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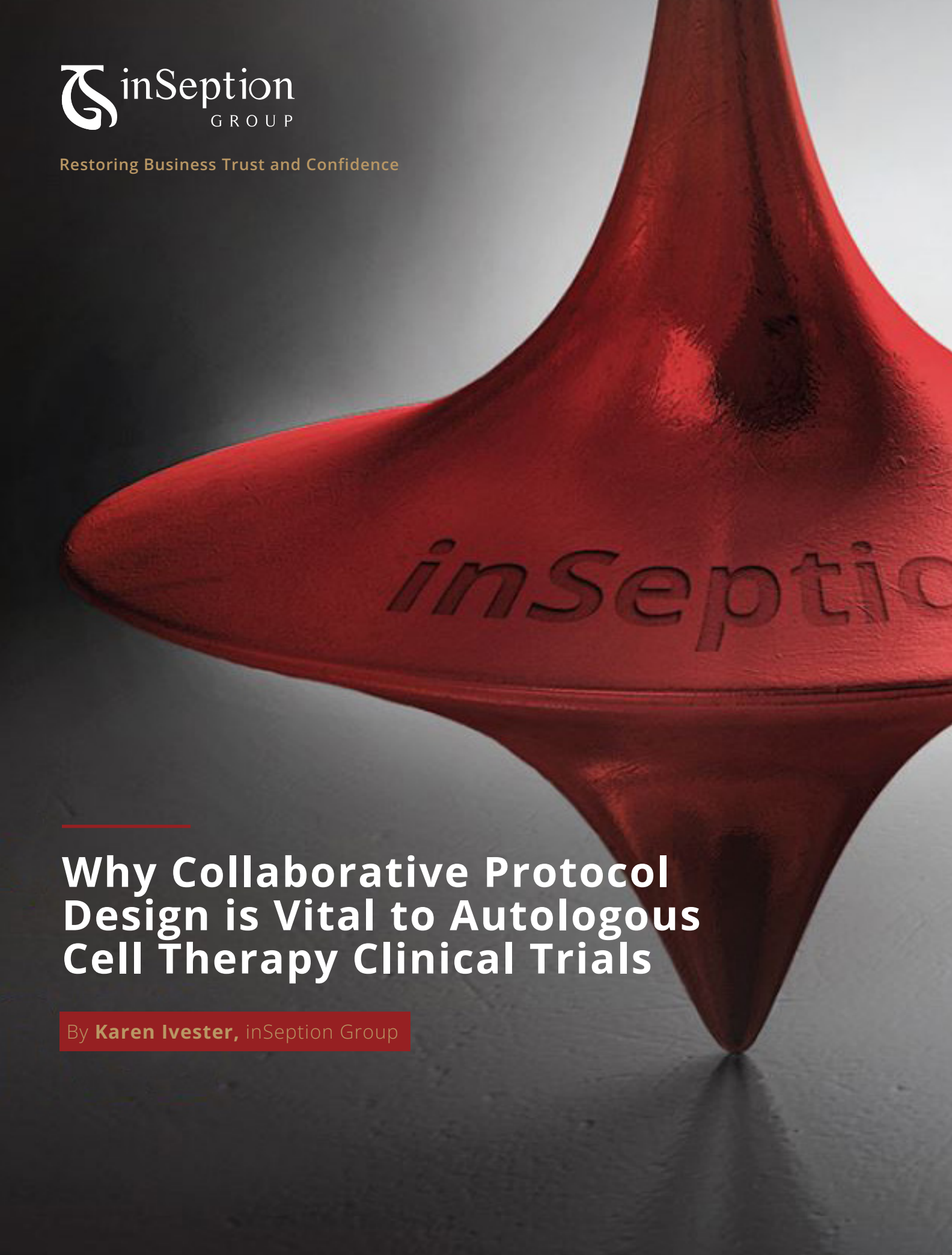

Why Collaborative Protocol Design is Vital to Autologous Cell Therapy Clinical Trials

By **Karen Ivester,** inSeption Group

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Autologous cell therapy preclinical and clinical protocol designs differ greatly from other types of pharmaceutical products. Sponsors with little knowledge or experience of the Investigational New Drug (IND) process may initially not realize the complexity of designing these protocols. Driven by competition for both market share and patient populations, an organization's desire for speed can override its rigor in ensuring protocol designs are feasible.

Consider that the manufacture of these therapeutic products may influence the protocol design, as sponsors typically cannot gather the type of pharmacokinetic (PK) data that normally informs pre-clinical steps. Autologous cell therapy cannot be performed in healthy volunteers and it is difficult to find tissue in animal models representative of the disease states seen in autologous cell therapy (e.g., hematology/oncology indications where patients have had many lines of treatment or chemotherapy).

Autologous cell therapy clinical trial protocol designs benefit greatly from the inclusion of multi-functional, multi-departmental stakeholders' input and feedback. Sponsors who can tap key opinion leaders to selectively vet and assess protocol elements will help ensure fewer protocol amendments, an IND submission that supports the proposed trial, and even (in some cases) fewer clinical holds — leading to shorter overall development and to-market timelines for successful products.

When there is a hand-off to clinical operations stakeholders without their input into the protocol design, problems may arise in many areas as they begin setting up and executing autologous cell therapy clinical trials.

COLLABORATIVE PROTOCOL DESIGN FILLS KNOWLEDGE GAPS

Collaborative protocol design involves soliciting input from, first and foremost, the patients; then the sites specializing in cell therapy research and principal investigators (PIs). Depending on the therapeutic indication, the list may also include (but is not limited to) research personnel, vendors, suppliers, cold chain and logistics providers, pharmacy personnel, imaging, safety, cell therapy units, CMC, monitoring and data management personnel, as well as laboratory, operating room, hospital, and regulatory staff.

