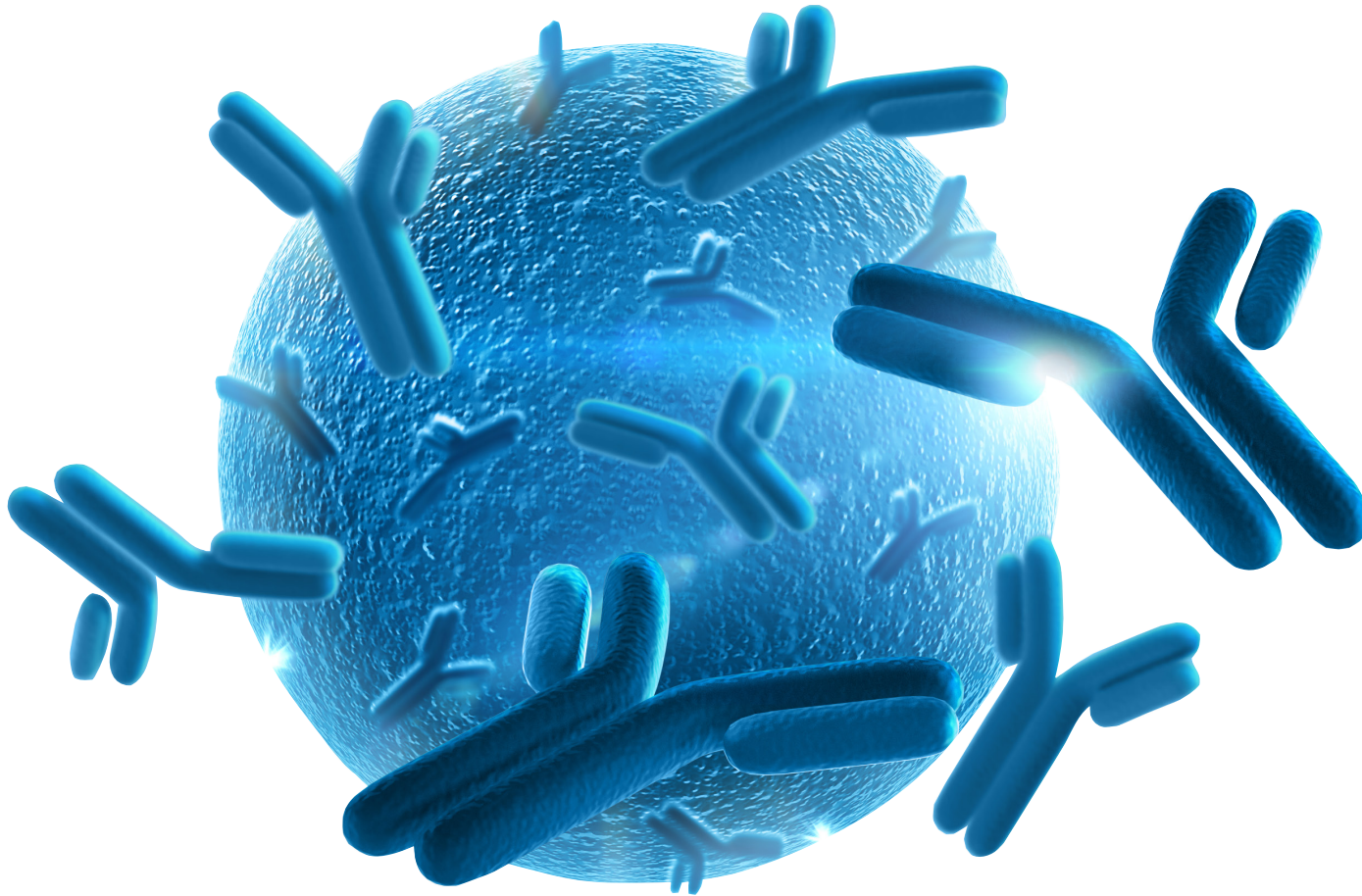


ADDRESSING CHALLENGES IN IMMUNE-MEDIATED INFLAMMATORY DISORDER CLINICAL TRIALS



SUMMARY

Immune-Mediated Inflammatory Disorders (IMIDs) clinical trials present challenges including longer than usual duration, highly competitive enrollment and lack of patients motivated to try new treatments. By identifying these challenges beforehand and proactively addressing them you can protect your objectives, investments and resources.

