# 7 Ways

## to Reduce Inflammation Study Challenges

Best Practice and Solutions in the New Inflammation Paradigm

COVANCE®

# Introduction

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

Historically, these diseases have been addressed in a piecemeal fashion, dictated by the physical site of the disease (e.g. lungs, guts, joints, etc.), with a focus on symptoms and little or no integration of research and clinical trial design.

However, a paradigm shift has occurred: it is now acknowledged that some underlying immune system response mechanisms may be common to this group of diseases – which are now referred to as **Immune-Mediated Inflammatory Disorders (IMIDs)**. More than a name and classification, IMIDs represent a significant shift in the approach to the management of traditional inflammatory diseases from organ-based symptom relief to mechanism-based treatment.

For pharmaceutical companies, this represents a growing opportunity to develop new treatments designed to modify these disease states, enter new markets and expand market share. However, IMID trials are known to face a number of operational challenges that can derail your efforts. The following offers you seven approaches recommended by Covance to reduce common inflammation clinical study challenges. These proactive approaches are based on our experience carrying out clinical trials in this area, as well as an acknowledgement that the re-applicability of therapies to different IMIDs also enables operational improvements to the conduct of IMID clinical trials. Operationally approaching IMIDs, as an interconnected area, makes practical sense and makes it possible to leverage operational best practice and experience across diseases, as illustrated in the following:

## 1) Reduce placebo response rates

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



**Covance recommends**

In effect, placebo response rates are often related to eligibility creep. Eligibility creep reflects a tendency for subjects with in fact milder disease to be enrolled by sites in order to meet recruitment targets and timelines as the trial recruitment progresses (i.e. the subjects are assessed as suffering from a more severe disease than they in fact are at baseline, in order to qualify and meet inclusion criteria). This dynamic, however, makes it harder to observe a treatment difference versus placebo and is likely to place the trial at significant risk of failure.

This, coupled with the unpredictable chronic remitting and relapsing pattern of some inflammation diseases, means that it is crucial to confirm severity and ensure stable disease at baseline on at least two separate assessments and to ensure that study assessments are conducted by the same evaluator throughout the study at a site in order to control and mitigate the risk of a large placebo response in this program. It is also crucial to provide specific training to site staff who will be performing certain assessments (e.g. for ACR20 assessments in rheumatoid arthritis studies). This training, put into context within the specific study, reduces inter- and intra-variability of patient assessments and provides much more robust data.

## 2) Better integrate the use of patient reported outcomes (PROs)

PROs play a major role in many inflammation diseases due to the subjective character of the drug outcomes (e.g. lessening of joint pain, etc.). However, misapplication of poor or out-of-context PROs can leads to great heterogeneity, resulting in incomplete data, spurious data, or both.

**Covance recommends**
Effective selection and management of PROs is crucial. Integration between the Covance clinical development, health economics and outcomes research teams provides the highest level of PRO experience for clinical trials. These combined teams provide inflammation trial site personnel with clear instructions regarding the expectations for the completion of the questionnaires or other PRO instruments, and most importantly, site personnel will be instructed to review each questionnaire as soon as possible after completion so any missing data or required corrections can be addressed without delay.

When appropriate to the specific trial, protocol, and PRO instrument, Covance may recommend the use of an electronic or ePRO device to expedite data integration into databases. This helps to relieve site burden from reviews and ensure appropriate and complete item responses are obtained for all ePRO administered PROs. Overseen by our own PRO experts, to ensure a quick uptake of the study protocol, our preferred ePRO vendors have extensive experience in setting up and supporting ePRO and related systems (e.g., eDiary). The advantage is a clear flow of data from patient to database without the need or intervention of any staff.

## 3) Centralize assessment of objective endpoints

Objective endpoints provide data that is generally considered more precise and less open to the wide variability of subjective endpoints, such as a patient's evaluation of pain. Typical objective endpoints utilized in inflammatory diseases include radiographic imaging to identify structural damage in rheumatoid arthritis patients; photographic images to spot lesion changes in psoriasis patients; and spirometry for Pulmonary Function Test (PFT) changes in asthma patients.

**Covance recommends**
Images obtained as objective endpoints should be reviewed or analyzed *centrally* to reduce variability in data. The fundamentals of the process are exactly the same as centralized review of tumor images, which are frequently employed in oncology studies and, in fact, the same endpoint review vendors are often used for inflammatory disease studies.

