RHEUMATOID ARTHRITIS: KEY CONSIDERATIONS FOR SUCCESSFUL STUDY DELIVERY

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Development of new therapies to treat rheumatoid arthritis (RA) shows no sign of waning. The current (September 2017) clinical trial environment includes >120 planned or ongoing industry-sponsored Phase II-III RA studies (>580 when you consider any phase or any type of study sponsor).[1] Given this backdrop, it is essential that studies are well designed, meticulously planned, include ongoing data surveillance and have a well-orchestrated patient recruitment strategy. It truly is a case of survival of the fittest – investigators will typically sway towards studies that not only offer their patients access to the newest therapies but which are the easiest to participate in, with minimal additional patient and site staff burden.

Study Planning

The saying "fail to plan, plan to fail" could not be more appropriate with respect to RA clinical studies – there simply is no room for anything but rigorous planning. The following factors represent a number of key considerations during the planning stages:

- **Country and site selection** – Marketing objectives aside, there are a number of factors to consider when deciding upon the target geography for the study:
  - **Competitive environment** – the extreme competition has already been highlighted. In an indication such as RA, where the study environment is consistently crowded, it is impractical to exclude significant numbers of countries, particularly key markets, on the basis of competition. However, utilizing the data obtained from competitive environment analyses allows the ability to make informed decisions regarding geographic placement of the study. The crowded landscape will require robust navigation during site identification activities and it is not uncommon to have to initially approach at least three times the number of sites required for activation to ensure sufficient appropriate sites respond to the initial outreach and are ultimately approved for study participation.
  - **Biologic naïve versus biologic experienced patients** – the target patient population will be a significant factor in country selection. In general, biologic experienced patients will be easier to identify in the more affluent countries whereas biologic naïve patients have been traditionally easier to identify in regions such as Eastern Europe and Latin America. However, this disparity is diminishing and with the advent of aggressive early therapy with biologics, identifying biologic naïve patients is becoming more difficult by the day. Nevertheless, a bias in geography is still recommended dependent upon the target patient population.
  - **Historical recruitment rates** – through the provision of Covance Central Laboratory Services (CLS), Covance can view patient recruitment data from more than 40 percent of all ongoing global clinical trials, irrespective of whether the clinical aspect is conducted by the sponsor or via a CRO (i.e. the source of these metrics is industry-wide). This data feeds our Xcellerate® Trial Design tool, enabling analyses of historical recruitment rates at the region, country and site level and providing striking insights. For example, Figure A shows the median regional recruitment rates from Phase II-III RA studies since 2012 and clearly shows that recruitment rates in Eastern Europe and Latin America have been approximately 2x those observed in Western Europe and North America.[2] Depending upon the target population, a bias in geography towards Eastern Europe and Latin America provides the potential to minimize the recruitment window and/or numbers of participating sites. Xcellerate contains patient recruitment metrics for over 1,400 rheumatologists who have been active in clinical trials over the past five years. Even before any site outreach, this data allows identification of countries/sites that have consistently performed well in RA studies.

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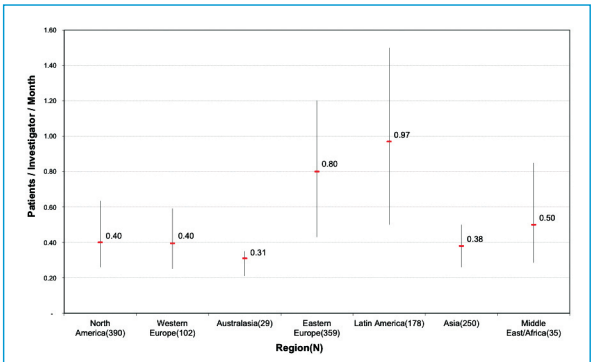
Figure A: Median and inter-quartile regional patient recruitment rates



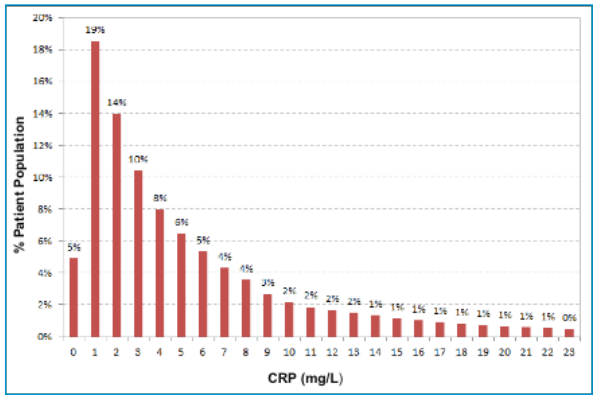
Figures in parentheses represent number of unique investigators contributing to the data.