IMIDs

CHALLENGES

LONGER THAN USUAL DURATION
HIGHLY COMPETITIVE ENROLLMENT
LACK OF MOTIVATED PATIENTS

Protect your objectives • investments • resources



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HOW TO DEAL WITH ELIGIBILITY CREEP IN IMMUNE-MEDIATED INFLAMMATORY DISORDERS STUDIES

Placebo response rates can obscure treatment effects, putting effective drugs at risk

One of the confounding factors in clinical studies that can contribute to difficulty in discriminating an active treatment effect versus placebo is subject eligibility creep when subjects (e.g. with milder forms of disease severity at baseline) may get enrolled inappropriately by sites when struggling to meet recruitment targets and timelines. Baselines are skewed and misrepresented since subjects initially may be assessed as suffering from the more severe disease grades required to meet inclusion criteria.

High placebo response

can result in a failure to observe treatment effects and place otherwise effective drugs at risk of the study not meeting the primary endpoint.

The inclusion of *de facto* milder patients can make it more difficult to observe a treatment difference versus placebo and is, unfortunately, likely to place the trial at significant risk of failure. Multiple other factors also play a role in the so-called placebo response; placebo response rates of 14 to 20% have been observed in trials such as psoriasis, and nearly 30% in placebo-controlled studies in rheumatoid arthritis. Even higher rates have been observed in ulcerative colitis studies. High placebo response can result in a failure to observe treatment effects and place otherwise effective drugs at risk of the study not meeting the primary endpoint.

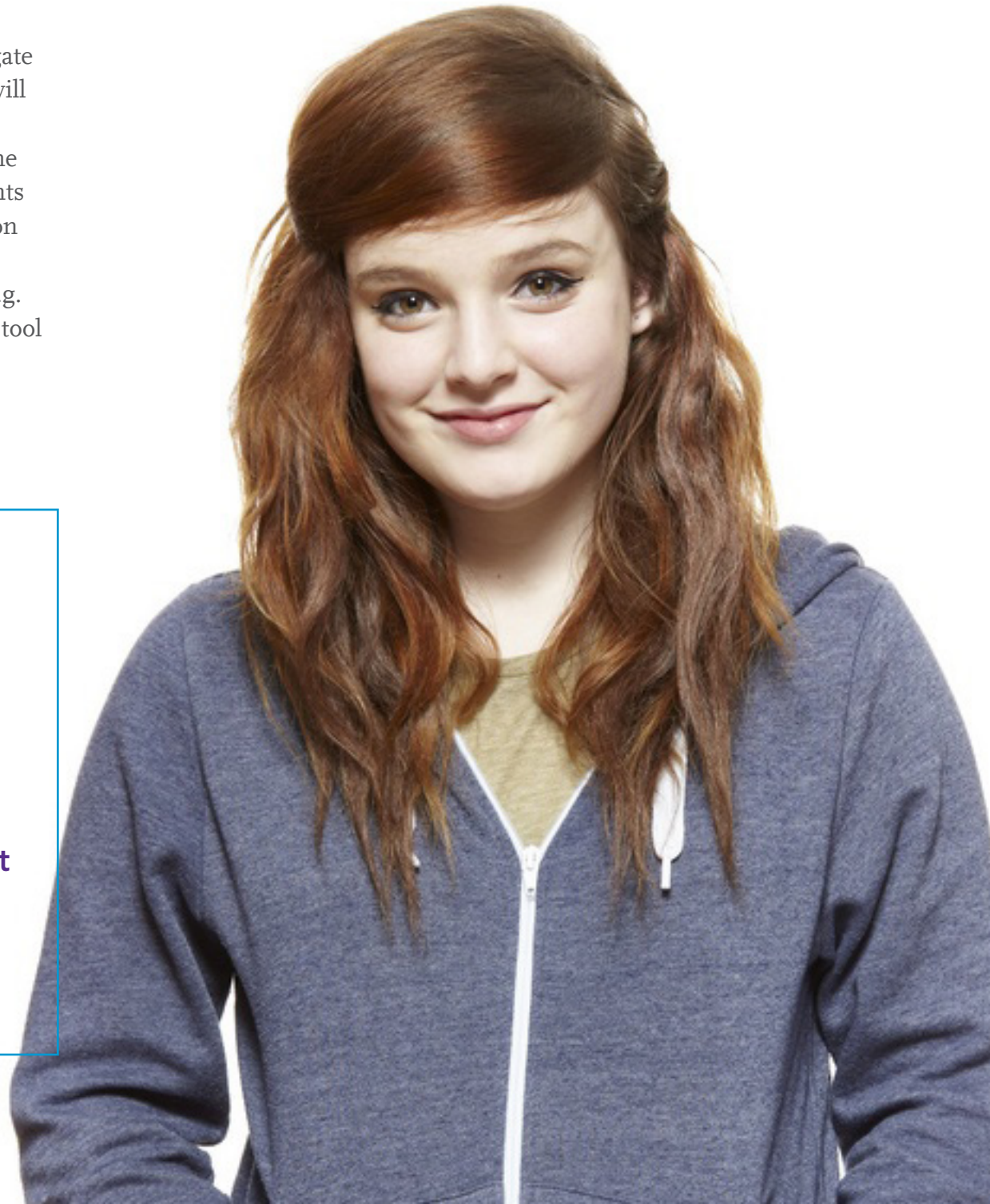
In addition, Immune-Mediated Inflammatory Disorders (IMIDs) have a tendency to have unpredictable, chronic remitting and relapsing patterns. This makes it crucial to confirm severity and ensure stable disease at baseline

