Immunology Trials

Innovation Brings Hope, Fresh Challenges

The cost of developing drugs continues to escalate. Estimates vary, but the Tufts Center for the Study of Drug Development estimated the out of pocket pre-tax costs to be $1.4 billion per approved new product in 2013 dollars[1]. It is not unreasonable to assume that this has continued to rise over the intervening years, especially with the increasing complexity brought by developments in the areas we discuss in this paper. In view of these rising costs it is more crucial than ever before that Sponsor companies try to mitigate against failure and delay in their drug developments.

In this article, we will explore aspects of immunology clinical trials that deserve particular focus in order to provide the greatest opportunity for success.

Immunological therapies are now offering hope to thousands of patients across diverse therapeutic areas. Although immunology may seem like a very modern development, it is, in fact, partly rooted in the discoveries of phagocytosis and neutralizing antibodies in the late 1800's. Fast-forward to the 1960's when transplantation biology and immunochemistry laid the foundation for much future work, and B lymphocytes (antibody producers) and T lymphocytes (immunity regulators and effector cells) moved to the focus of attention. The invention of monoclonal antibodies, laboratory-made proteins that reproduce the immune system's ability to target specific antigens, has moved immunotherapy into a new era[2]. The first clinical therapeutic monoclonal antibody, Orthoclone OKT3® (muromonab-CD3), was approved by the FDA in 1986. The growth in this area has continued, and in recent years FDA has approved multiple monoclonal antibodies each year across many therapeutic areas.

In addition to the use of small molecules, a variety of factors make the immune system a favorable target for a broad array of cell and gene therapy interventions. For example, lymphocytes have a unique capacity for clonal selection and expansion during immune development, and in response to infectious disease or cancer. This means that genetic interventions targeting a small number of parent cells can result in expansion of large

populations of engineered immune effector cells. Furthermore, the stem cells that supply the entire hematopoietic system are derived from precursors that can be isolated and manipulated in vitro using established methods. This makes it much easier to genetically modify immune compartments compared to other tissue types such as muscle or neurons. The first approved product officially recognized by the FDA as "gene therapy" was a genetically engineered T cell product (KYMRIA™).

The Challenge of Subjective Endpoints

Many diseases that are the target of immunotherapy have subjective clinical trial endpoints and rely on the patient for accurate reporting of symptoms. Arturo Morales, PhD is Vice President, Data and Technology Solutions at WCG and has extensive experience in the real-time review and assessment of clinical data, with the aim of correcting issues that may negatively affect their outcome. He says: "Anytime we ask a subject or rater to report a symptom in a trial, we are attempting to convert a subjective measure into an objective one." Crohn's Disease is a good example, where patients needs to accurately report number of stools as well as report on their pain – a well-known subjective endpoint. In another example, atopic dermatitis, although the size of skin lesions may be measured, reporting of subjective symptoms such as itching is also key. Oncology and rheumatology trials are prime examples which include objective radiological primary endpoints but usually include key secondary endpoints that are subjective, such as pain and quality of life evaluations.