- **Joint assessment training** – as joint assessments generally form a core part of the primary and secondary objectives, it is recommended that sites receive specific training on these assessments:
  - Include a workshop in the agenda for the investigator meetings and include a key opinion leader (KOL) to assist with training delivery.
  - While investigators will be familiar with these assessments within their own practice, it is important that all joint assessors understand the significance of these assessments within the context of each specific protocol and that reduction of inter-observer assessment bias is paramount to meeting the study objectives.
  - Consider allowing only appropriately trained assessors to complete the joint count assessments (i.e. following study-specific training, each examiner is certified).
- **Placebo response** – placebo response is a recognized phenomenon in RA studies.[3] To minimize the effect, we recommend:
  - During protocol finalization, the eligibility criteria are written in a manner to avoid vagueness (no ambiguity in requirement).
  - As often as possible, each patient is assessed by the same assessor throughout the study. The aforementioned joint assessment training is also exceptionally important to minimize variability in the rating of patients.
  - To further mitigate this risk, speak openly about the potential for placebo response to investigators and declare a state of enhanced surveillance.
  - Undertake careful review of stability of required RA therapy at screening, e.g., stability of the methotrexate (MTX) dose and treatment failure at the dose at the point of the screening visit.
  - Utilize the quantitative patterns of the study, such as screen failure rates (SFRs) to trigger enhanced scrutiny, i.e. low SFRs at individual sites may be indicative of less than robust patient selection, thus prompting a for cause monitoring visit.

The implementation of the above strategies is perhaps even more important where historically there has been a trend to see higher placebo responses, e.g. within the Latin America region.

- **Minimizing patient and site staff burden** – it is human nature, we typically take the course of least resistance. It is the same when running multiple studies for the same indication – there is an automatic draw to the one that is easiest to run. This is a critical consideration given the competitive trial landscape. It starts with protocol design (e.g., only collect "must-have data," avoid over-restrictive eligibility criteria) and continues into the patients' clinic visits. Consider working with each individual site to structure clinic visits with the aim of avoiding waiting time in between assessments/procedures, provide user friendly "stripped down" electronic case report forms (eCRFs), provide site personnel with study tools (e.g., consent aids) and color code trial supplies to make them stand out and easily recognizable as belonging to the study.
- **Patient eligibility criteria** – for example, RA protocols vary widely with respect to the C-reactive protein (CRP) eligibility criterion. Analysis of CRP eligibility levels in RA studies listed in Citeline Trialtrove indicates a range of 3.0 - 30.0 mg/L. The level of CRP chosen for eligibility can have a dramatic effect on the available patient pool, e.g., introducing a CRP eligibility criterion of ≥10 mg/L reduces the patient pool by approximately 80%, whereas a level of ≥5 mg/L reduces the patient pool by approximately 62%[4] – suddenly, your potential patient population has doubled (see Figure B). While it is obviously not quite that simple, it is evident that greater consideration during protocol development can significantly affect your ability to recruit patients in a crowded trial environment.

Figure B: Distribution of CRP level in RA patients



Patient Recruitment

Sites will need significant support from study sponsors to effectively recruit patients – this is a simple fact. As an industry, we have to acknowledge this and plan both logistically and financially to provide the level of support that sites will need. In theory, there is no shortage of patients with RA. However, we are faced with the fact that only approximately 10% of patients participate in clinical trials.[5] Accessing the 90% of patients who do not currently participate in clinical studies has obvious benefits to all parties. Consequently, patient recruitment plans need to be multifaceted – the following provide a number of factors that should be considered for inclusion:

- **Patient pre-identification** – RA is a chronic condition and, therefore, it is an inherent factor that a large proportion of patients entered into clinical studies will already be known to the investigators. Site personnel can pre-identify potential patients while awaiting study approvals which should enable an initial bolus of recruitment immediately following site activation. To leverage this approach to its full potential, sites will require significant encouragement and even on-site support to effectively review their databases and patient records.

- **Site-specific patient recruitment "road map"** – not all sites recruit patients in the same way. Many broad recruitment strategies fail as they do not acknowledge this fact. To maximize recruitment potential, you need to understand the mechanics at each site and subsequently work with each site to develop site-specific recruitment plans. The site-specific road map should clearly identify the underlying recruitment process and which site personnel are involved and how they interact with each other. Understanding this enables clinical research associates (CRAs) to clearly identify any issues during the study and to assist with further optimizing recruitment strategies.