on at least two separate assessments and with follow up treatment evaluations conducted by the same evaluator throughout the study to control standardization and mitigate assessment variability. Specific training of site staff who will be performing certain study assessments, such as ACR20 assessments in rheumatoid arthritis studies, is critical. The training is a way to reduce variability of patient assessments across sites and regions and ensure greater standardization across the study to provide more robust data. Blinded, standardized, centralized reading of some assessments, e.g. long-term radiographic evaluations, is likewise a valuable tool to help minimize bias and endpoint variability.



The key to combating eligibility creep

is to bear these challenges and the natural history of the disease when recruiting subjects and proactively putting in place the measures aimed at improving the quality of enrollment and the rigorous standardization of baseline and endpoint assessments.



EFFECTIVELY MANAGING INVESTIGATORS AND SITES IN INFLAMMATION CLINICAL TRIALS

Ensure your ROI and keep studies on track

The good news

The surge in the number and size of industry-sponsored trials in inflammation presents opportunity.

The not-so-good news

The surge also presents a challenge.

Clinical trials for Immune-Mediated Inflammatory Disorders (IMIDs) present certain pressures for even the most committed investigators and sites: IMID trials frequently have longer than usual duration and enrollment can be highly competitive. Additionally, patients whose disease is well-managed by the new treatments available may not be motivated to try something different.

To have investigators who are able to deliver approvable data enrolled on a timely basis, action should be taken to attract and retain investigators through a variety of measures. These include:

- ▶ Protocol simplicity
- ▶ Reasonable sample size requirements
- ▶ Competitive investigator remuneration paid promptly
- ▶ Thought leader engagement and professional meeting presentations