## 4) Embrace the need to address patient compliance

Many of the new therapies targeting inflammatory diseases are biologicals which are administered by injection, (e.g. sub-cutaneously). However, self-administration of an injectable drug poses several issues, (e.g. patient apprehension and poor injection technique). These issues can lead to non-compliance and reduced drug efficacy.

**Covance recommends**
It is critical that patients are provided with drug administration training at the start of the study and to continually check on technique and offer further training as required throughout the study. For example, patients can be provided with placebo doses during the screening period and/or can be observed self-administering in the clinic at the screening/randomization visits.

## 5) Protect investigator interest

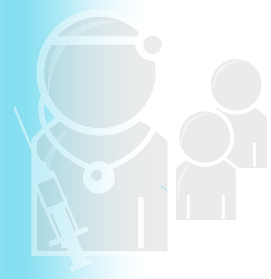
Investigator interest may be lacking and difficult to maintain in a highly competitive clinical trial space such as inflammation – also for trials of longer duration.

**Covance recommends**
Covance carefully analyzes the competitive situation each drug will be facing and plans accordingly. For example, the surge in the number and size of industry-sponsored trials in inflammation is anticipated to continue, particularly with the intense activity surrounding biosimilars. Proactive measures are necessary to ensure timely enrollment, and getting investigators on board who are able to deliver approvable data. The novelty of an investigational drug and its mechanism of action may be either a positive or a risk – either way, Covance provides customized recommendations around using approaches such as protocol simplicity, reasonable sample size requirements and competitive investigator remuneration, in indications of intense recruitment activity, as key drivers to establish and protect engagement among target investigators. Other examples to include drawing on thought leaders and professional meetings to create interest among investigators.

## 6) Proactively optimize patient retention

Success doesn't stop with recruiting the patients – it is crucial to retain them as well. This is a particularly important consideration when the study duration is long, (i.e. rheumatoid arthritis studies with endpoints focused upon radiographic response and/or physical function will require patients to be followed for up to two years).





**Covance recommends**
To proactively encourage continued participation, we pressure test each protocol and study, and also consider the investigator and country mix when providing custom recommendations on an effective retention strategy. Various approaches will be coordinated to ensure trial success, for example:

- Pre-existing patient relationships – these target indications are chronic conditions and, as a consequence, the majority of patients entered into clinical studies are already known to the investigators. Therefore, the investigator is able to make an educated assessment of the patient's reliability and compliance levels before deciding whether to invite the patient to participate. Investigators will have direct involvement with patients and family members during each visit.
- Continued patient education – provide the patient with general study updates and health-related information as it is available.

- Study reminders - postcards or text messages to patients prior to scheduled appointment. Study visual reminders such as magnets, calendars, notepads, etc., may also be provided.
- Site staff to telephone patients in between scheduled appointments to check on well-being, protocol compliance (particularly diary completion) and to remind patients about next scheduled visit.

### 7) Optimize site selection and proactively review performance



Non- or low performing sites can have a significant negative impact on study timelines and endanger both timeliness and data quality, as well as undermine clinical return on investment (ROI) by drawing on resources, but delivering no trial input.

**Covance recommends**
To proactively prevent delays and waste, Covance creates an escalation plan for non/low-performing sites within the appropriate timeframe, and facilitates close-out, if necessary. Covance also identifies and brings additional sites through regulatory approval, but holds activation until accurate recruitment is known, or sites that may fail are identified. This usually occurs within the first three months of site activation, and standby sites can be immediately deployed to fill the gap, hence keeping the trial on track and maintaining ROI. Our core approach tool to avoid non- or low-performing sites is Xcellerate®, our proprietary clinical knowledgebase. With Xcellerate®, Covance provides custom recommendations on site, investigator and geographic selection that proactively identify the investigators and sites most likely to deliver patient enrollment, leading to a reduction of resource consumption, decrease in trial timelines and increase in return on clinical investments.

## Conclusion

The revolutionary shift in the approach to the management of traditional inflammatory diseases is enabling drug developers and manufacturers to enter new markets, expand market share, and – most importantly – help more patients to better manage their disease and improve their quality of life.

However, inflammation or IMID clinical trials are still at risk of potential pitfalls. You need an IMID clinical trial partner who is aligned with the new IMID drug development paradigm and who can provide 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 to identify and address potential issues in the clinical trial process to enable you to make better decisions faster.
- Offering a dedicated team to work closely with you to understand your specific objectives and challenges and to create the most effective and flexible solutions to meet your needs, as your clinical trial progresses.
- 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 preventative measures can help improve cycle times and increase the likelihood that your trial begins and end on time.

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