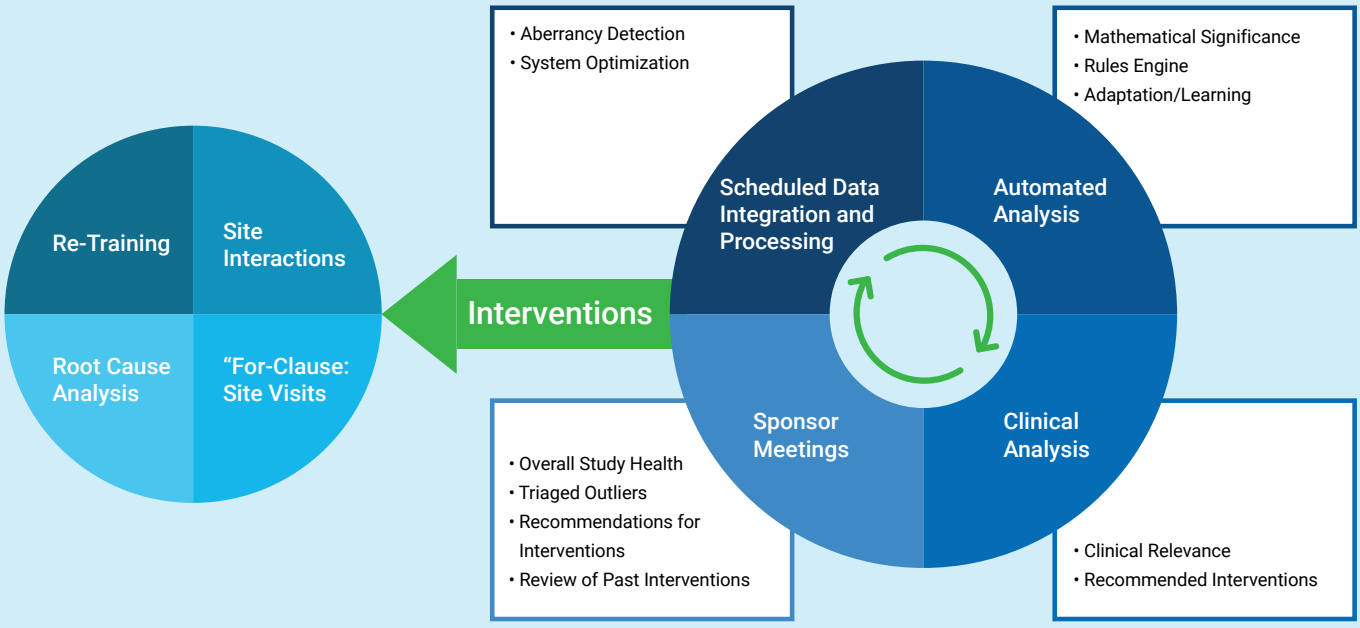
The key to the success of Dr. Morales and his colleagues at WCG Analgesics Solutions, is to identify quality biomarkers that can act as surrogates of underlying data quality issues that affect the ability to separate the investigational drug from placebo or other treatments. Dr Morales goes on to say that: "We depend on the accuracy and consistency of that 'conversion' to evaluate the success of the trial. To give the drug the best chance to show if it works, we must monitor for issues with data quality, integrity and accuracy and we must attempt to correct issues in real time."

These digital biomarkers of quality are then used to monitor blinded trials and systematically deploy interventions to address issues as they are identified. *What does this look like in practice?*

- An ulcerative colitis trial used both the Inflammatory Bowel Disease Questionnaire (IBDQ) and the 36-Item Short Form Survey (SF-36) to evaluate participants. Concordance is expected between IBDQ item 8 and SF-36 item 32; both assess the impact of health issues on social activities.

- At the subject level, 16 out of 228 participants (10 on drug and six on placebo) showed a high level of discordance between these two items and did not separate drug from placebo validating this as an accurate predictor of assay sensitivity.
- At the site level, we showed that sites with low discordance on these same items separated drug from placebo, while those with high discordance did *not* separate drug from placebo. This is based on normalized scales aligned in the same direction, where we find that >30% normalized discordance between similar questions is usually significant.
- We applied this same principle to other measures in the trial, for example the concordance between item 1 on the SF-36 (general health) and daily diary well-being, with the same outcome.
- If sites are monitored throughout the trial for signs of discordance in ratings such as those described above, then issues will be detected early and remediation can take place that improve trial outcomes by improving the quality of the data without introducing bias (see Figure 1). Remediation includes re-training of site staff and participants, depending on the outcome measures, as well as monitoring for data quality. Discussion with the sponsor about the trial screening criteria, where the goal is to balance appropriate patient selection with the right disease state and the ability of those patients to report their symptoms accurately, is also an important part of this process.