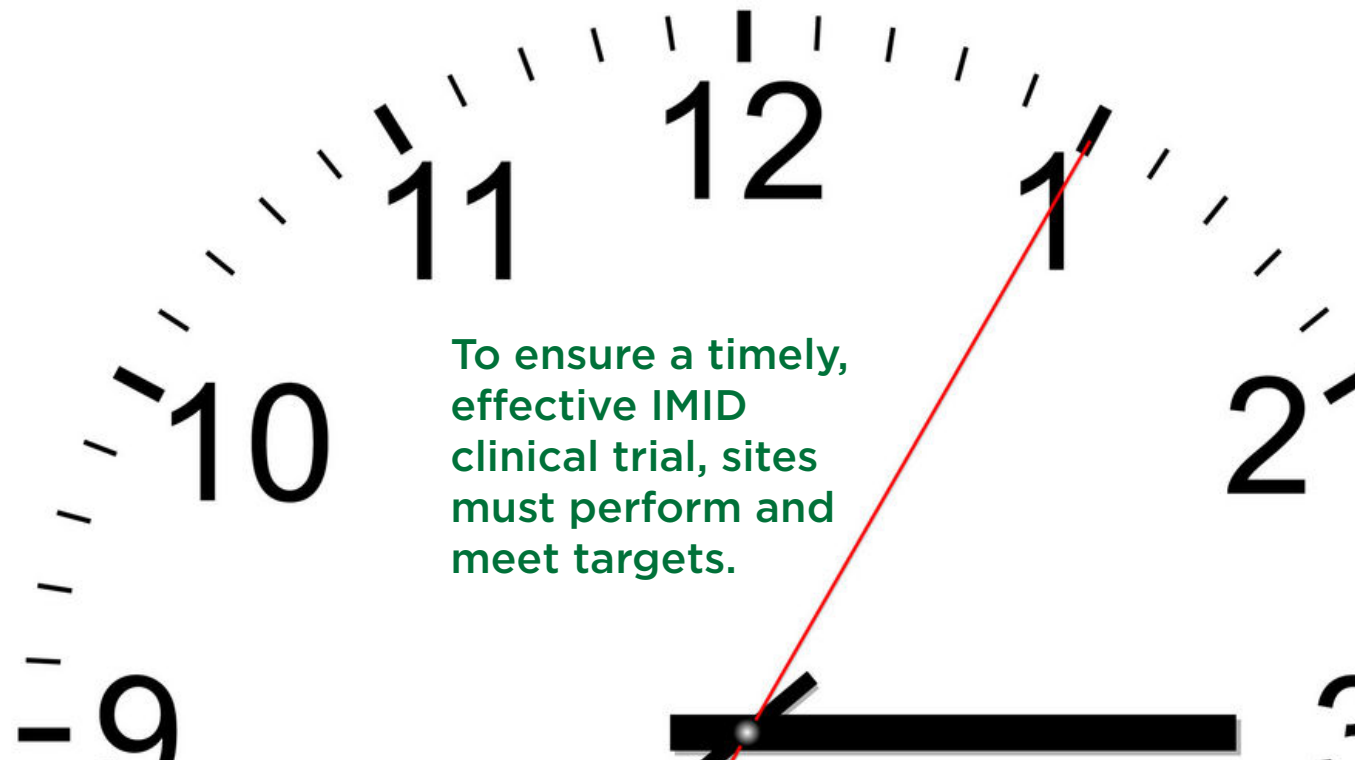
To ensure a timely, effective IMID clinical trial, at the most basic level, sites must perform and meet targets. Non-performing and under-performing sites will generate unnecessary delays and waste resources for all concerned stakeholders.



With your CRO, you can take the following steps:

- ▶ Have an escalation plan in place for non/under-performing sites that facilitates close-out if warranted.
- ▶ Recruit more sites than needed and bring them through regulatory approval, holding their activation until needed. Usually failing sites are identified within three months of activation and standby sites can be readily deployed to fill the gap without compromising time or quality.
- ▶ Be able to draw on a knowledge base that enables site, investigator and geographic selection to meet study needs for patient enrollment.

Although, IMID studies present challenges, identifying these challenges beforehand and proactively addressing them can protect your objectives, investments and resources.