Without that context, an expectation can form that autologous cell therapy trials are similar, operationally, to trials with small molecules. But in cell therapy, the assays required and the timeline for completing those assays are much more difficult to determine, even with the help of an in-house translational scientist. Additionally, sometimes a misconception exists that protocols can be written within the organization. However, frankly, sponsors sometimes don't know what they do not know regarding the complexity of designing these protocols.

For example, patient enrollment may need to be staggered to limit the number of patients exposed until some level of safety is established. Long-term monitoring of many cell therapy trials requires the informed consent form (ICF) to be written to allow patients to consent (prior to their participation in the trial) to long-term follow-up. Consider an independent data monitoring committee (DMC) instead of a typical safety review committee — consisting of the clinical trial medical monitor and PIs — if the trial anticipates substantial risks to patients. Reaching out to key opinion leaders (KOLs), PIs, or translational scientists who may have worked on early-phase or preclinical aspects of cell therapy trials is critical.

Overall timelines and clinical confusion are reduced substantially by seeking the aforementioned input up front. While regulator questions about an IND are not uncommon in cell therapy, the goal is to avoid excessive or unnecessary delays. Seeking advice in pre-IND meetings with the FDA to better understand what it expects from regulatory submissions relevant to the product, patient population, and indication may increase the likelihood an IND submission will support the proposed trial.

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EARLY COLLABORATION'S IMPACT: COMMON CELL THERAPY TRIAL CHALLENGES

Often, site research centers and partners are not aware of the high burdens they will face until a patient is enrolled. A protocol may go through Scientific Review Committee (SRC), Institutional Review Board (IRB), and Institutional Biosafety Committee (IBC) review; however, the challenges are not always known until the first patients are enrolled and the products are administered to them.

Sites are using investigational product derived from the patients' cells, but they're also sometimes using special devices, novel procedures, customized preparation techniques, or specialized handling of products. Such technical issues can necessitate revisions to institutional policies, all of which require up-front discussion: does this interfere with the site's protocols for leukapheresis or standard of care?

For example, maybe an MRI of a solid tumor should be collected in advance of when that step is taken per standard of care. That change re-

quires all parties to understand and acknowledge why that step is being taken (i.e., when tissue is excised from the solid tumor, it is useful to have a baseline image for comparison). Surgery and treatment may lead to changes later, so having a baseline soon after surgery may be necessary.

Additionally, sites may have seen the protocol before the schedule of events and assessments have been thoroughly vetted. A protocol rolled out later will include input from many more people, or several exploratory aspects may have been added based on a stated desire by regulators to know those project elements earlier. All of this comes full circle to considering and minimizing the burden a Phase 1 autologous cell therapy clinical trial imposes on the site and patients.

For example, if numerous assays — requiring numerous blood draws from each patient — must be completed up front, that can create a problem. The first patient arrives on-site and, while walking that patient through the timing of the schedule of assessments, the site realizes, "this is way too much." Or the patient may need EKGs, MRIs, and other testing — some of it before patient eligibility is determined. Good communication can help prevent issues at this stage, but collaborative input in advance is much more effective in presenting protocol ideas to a site and determining whether they fit with the institution's capabilities and established practices.

This is accomplished by involving PIs and their teams early; the patient journey should be mapped out and understood as much as possible before a site initiation visit (SIV) even takes place. So, training for clinical research personnel must be considered up front — not just procedures, but also any devices that will be used (e.g., catheters for solid tumor treatment). Does the product have designated storage requirements? Does the patient have to be physically present at specific times prior to thawing and administration of that product?

If you're going to suggest certain treatments in your protocol, does that contradict the wishes of investigators (i.e., do they want to use treatment protocols established by their institution)? If leukapheresis or apheresis is different from protocols the sites have experienced, they may request to simply use their institutional protocol. You cannot assume sites will use what a sponsor dictates for leukapheresis or apheresis if a good reason exists to do it differently. Or, if the patients are in an advanced disease state, will they be able to tolerate apheresis, or will it result in enough viable cells being returned to the patient? A sponsor that hasn't vetted the patient population with KOLs or people conducting these trials regularly may even fail to identify the correct patient population.

COLLECT DATA EARLY AND OFTEN

Autologous cell therapy clinical trial protocol design is not a one-off task; it is a continuous process. Beginning far in advance, identify and gather information from key opinion leaders, PIs, site teams, and potential patients. As more stakeholders are engaged, new drafts of the protocol are rolled out. Often, if they believe in the product and the potential of your treatment, stakeholders are happy to share their time, provided they are given advance notice.

The process can be frustrating, at times, feeling as if more questions are being created than answers. This is a byproduct of integrating so many different people and functions, but the ends justify the means. For example, the lab performing the assays may ask whether the volume of fluids being drawn from patients is appropriate and minimally burdensome. This is important for the Informed Consent Forms (ICF's) that will be reviewed in advance by the IRBs. If those questions about volumes were not considered prior to the IRB submission, the board may reject the

application, stating the proposed draw volumes are unsafe or too burdensome. Now, the study is in a protocol amendment before completing a single IRB approval.

Considering these trials' demand for specialty logistics, laboratories, and manufacturing, a collaborative effort by individuals operating in this therapy area is warranted to establish what could be standardized. Obviously, not everything can be standardized, but many elements could be (e.g., make leukapheresis or apheresis the same across sites with similar cell processing and cell collection instruments, so it is safer and faster to introduce new sites into cell and gene therapy).

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