Figure 1: System for identifying predictors of effect size, monitoring them and providing actionable recommendations



Strengthen Trials with Central Imaging

Trials should have objective endpoints, where possible; in several immunological indications, such as oncology and rheumatology, imaging provides that objective assessment. ISO-certified central imaging services, such as WCG Intrinsic Imagining, provide access to a network of over 500 fellowship-trained, board-certified radiologists in the required sub-specialties. Getting the best advice on the appropriate methodologies for assessing changes in disease state is critical. For example, plain film radiography used to be the gold standard for assessing changes in rheumatoid arthritis, however, MRI and ultrasound now have a much greater role to play.

John Clement, MD a radiologist at WCG Intrinsic Imaging, says, "Both ultrasound and MRI have made great strides in imaging the anatomic changes in rheumatoid arthritis. Both ultrasound and MRI allow for earlier detection of disease, before irreversible damage to joints has occurred."

"As clinical management continues to shift toward earlier detection of disease and aggressive therapeutic management, these imaging modalities will play a greater role in both disease diagnosis as well as the rapid assessment of response to DMARDs and biologic agents. The OMERACT MR and Ultrasound task forces continue to refine scoring systems for quantifying the changes seen in rheumatoid arthritis. Established imaging scoring systems will allow a more uniform approach to determining the effectiveness of therapies targeted to rheumatoid arthritis, both in the clinical and research arenas."[3]

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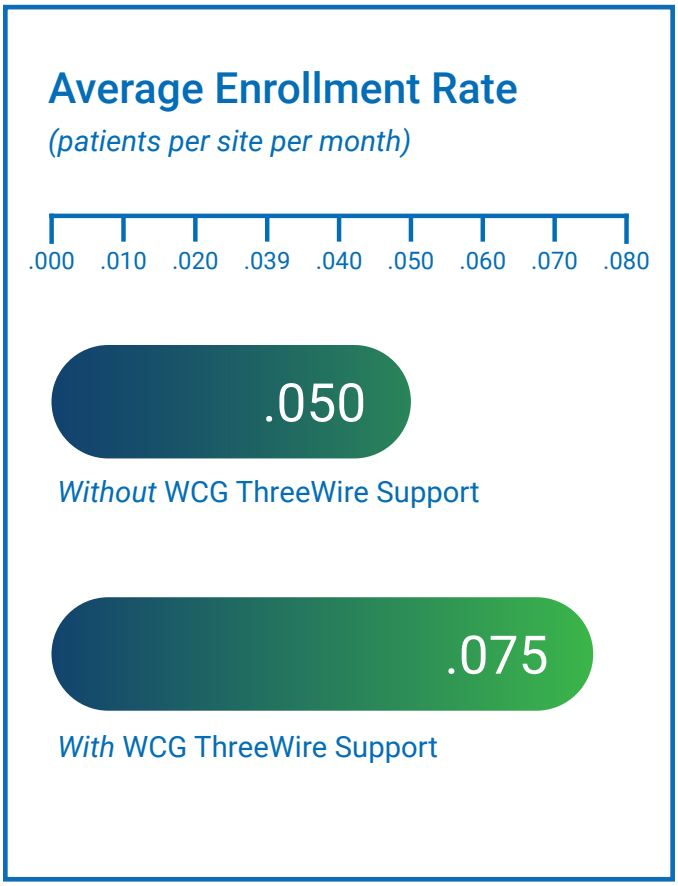
Managing the Funnel of Eligible Trial Participants

Some immunology trials are unique in that trial participants whose disease is stable must wait for flare-up before they are eligible for trial entry. This presents some special challenges

around maintaining the interest of potential participants in the trial, tracking disease status and ensuring that they consider the trial as soon as they are eligible and before embarking on therapy that will likely exclude them from trial participation. The situation is compounded when there are multiple trials seeking participants in a highly competitive therapeutic area.

