Inflammation Studies: Seven Solutions for IMID Challenges

Inflammation-related diseases represent an escalating global threat in terms of morbidity, mortality and quality of life. Examples include asthma, COPD, psoriasis, rheumatoid arthritis, lupus and inflammatory bowel disease (ulcerative colitis and Crohn's disease).

In the past, the medical community addressed these diseases in piecemeal fashion at the physical site of the disease (lungs, guts, joints). We saw a strong focus on symptoms and little integration of research or clinical trial design.

Today, a paradigm shift has occurred. We now know that underlying immune system response mechanisms may be common to the group of diseases called **immune-mediated inflammatory disorders (IMIDs).** More than a name and classification, IMIDs represent a significant revelation in managing inflammatory diseases: from organ-based symptom relief to mechanism-based treatment.

For pharmaceutical companies, there is an opportunity to develop new treatments, enter new markets and expand market share; however, IMID trials involve operational challenges that can derail your efforts.

Covance scientists have identified current best practices for managing common challenges in inflammation clinical studies. We base these proactive approaches on our experience conducting IMID clinical trials and success re-applying therapies among various IMIDs. An interconnected approach for IMIDs makes practical sense and allows us to leverage operational best practice.

Following are seven common challenges, and corresponding Covance solutions, for your IMID trials:

1. Reduce Placebo Response Rates

We have observed placebo response rates of 14-20% in trials for psoriasis, almost 30% in placebo-controlled studies for rheumatoid arthritis and even higher rates in ulcerative colitis studies. High placebo rates can result in failure to observe treatment effects and place otherwise-effective drugs at risk.

Covance Solution:

Placebo response rates are often related to eligibility creep: a tendency of sites to enroll subjects with milder disease to meet recruitment targets and timelines. They may assess these subjects as suffering from a more severe disease than baseline, to qualify and meet inclusion criteria. This dynamic makes it harder to observe a treatment difference versus placebo and can place the trial at risk of failure.

Eligibility creep is coupled with the unpredictable chronic remitting-and-relapsing pattern of some IMIDs. We recommend confirming severity and ensuring stable disease at baseline on at least two separate assessments. Also, ensure that the same evaluator throughout the study conducts study assessments; this helps control and mitigate the risk of a large placebo response. Provide specific training for site staff performing assessments, such as ACR20 assessments in rheumatoid arthritis studies. This training reduces inter- and intra-variability of patient assessments and provides more robust data.

2. Integrate Patient Reported Outcomes (PROs)

PROs play a major role in many inflammatory diseases due to the subjective character of the drug outcomes, such as lessening of joint pain. However, misapplication of poor or out-of-context PROs can lead to great heterogeneity, resulting in incomplete and/or spurious data.

Covance Solution:

Ensure effective selection and management of your PROs. Integration of Covance clinical development, health economics and outcomes research teams provides the highest level of PROs for trials. They provide site personnel with clear instructions for completing questionnaires and other PRO instruments. We also instruct site personnel to review each questionnaire soon after completion to address missing data or corrections.

Covance may recommend using an ePRO (electronic) device to expedite data integration into databases. These devices can relieve the burden of reviews and ensure complete item responses. Our PRO experts oversee preferred ePRO vendors to ensure quick uptake of the study protocol. We have extensive experience setting up and supporting ePRO and systems such as eDiary. You receive a clear flow of data from patient to database, without intervention from your staff.

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3. Centralize Assessment of Objective Endpoints

Objective endpoints provide precise data not subject to wide variability of subjective endpoints, such as a patient's evaluation of pain. Typical objective endpoints for inflammatory diseases include radiographic imaging to identify structural damage from rheumatoid arthritis, photographic images to spot lesion changes from psoriasis plus spirometry for Pulmonary Function Test (PFT) changes from asthma.

Covance Solution:

Centrally review and analyze images obtained as objective endpoints to reduce variability. This review is similar to the centralized review of tumor images employed in oncology studies; these same endpoint-review vendors often assist with IMID studies.

4. Address Patient Compliance

Many new therapies targeting inflammatory diseases are biologicals administered by sub-cutaneous injection. Self-administration of an injectable drug can involve patient apprehension and poor injection technique, leading to non-compliance and reduced drug efficacy.

