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# ACT NOW – Cancer Trials At The Leading Edge

by

Adoptive Cellular Transfer (ACT): Novel Cancer Trials Demand That Participating Sites Act Differently

As more pharma and biotech companies bring their ACT platforms to the clinic, there is a need for the assistance of clinical research organisations (CROs) to support the conduct of clinical trials. Valued for their relationships with trial centres, CROs have been thrust into the forefront of operationalising ACT studies. So what can sites expect and commit to when participating in ACT trials?

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In the past five years the evolution of adoptive cellular transfer (ACT) for the treatment of lymphoma, leukaemia and myeloma patients has grown exponentially as the efficacy and specificity of these treatments offer curative promise, creating new hope for patients. With European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approvals of Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) autologous CAR T therapies, ACT is moving towards the frontline setting, expanding the clinician's armamentarium of cellular cancer treatments. High cost remains a concern but the explosion of commercial companies exploring allogeneic, polycistronic, switchable constructs and novel local manufacturing approaches is likely to reduce future costs, whether through competitive pressure and/or technological advances. Access to ACT therapies will broaden globally, engaging smaller community settings. The successful development of cell

therapies is dependent on the growing number of academic medical or hospital centres which are able and willing to participate in clinical trials. Until now, the expertise has resided in larger specialised haematology centres in the US, Europe and China. However, with more technologies come more trials, and solid tumour interests are increasingly penetrating the field.

As more pharma and biotech companies bring their ACT platforms to the clinic, there is a need for the assistance of clinical research organisations (CROs) to support the conduct of clinical trials. Valued for their relationships with trial centres, CROs have been thrust into the forefront of operationalising ACT studies. So what can sites expect and commit to when participating in ACT trials? Based on our CRO experience, there are four areas of focus: Regulatory, Logistical, Patient Safety and Data Management.

Regulatory knowledge is paramount. ACT studies are classified in the genetically modified organism (GMO) category, which has bespoke requirements. In many countries, applications must be submitted to specialised local and/or national agencies. Additional time for the regulatory set-up period should be anticipated and it is essential to have a team on hand that is familiar with navigating GMO regulations, as these regulations are constantly evolving. For example, the US National Institutes of Health (NIH) is reevaluating gene therapy oversight to eliminate duplicate reporting. In large academic centres, regulatory expert groups are well established. However, as competition for ACT studies grows, and established centres of excellence experience resource constraints within their own regulatory groups, there will be an evolving drive and opportunity for community hospitals to engage in ACT clinical development. These institutions will need to equip themselves with regulatory expertise. Another perspective is that even in the centres where ACT is established, it has been focused in the haematology-oncology divisions. With the advent of new therapeutic targets against sarcomas and other solid tumours, oncology departments will need to familiarise themselves with information that may already be resident elsewhere within their own hospitals.

The intensive and demanding logistics of conducting ACT trials necessitates a high degree of organisation within institutions and sophisticated inter-departmental cooperation. Apheresis is a core component of autologous ACT requiring the engagement of transplant units at the centre of the process, including lymphodepletion and infusion of cells. Apheresis unit/materials and transplant unit audits are mandatory practices in an ACT clinical trial. Each commercial sponsor is likely to have its own audit requirements. So transplant units working on multiple studies for different pharmaceutical companies should be prepared to entertain many audits. Standardisation or universal accreditation of ACT studies remains an aspiration. Sites that have revised their infrastructure to meet demands of ACT have been the most successful in conducting studies. For emerging allogeneic approaches, apheresis is not part of the treatment paradigm but transplant units remain pivotal with their role in lymphodepletion and T-cell infusion. In autologous approaches, the chain of identity which ensures a patient receives their own cells post-modification requires careful coordination through form filling and registration.

This is no small feat of resource management. Patient scheduling is also a sensitive matter as with autologous therapies, there are manufacturing scale capacity and limitations at facilities where cells are modified via viral vectors, plasmids, transposons, etc. Managing site and patient expectations is a key factor as well as scheduling the patient treatment pathway across the various clinical care teams. Larger academic institutions have established specialised ACT units that specialise in cellular therapy studies.

The positive results with ACT come with concomitant safety risks that require skilled patient management. Sites require robust standard operating procedures (SOPs) specific to ACT-related adverse events. During the acute infusion phase, the inpatient setting provides good access to health care experts in the supervision of the greatest potential risks such as cytokine release syndrome, neurotoxicity or graft versus host disease (GVHD; allogeneic approaches). However, once the patient is discharged, a dedicated line of communication for them is recommended, as well as immediate proximity to skilled urgent care.

ACT studies generate large amounts of data over a short period of the treatment cycle including laboratory, other safety data, prior treatments and concomitant medications – these patients have multiple lines of prior therapy. As such, robust, validated electronic medical record systems are required.  Data quality and currency become a challenge with the large volumes of data, estimated to be up to 10 times that observed in other oncology studies. The site's data coordinators must have sufficient time to enter data expeditiously as sponsor companies and regulators are constantly looking for updated safety information. Considering the numerous and still evolving risks of ACT therapies, the importance of data currency cannot be understated.

ACT will continue to make significant inroads into both haematological and solid malignancies with increasingly sophisticated and diverse cell constructs. Whilst the good news is that this is providing increased access for patients to treatments across a broader swath of health care facilities, there is also increased competition for study site resources. Being prepared with regulatory intelligence, scalable logistics, resource commitments, as well as dedicated patient safety and data management teams will present challenges that surpass those of other oncology clinical trials. This is life at the leading edge.

About ICON

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