In a multi-protocol program in ulcerative colitis and Crohn's disease WCG's on-site clinical research coordinator (CRC) support was able to increase enrollment by an average of 50% (see Figure 2), through a combination of tactics which included

- The creation of a virtual waiting room where patients who were eligible for the trial could be tracked and supported pending the flare that would likely make them eligible for the study. CRCs contacted these people regularly to maintain their interest in the trial and keep it top of mind.
- Retrospective and prospective chart reviews fueled the pipeline of potential participants.
- Establishing a network of referral physicians, which was key in this competitive trial landscape. The CRCs performed multiple activities such as outreach, education and chart review with referral physicians.
- Creation of a central study website. Because of the disease awareness in these indications this was an effective tactic. CRCs performed media referral processing, following up with potential participants very quickly to ensure that they did not get lost between responding on the website and being seen at an investigational site.



Cell and Gene Therapies Bring New Challenges

At the end of 2020 there were at least 1,220 industry sponsored trials on-going in cell and gene therapy. This is a new development paradigm for many involved in those trials

and so the use of a trusted partner with experience in this this area is key to success. Our in-house expert and Senior Scientific Advisor for gene therapy, Dr Daniel Kavanagh PhD, RAC, can draw on his vast experience in this area to assist sponsors in designing and operationalizing their cell and gene therapy clinical trials.

The following are four areas of this emerging treatment area that require special focus:

1) Protocol Design

- With any relatively new scientific area, protocol design and statistical decisions are especially challenging because of the lack of prior data and precedents.
- WCG Statistics Collaborative is led by Janet Wittes, PhD, who was a member of the FDA Cell and Gene Therapy Advisory Committee from 2015 to 2019. WCG Statistics Collaborative have experience supporting over 35 protocols in cell and gene therapy.

2) The Need for IBC Review in Conjunction with IRB Review

- WCG has been providing IBC services to hundreds of clinical trial sites since the year 2000 and can assist with expert advice on the applicability of the NIH guidelines, document preparation and review.
- WCG IBC has extensive experience which includes vaccines, oncology immunology, and cellular immuno-oncology, as well as clinical trials modulating the immune response in the eye.
- Dr. Kavanagh has deep expertise in the use of IBC review having assisted with the administration of over 400 IBCs around the world.

3) Finding Best-Fit Sites

- Our proprietary data base provides a view to over 95% of industry sponsored studies and a proprietary data base of over 220,000 investigators and more than 3,100 institutions.
- Cell and gene therapy trials require specific investigator expertise and experience and using out Site Intelligence analytics platform, we are able to identify investigators who have the patients, cell and gene expertise, quality, and capacity to take on your trial.

4) Site Training

- Many sites are interested in participating in cell and gene therapy trials but not all are accredited or trained.
- FACT accreditation (http://factwebsite.org) is necessary for sites participating in cellular therapy. WCG has deep-rooted relationships with 209 of the 221 FACT accredited institutions. Our experts can assist you in navigating the accreditation pathway and provide specific on-demand training for your sites.

Immunology and the Future

Because immunological mechanisms play important roles in many aspects of the basic biology of disease, immunological therapies are being developed to address a wide variety of indications and disease states. These approaches may engage lymphocytes such as T cells, B cells and Natural Killer cells, as well as myeloid cells such macrophages and dendritic cells. Genetic modification tools being applied in this area include traditional viral vectors for gene delivery, as well as gene editing, base editing, and nanoparticle-mediated mRNA transfer.

As the breadth of potential intervention expands, immunological cell and gene therapy approaches are offering new hope in areas as diverse as oncology, infectious disease, autoimmunity, and diseases of the central nervous system.

The clinical trials in this exciting and ground-breaking area are complex and present particular challenges to sponsors and investigators. Expert advice and support will be needed to give each therapy the optimal chance to show its efficacy.

References

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3. Clement, J. Advances in Imagining of Rheumatoid Arthritis. Intrinsic Imaging 2016, vol 6, issue 5.

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