Covance Solution:

Provide patients and caretakers with drug administration training at the start of the study. Continually check on technique and offer further training throughout the study. For example, we provide patients with placebo doses during the screening period and observe them self-administering at the screening or during randomization visits.

5. Protect Investigator Interest

Investigator interest may be lacking and difficult to maintain during highly competitive IMID clinical trials – and for long trials.

Covance Solution:

We carefully analyze the competitive situation each drug faces and plan accordingly. For example, we see a surge in industry-sponsored trials for inflammation, with intense activity surrounding biosimilars. We take proactive measures to ensure timely enrollment and use investigators able to deliver approvable data.

The novelty of an investigational drug may be either a positive or a risk. Either way, we customize recommendations in indications of intense recruitment activity – using protocol simplicity, reasonable sample size requirements and competitive investigator remuneration. These key drivers establish and protect engagement among target investigators.

The extensive Covance and LabCorp data set allows us to look at the impact of lab-based, inclusion-and-exclusion criteria on available patient populations. We also employ thought leaders and participate in professional meetings to create interest among investigators.

6. Optimize Patient Retention

Success doesn't stop with recruiting patients – we also want to retain them. Retention is particularly important for long studies. For example, rheumatoid arthritis studies with endpoints focused upon radiographic response and physical function may require patients to be followed for two years.

Covance Solution:

Covance pressure tests each protocol and study to encourage continued participation. We also consider the investigator and country mix when providing custom recommendations on a retention strategy. Our team coordinates approaches to trial success, including:

- Pre-existing patient relationships – Because these target indications are chronic conditions, investigators know most patients entered into clinical studies. They can make an educated assessment of their reliability and potential compliance levels. Further, investigators have direct involvement with patients and family members during each visit.
- Continued patient education – We provide patients with general study updates and health-related information.
- Study reminders – Teams send postcards or text messages to patients prior to their scheduled appointment. Visual reminders can include magnets, calendars or notepads.
- Phone calls – We telephone patients between scheduled appointments to check on well-being, and protocol compliance, such as diary completion and to remind patients of the next scheduled visit.

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7. Optimize Site Selection and Review Performance

Non- or low-performing sites can affect study timelines, endanger data quality and undermine clinical return on investment (ROI). They draw on resources but deliver no trial input.

Covance Solution:

To prevent delays and waste, Covance creates an escalation plan for non- or low-performing sites within the appropriate timeframe and facilitates closeout, if necessary. We also bring additional sites through regulatory approval but hold activation until we know accurate enrollment forecasts or identify sites that may fail – usually within three months of site activation. We can then immediately deploy standby sites to fill the gap. This plan keeps your trial on track and maximizes ROI.

Our core tool for avoiding non- or low-performing sites is Xcellerate Forecasting & Site Selection, our proprietary clinical knowledgebase and part of our Xcellerate® Informatics platform. With Xcellerate, Covance provides custom recommendations for site, investigator and geographic selections. We identify investigators and sites more likely to deliver patient enrollment. This process reduces resource consumption, decreases trial timelines and increases your return on clinical investments.

Reduce risk in your IMID clinical trials by securing a clinical trial partner aligned with the new best practices for IMID drug development. You will achieve dedicated service, dependable project management and fast, effective issue resolution.

Covance delivers IMID clinical trial confidence by:

- Taking a personalized, proactive approach to your study. We identify and address potential issues in the clinical trial process to enable better and faster decision making.
- Offering an experienced, dedicated team that works to understand your specific objectives and challenges. We create effective, flexible solutions to meet your needs as trials progress.
- Maximizing the value of your product. You need reliable data and an accelerated clinical trial timeline – and Covance delivers. Our proven operational platform of proactive, predictive and preventive measures improves cycle times, helping ensure that your trial begins and ends on time.

Revolutionary new approaches for managing traditional inflammatory diseases are enabling drug developers and manufacturers to enter new markets and expand market share. Most importantly, the new paradigm is helping more patients manage their diseases and improve quality of life. We can help solve your IMID study challenges to deliver results.

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