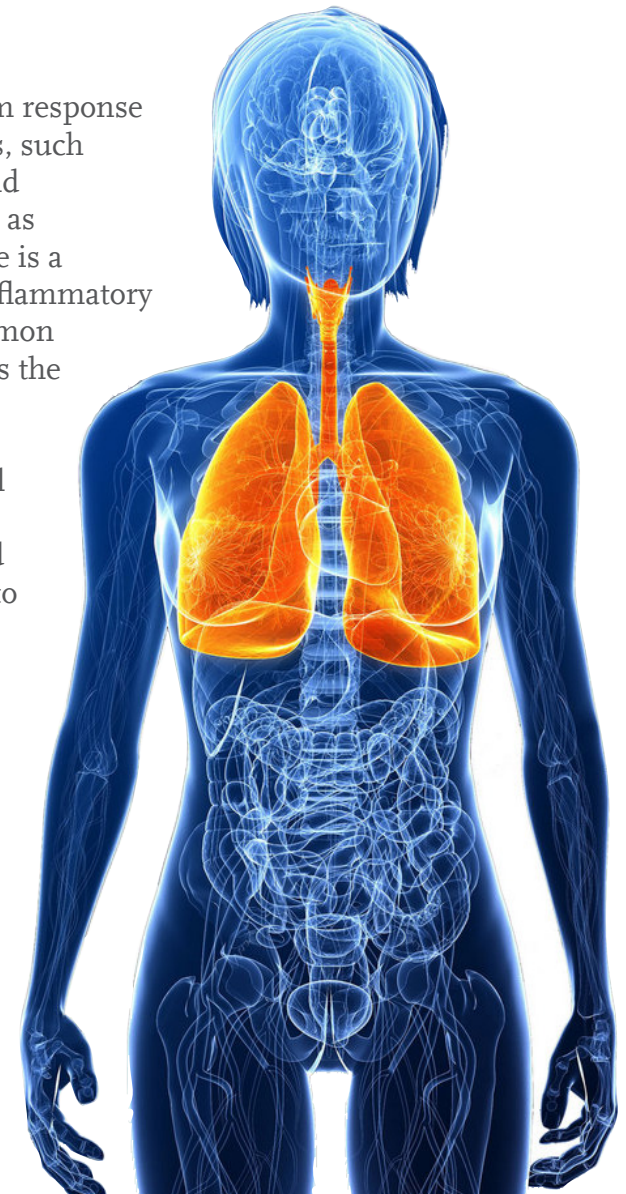


MORE ATTENTION TO PATIENTS CAN INCREASE INFLAMMATION STUDY EFFECTIVENESS

Patient-reported outcomes, compliance and retention are key components of success

Recent research contends some underlying immune system response mechanisms are common to inflammation-related diseases, such as asthma, COPD, psoriasis, rheumatoid arthritis, lupus and inflammatory bowel disease. These diseases are referred to as Immune-Mediated Inflammatory Disorders (IMIDs). There is a significant shift in the approach to managing traditional inflammatory diseases from organ-based symptom relief to tackling common underlying pathways of immune dysregulation which offers the hope of disease modification.

This shift translates into an opportunity for pharmaceutical companies to develop new treatments specifically geared toward modifying disease states, entering new markets and expanding market share. Although IMID trials are known to face a number of challenges that could easily derail efforts, there are ways to proactively address and reduce these challenges. A number of these ways are associated with the role of the patient – here we focus on patient-reported outcomes, patient compliance and retention.



Manage use and integration of patient-reported outcomes (PROs)

PROs play a major role in many inflammation diseases because of the subjective nature of symptomatic improvements in treatment outcomes, such as lessening of joint pain. Misapplication of poor or out-of-context PROs can lead to incomplete and/or spurious data.

To effectively prepare for this challenge, pharmaceutical companies can work with their CROs to carefully select and manage implementation of the appropriate and validated disease-specific PROs. Ideally, this entails integration between clinical development, health economics and outcome research teams, leveraging their collective expertise and experience. The approach provides the following benefits:

- ▶ **Clear instructions about expectations for questionnaire or other PRO instrument completion**
- ▶ **Clear instructions for site personnel to review each instrument as soon as possible after administration so any missing data or clarification can be addressed swiftly**

In addition, use of an electronic device for data capture can expedite real-time data capture and integration into the database and minimize errors.

Proactively address patient compliance

Many of the new therapies to address inflammatory diseases are biologics administered by injection. Self-administration of an injectable drug; however, poses several issues, including patient apprehension and poor technique, and can lead to non-compliance and reduced drug efficacy.

Training and continual technique checks are critical to increase patient comfort and compliance with self-administration. During the screening period, placebo doses can be used and observed in the clinic or screening/randomization sites.

Optimize patient retention

Success doesn't end with recruitment; the patients need to be retained as well, especially when the study requires a long-term commitment, such as rheumatoid arthritis studies with endpoints focused on radiographic response and/or physical function that requires patient follow-up for up to two years.

The following are ways to increase continued patient participation:

- ▶ **Leverage pre-existing patient relationships**—For indications that are chronic conditions, as such, the majority of patients entered into clinical studies will be already known to investigators. Investigators will have direct involvement with patients and family members during each visit.
- ▶ **Educate patients on an ongoing basis**—Provide patients with general study updates and health-related information.
- ▶ **Send study reminders**—Using postcards or text messages, communicating with patients prior to scheduled appointments can keep commitments top of mind. Visual reminders, such as magnets, calendars and notepads can also be effective.
- ▶ **Telephone contact**—Site staff can phone patients between scheduled appointments to check on well-being and protocol compliance and remind patients of their next scheduled visits.

Patient-reported outcomes

play a major role in many inflammation diseases because of the subjective nature of symptomatic improvements in treatment outcomes, such as lessening of joint pain.

By taking these steps with patients, you can effectively address the clinical trial challenges IMIDs face.

ABOUT THE AUTHORS



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