Adaptive Trial Designs in Rheumatology: Report from the OMERACT Special Interest Group

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ABSTRACT. ***Objective.*** Adaptive trial design was developed initially for oncology to improve trial efficiency. If optimized for rheumatology, it may improve trial efficiency by reducing sample size and time.
Methods. A systematic review assessed design of phase II clinical trials in rheumatoid arthritis.
Results. Fifty-six trials were reviewed. Most trials had 4 groups (1 control and 3 intervention), with an average group size of 34 patients. American College of Rheumatology 20 measured at 16 weeks was the most commonly used primary endpoint.
Conclusion. The next step is to undertake a systematic review of adaptive designs used in early-phase trials in nonrheumatic conditions. (First Release February 15 2019; J Rheumatol 2019;46:1406–8; doi:10.3899/jrheum.181054)

Key Indexing Terms:
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Randomized controlled/clinical trials are the gold standard in evidence-based medicine. However, an editorial in *The Journal of Rheumatology*, "Arthritis Clinical Trials at a Crossroad" in 2015 by Pope, *et al* highlighted the "critical state of rheumatology clinical trials"[1]. Clinical trialists struggled to recruit patients because of inefficient trial design, funding, and regulatory requirements. Recruiting patients from countries with less access to expensive treatment has become more common but increases the risk of higher placebo response. This is a common issue and not unique to rheumatology. Clinical trials are resource-intensive in time, personnel, finances, and available patient pool. Some of these obstacles could be mitigated by using adaptive trial designs, which have been developed to improve clinical trial efficiency. Adaptive clinical trial designs have been increasingly used in oncological and cardiovascular (CV) diseases. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) accept adaptive clinical trial designs, issuing guidance on aspects that require special consideration[2,3].

An adaptive clinical trial is defined as a design that allows modifications to the trial, and/or statistical procedures of the trial, after its initiation without undermining its validity and integrity[4]. The purpose is to make clinical trials more flexible and efficient. However, modifications and adaptations should be planned prospectively and based on analyses of interim data collected at planned timepoints within the study, with or

without formal statistical hypothesis testing in an unblinded manner[5].

Adaptive clinical trial designs are attractive and promising because ineffective doses or treatments may be dropped early, and the proportions of patients in treatment arms can be adjusted based on interim analyses. Moreover, these designs allow for tailored dose titration of individual agents based on observed results so that the optimal dose may be more rapidly and efficiently identified. If the statistical and methodological principles of adaptive clinical trial designs can be optimized in rheumatic diseases, it will address some of the issues highlighted by Pope, *et al* by improving clinical trial efficiency and reducing sample size, exposure to inadequate doses, time, and cost to the benefit of funders, researchers, and patients.

Adaptive Trial Design Steering Committee

Members of the steering committee of the adaptive trial design Special Interest Group (SIG) include rheumatologists, clinical trialists, epidemiologists, and statisticians from academia and industry. Regular teleconferences have been held to discuss objectives and research plans, and to report progress.

Adaptive clinical trial design is novel to rheumatology, so the initial focus of the SIG will be in rheumatoid arthritis (RA) because the RA OMERACT core outcome set already exists, with established composite outcome measures such as the American College of Rheumatology (ACR) responses criteria and Disease Activity Score (DAS), which are the established gold standards and are widely used as primary endpoints in clinical trials. For adaptive design trials, it is important to establish the clinical relevance and discriminatory performance of these outcome measures at earlier, relevant interim timepoints, in particular their ability to predict final outcome to select the best outcome measure for interim analysis.

The key objectives of the adaptive trial design SIG are to:

1. Define optimal study design(s) including determination of the best outcome measure[6], timepoint, and sample size for interim statistical analysis,
2. Identify potential barriers in implementation of adaptive trial design in practice and address issues raised by the FDA and EMEA in RA,
3. Investigate the types of bias that could occur related to inference from adaptive trial designs in rheumatology, and
4. Analyze how adaptive trial design may be applied in different phases and types of clinical trials, e.g., phase I–IV drug development trials, head-to-head comparison trials, and pragmatic strategy trials.

Systematic Review of Early-phase Clinical Trials in RA

We conducted a systematic review that included 56 early phase II trials in RA and found only 1 trial with an adaptive design. Most phase II trials in RA had 4 groups (1 control and 3 intervention), and an average sample size for each group of 34 patients. ACR20 measured at 16 weeks was the most commonly used primary endpoint. The search also identified a statistical simulation study suggesting that adaptive designs can be applied to early-phase trials in RA. This systematic review identified the typical study design of phase II trials in RA including the number of intervention groups, sample sizes, and the primary endpoint. Adaptive trial design would need to demonstrate superior efficiency for it to be adopted for RA.

Regulatory Requirements

Both the FDA in the USA and the EMEA, in principle, accept adaptive design trials. However, they have also highlighted methodological issues, which will be addressed by the SIG.

These include:

- Dissemination of interim results, especially if not fully blinded or incorporate some subjective element/analyst access to unblinded interim results and how they may influence investigators managing the trial (who must remain unequivocally objective), i.e., by introducing operational bias,
- Minimum sample size or number of included participants that would have to reach an interim timepoint for decisions to adapt a study,
- Results based on p values alone,
- Control of the type I error rate,
- Interpretation of study results when the study design has changed as a result of interim analyses,
- Rejection of a global null hypothesis across all stages, which may not be sufficient or methodologically sound,
- Involvement of sponsor personnel in interim decision making,
- Differential population for recruitment before and after modification, which will affect treatment effect,
- Making hypothesis claims from results of interim analyses,
- Interim analyses/adaptation choices that provide multiple opportunities to show a successful treatment effect (with greater likelihood of doing so than if no such analyses existed), thus introducing inherent multiplicity bias,
- The potential to select a modification as a result of an interim analysis that, by random chance, is more favorable than the true value, thus creating bias that will lead to an overestimate of the true treatment effect,
- Limiting the opportunity to reflect on the data, including safety issues, and thus limiting the design of future well-thought research,
- An increase in pressure to make assumptions, even when only limited prior information exists, and
- Investigative adaptive design study flaws, which could lead to subtherapeutic dose selection in subsequent (adequate and well-controlled) trials.

Research Plan

After several iterations, the steering committee decided on 2 work packages and discussed options for a third work package.

Work Package 1: Optimal Design of Phase II Adaptive Trial Designs in RA

Systematic review found that ACR20 was the most commonly used primary outcome measured in early-phase clinical trials. However, a continuous variable, such as the 28-joint count Disease Activity Score, Simplified Disease Activity Index, or Clinical Disease Activity Index, may perform better for interim analyses. Primary outcome and the outcome for interim analyses do not need to be the same. However, if different, time effect and correlation between these outcome measures need to be examined. Some studies have shown that response at Week 4 may be predictive of response at 3 months, suggesting that this should be assessed as a potential first timepoint for interim analysis. A statistical simulation/analysis plan is being developed to assess the discriminatory performance of outcome measures at weeks 4, 8, and 12.

Work Package 2: A Systematic Review of Adaptive Designs Used in Early-phase Trials in Other Conditions

In accordance with the OMERACT Technical Advisory Group recommendations[7], the SIG will undertake a systematic review of adaptive trial designs in early-phase clinical trials beyond musculoskeletal conditions. A preliminary search found most of these trials in oncology and CV diseases.

Options for Work Package 3

Several options for work package 3 were considered, such as developing/identifying the:

- Best composite outcome measures for clinical trials,
- Safety issues regarding high-risk patients, and
- Potential use of adaptive designs in phase III and IV trials.

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