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

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Key words: adaptive trial design, OMERACT core outcome set, early phase clinical
trial, **R**heumatoid arthritis, systematic review

Abstract

Objective

Adaptive trial design was developed initially for oncology to improve trial efficiency. If optimised for Rheumatology, it may improve trial efficiency by reducing sample size and time.

Methods

A systematic review assessed [current](#) design of phase-~~II~~ [II](#) clinical trials in Rheumatoid Arthritis [regulatory requirements for adaptive design was also reviewed.](#)

Results

~~56 trials were reviewed.~~ Most trials had 4 groups (~~1 control and 3 intervention~~), with an average group size of 34 patients. ACR20 ~~measured at 16 weeks~~ was the most commonly used primary endpoint. [Regulatory review established a list of methodology issues.](#)

Conclusion

The next step is to undertake a systematic review of adaptive designs [utilised in early phase trials](#) in non-Rheumatic conditions [and produce a statistical analysis plan for assessing outcome measures for interim analysis.](#)

Introduction

Randomized controlled/clinical trials are the gold standard in evidence-based medicine. However, an editorial in the Journal of Rheumatology, "Arthritis Clinical Trial 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 terms of time, personnel, finance 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 diseases. [2-6] Both the U.S. Food and Drug Administration (FDA) and European Medicine Agency (EMA) accept adaptive clinical trial designs, issuing guidance on aspects that require special consideration. [7, 8]

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. [9] 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 pre-planned timepoints within the study, with or without formal statistical hypothesis testing in an unblinded manner.

[10]

Adaptive clinical trial designs are attractive and promising as ineffective doses or treatments may be dropped early, and [a larger number of patients allocated to therapeutically promising 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. [This will also reduce the number of patients receiving subtherapeutic doses in early phase II trials. In large intervention trials, such as surgery, non-promising therapies, can be terminated early.](#) 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, reducing sample size, exposure to inadequate doses, time and cost, ~~to the~~ [which will](#) benefit ~~of~~ funders, researchers and patients.

Adaptive Trial Design Steering Committee

Members of the steering committee of the adaptive trial design SIG include Rheumatologists, clinical trialists, epidemiologists, and statisticians from academia and industry. Regular teleconferences have been held to discuss objectives, research plan and report progress.

Adaptive clinical trial design is novel to Rheumatology, so the initial focus of the SIG will be in Rheumatoid Arthritis as RA OMERACT core outcome set already exists with established composite outcome measures such as American College of Rheumatology (ACR) responses criteria and Disease Activity Score (DAS), which are

widely used as primary endpoint 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 particularly their ability to predict final outcome to select the best outcome measure for interim analysis. ~~Rheumatoid arthritis (RA) will be the initial focus of the SIG since OMERACT core outcome measures are the established gold standard and are widely used in clinical trials.~~

The key objectives of the adaptive trial design SIG are:

1. Define optimal study design(s) including determination of the best outcome measures, [116] time point and sample size for interim statistical analysis
2. Identify potential barriers and the methodological issues to implementation of adaptive trial design in practice and address issues raised by FDA and EMA in RA
3. Explore the types of potential biases that could occur related to inference from adaptive trial designs in Rheumatology
4. Explore how adaptive trial designs s may be applied in different phases and types of clinical trials (e.g. phase I-IV drug development trials, head-to-head comparison trials, pragmatic strategy trials).

Method

First, a systematic review of early phase clinical trials in RA was conducted to establish current practice. Adaptive trial design will need to be more efficient that

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[these standards for it to be adopted. Second, a review of regulatory requirements to identify key methodological issues that should be addressed.](#)

1. 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 one trial with an adaptive design [12]. 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 primary endpoint. Adaptive trial design would need to demonstrate superior efficiency for it to be adopted for RA.

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2. Review Regulatory Requirements

Both the Food and Drug Administration (FDA) in the US and European Medicine Agency (EMA) 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. operational bias;

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- ~~define the minimum sample size or number of included participants that would be required for have to reach an interim analysis time point for decisions to adjust protocols a study;~~
 • define the minimum minimum sample size or number of included participants that would be required for have to reach an interim analysis time point for decisions to adjust protocols a study;
- define the risk of 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 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 favourable 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-through research;
- an increase in pressure to make assumptions, even when only limited prior information exists;

- exploratory adaptive design study flaws, which could lead to sub-therapeutic dose selection in subsequent (adequate and well-controlled) trials;

Research Plan

After several iterations, the steering committee have decided on two 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 DAS28, SDAI or CDAI, 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 needs 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 time point for interim analysis. A statistical simulation/analysis plan is being developed to assess the discriminatory performance of outcome measures at timepoints, week 4, 8 and 12.

Work Package 2: A systematic review of adaptive designs utilised in early phase trials in other conditions

In accordance with OMERACT Technical Advisory Group recommendations, [\[137\]](#) the SIG will undertake a systematic review of adaptive trial designs in early phase clinical

trials beyond musculoskeletal conditions. A preliminary search found a majority of these trials in oncology and cardiovascular diseases.

Options for Work Package 3

Several options for work package 3 were considered, these included:

- develop/identify best composite outcome measures for clinical trials
- safety and high-risk patients
- potential use of adaptive designs in phase III and IV trials

Potential Limitations

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[One potential limitation for adaptive design is change in regulatory requirement for clinical trials in Rheumatology e.g. time for escape therapy, placebo control versus active controls. The SIG will continue to review and update research agenda to address these issues.](#)

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