solid tumor indications). Prior to inSeption Group, she worked in biopharma, CROs, community-based research, and academic cancer center settings. She has worked across early product development and Phase II-III global clinical trials. Karen has extensive experience leading high functioning project and clinical operations teams in portfolio delivery of highly complex clinical trials (including Cell and gene therapy, umbrella, basket and immuno-oncology research).

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