- **Referral networks** – generally speaking, the industry probably does not do enough to leverage the potential of referral networks. It is often "suggested" to investigators and site personnel that they inform their referral networks about the study. The sponsor's project team may even provide "dear doctor" letters and study information leaflets. But how much do project teams actually do to provide real support to investigators in stimulating their referral networks? The importance of fully interacting with referral networks becomes all too apparent when you consider that many RA patients are managed on a day-to-day basis by their primary care physician. It is, therefore, conceivable that a clinical study's entire recruitment window may pass in between a patient's visits to their rheumatologist. Provision of real support by means of assisting study coordinators/nurses in reviewing patients' hospital records (note – there are vendors that specialize in this activity) and subsequently reaching out to these patients through the referral networks or directly will significantly increase the number of patients entering the screening funnel.

- **Patient recruitment vendors** – historically, specialist patient recruitment vendors have not been an over-utilized resource in RA studies, possibly due to disease prevalence. Despite this trend, the competitive trial landscape is now demanding their involvement. However, as any specialist recruitment vendor will tell you, success is very dependent upon understanding RA patients' preferences and behaviors. For example, patients cite the most popular means of hearing about clinical research is from their physician and yet, in reality, only about 23% of patients actually do hear about it from their physician.[6] Therefore, it is clear that, to be successful in recruiting patients, our partnerships with recruitment vendors need to include supporting the investigator and their staff in communicating with patients directly about clinical research. Of course, direct to patient advertising through social media, television, radio and print also has a major role to play. Recruitment vendors now provide portals that track patients who respond to advertising, ensuring that patients receive rapid follow-up and further maximizing patient recruitment. Again, we must work with sites to understand what type of advertising has previously worked well, and which has not, to augment success and avoid placing unnecessary burden upon them.

- **New investigators** – it is obvious that the current number of experienced RA investigators and their patient pool are not able to cope with the demand being placed upon them. Yet there appears to be reluctance within the industry to identify new investigators; rather the general practice is to re-engage with the same investigators each time a new study is initiated, even returning to those investigators who previously failed to meet expectations. This approach is not sustainable. The industry needs to identify rheumatologists who are naïve to clinical research and provide them with training and support to make them successful investigators. In doing so, we relieve pressure within the investigator community, gain access to an untapped patient population and these patients in turn gain the opportunity to access new therapies. Within the U.S., via our parent company LabCorp, Covance has access to a proprietary database of >70 million de-identified patients, of which over 324,000 are RA patients. These patients, and their treating physicians, are identified by RA-specific ICD9/10 codes on lab requisition forms. This data enables Covance to pinpoint RA patient densities/hotspots aligned with clusters of treating physicians who are not active investigators. This subsequently offers the potential to identify new investigators as well as neighboring referral sites. Furthermore, patients utilizing the laboratory facilities of LabCorp are being offered the option of opting in to be contacted directly about participating in clinical trials. Already, within the infancy of this initiative, >2,500 RA patients have opted in.

- **Patient advocacy/support groups** – national and international RA patient advocacy groups (e.g. Arthritis Foundation, National Rheumatoid Arthritis Society (NRAS)) not only provide patients with support but also offer a trusted source of information regarding clinical research opportunities. As an industry, we need to increase our communication with these groups to discuss how we can effectively work together to provide transparent information to RA patients about the research opportunities available. This relationship seems to work well between the industry and advocacy/support groups for rare diseases and there are clearly lessons that can be drawn upon for more prevalent diseases such as RA.

In summary, to succeed in this highly competitive RA arena, it is evident that a well-designed protocol which considers the burden placed upon patients and site staff is a critical factor. Additionally, considerable strategic planning and robust implementation of the plans will be the difference between a study recruiting to expectation and one that falters from the outset. The pharmaceutical industry generates a colossal amount of data – better use of this data provides the basis for evidence-based strategies to enable the conduct of more efficient clinical studies. There are many promising new drugs in development for RA – we owe it to the patients to get as many to market as possible within the shortest timeframe by designing and implementing clinical studies effectively and efficiently through conscientious planning.

1. Citeline Trialtrove
2. Covance Xcellerate data
3. Xu X, Dong B, Hsu CH, Hu C, Lei C, Song J, Lu J, Beutler A. Physician/Site Staff Assessments Contribute to High Placebo Response in Rheumatoid Arthritis Clinical Trials [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10)
4. LabCorp data
5. BBK Healthcare, Inc./Harris Interactive, "The Will & Why Survey." Reinventing Patient Recruitment: Revolutionary Ideas for Clinical Trials Success (Gower Publishing, Surrey, UK, 2006)
6. Report on the Decision to Participate. 2015 PERCEPTIONS & INSIGHTS STUDY. Center for Information and Study on Clinical Research Participation (CISCRP)

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