EXTENDED REPORT

Development of EULAR recommendations for the reporting of clinical trial extension studies in rheumatology

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ABSTRACT

Objectives Our initiative aimed to produce recommendations on post-randomised controlled trial (RCT) trial extension studies (TES) reporting using European League Against Rheumatism (EULAR) standard operating procedures in order to achieve more meaningful output and standardisation of reports.

Methods We formed a task force of 22 participants comprising RCT experts, clinical epidemiologists and patient representatives. A two-stage Delphi survey was conducted to discuss the domains of evaluation of a TES and definitions. A ‘0–10’ agreement scale assessed each domain and definition. The resulting set of recommendations was further refined and a final vote taken for task force acceptance.

Results Seven key domains and individual components were evaluated and led to agreed recommendations including definition of a TES (100% agreement), minimal data necessary (100% agreement), method of data analysis (agreement mean (SD) scores ranging between 7.9 (0.84) and 9.0 (2.16)) and reporting of results as well as ethical issues. Key recommendations included reporting of absolute numbers at each stage from the RCT to TES with reasons given for drop-out at each stage, and inclusion of a flowchart detailing change in numbers at each stage and focus (mean (SD) agreement 9.9 (0.36)). A final vote accepted the set of recommendations.

Conclusions This EULAR task force provides recommendations for implementation in future TES to ensure a standardised approach to reporting. Use of this document should provide the rheumatology community with a more accurate and meaningful output from future TES, enabling better understanding and more confident application in clinical practice towards improving patient outcomes.

INTRODUCTION

A randomised controlled trial (RCT) is the most objective means of evaluating an intervention and underpins regulatory decision-making and, if appropriate, the introduction of therapies into clinical practice. Many benefits of RCTs have been seen in the specialty of rheumatology, and particularly in the management of rheumatoid arthritis (RA).1–10 While the aim of RCTs is to demonstrate the efficacy and safety of an experimental agent, their observation period typically spans a relatively short time frame. However, the use of therapies in chronic diseases necessitates more long-term evaluation. The introduction of new disease modifying anti-rheumatic drug (DMARD) therapies for the treatment of RA has been associated with a significant number of post-RCT extension studies,11–17 henceforth termed ‘trial extension studies’ (TES), to report the longer-term outcomes of an experimental agent.

Role of TES

TES can evaluate in particular, the effects of cumulative exposure to a drug, capturing events through systematic reporting, monitoring of source data, and consistent coding, thus enabling further assessment of the long-term safety profile observed during the RCT.18

An additional benefit of TES that is cited is continued access to an effective but otherwise unlicensed treatment by RCT participants. However, since a favourable effect of the treatment may not have been clearly determined at the time of TES participation (with results from the preceding RCT and/or indeterminate prior studies not available), this raises legitimate ethical issues about the appropriateness of exposing patients to potentially ineffective or only partially effective treatments for additional periods of time.

Challenges of TES

While TES play a valid role, there are clear limitations that should be considered and potential weaknesses in the design and method of analysis that should be addressed.19 TES benefit from the systematic reporting on cumulative drug exposure but have clear limitations in the detection of rare and unexpected events. In addition, selection bias associated with TES populations and lack of generalisability are key factors. These issues are discussed in more detail in the online supplementary material.
This makes interpretation challenging and sometimes unreliable. While guidance for reporting of RCTs and safety data from biological DMARD registers are available, no recommendations for TES in rheumatology have been published to date. With this in mind, a task force was created with the principal aim of developing practical recommendations on key aspects of TES on the basis of the European League Against Rheumatism (EULAR) standard operating procedures, and thereby a recommended standardised format for future TES data reporting to achieve greater transparency. This manuscript reports the final recommendations as agreed by the task force.

METHODS
The task force agreed that a systematic literature review was not indicated for this initiative, as it would merely serve to further establish the lack of consistency in TES and emphasise the need for the development of a standard for future application.

The target population for these recommendations was chosen to be rheumatologists, trialists and researchers working in the field of rheumatology, patient organisations and policymakers. The general approach to this project followed the EULAR standardised operating procedures for the elaboration and implementation of evidence-based recommendations.

The two task force conveners (MHB and MB) set up a multidisciplinary task force with participants selected based on their field of expertise, knowledge and experience as well as approximate geographical distribution, primarily across Europe but also North America.

A first meeting of all task force members was convened in January 2011 to primarily define the domains for evaluation. This comprised two breakout sessions, with the task force split into two groups. Each group had a rapporteur who reported the outcome to the whole task force. After a final round of discussion, the task force agreed on the individual items for inclusion in a Delphi exercise. The Delphi method offers a consensus method that is widely used in health service research. The two-step Delphi exercise for this initiative was web based, which permitted opinions to be provided and votes on the level of agreement to be cast independently and anonymously.

At the initial meeting, the task force agreed on seven main domains to form the basis of the exercise. These are listed in box 1 with components within each domain that we wished to cover.

RESULTS
Task force composition
The multidisciplinary task force comprised 22 participants consisting of 17 rheumatologists, of whom six were clinical epidemiologists and 11 clinical trialists/expert clinicians, two biostatisticians, one fellow and two patient representatives. Participants represented 10 European countries, the USA and Canada.

Response rate
Of the 22 invited experts, three could not attend the first meeting (January 2011) but were subsequently apprised of the discussion and participated in the Delphi exercise. One of the patient representatives could not continue participation after the first meeting. Twenty of the 21 participants responded to the first and all 21 responded to the second Delphi exercise.

The two-step Delphi exercise was completed by January 2012, with subsequent analysis and dissemination of draft recommendations in March 2012. Final voting took place in May 2012. However, subsequent steps of involving additional stakeholders (see ‘Results’ section) and a meeting to discuss the recommendations (June 2013) led to a delay in establishing the recommendations for the purposes of submission. The task force approved this final document that included some modifications following the last step. More details on the timelines, responses and involvement of other stakeholders are detailed in the online supplementary material.

Domains for evaluation
At the initial meeting, the task force agreed on seven main domains to form the basis of the exercise. These are listed in box 1 with components within each domain that we wished to cover.

Final results
Percentage agreement for each recommendation (following the second Delphi exercise) is given. Where appropriate, mean (SD) scores have also been provided. Median (range) scores were also calculated and are included in the online supplementary material.

Definition of a TES
- **Study design definition (100% agreement):** A TES is a study that follows all patients beyond a pre-specified trial period whether the trial was (a) a placebo-controlled RCT with the possibility to cross over to an open-label experimental drug or (b) a placebo-controlled RCT with the possibility to cross over to usual care or (c) an active comparator RCT.
- **Start of a TES (100% agreement):** Should be stated in the pre-specified protocol with clear justification, and should be at the point of exposure to the experimental drug of interest. For the experimental randomised arm, this will be the start of the original RCT, while for those randomised to placebo/active comparator arm, this point will be on switching to experimental treatment.

Box 1 The key domains underpinning the Delphi exercise

1. Definition of a trial extension study (TES)
- Study design definition
- Definition of start of TES
- Duration of TES
- Patient population of TES
2. Development of a checklist of minimal data items/outcome necessary for a TES
- Minimal information a TES should collect
- Elements not amenable to accurate assessment by a TES
- Safety elements that may be elicited
- Efficacy
3. Additional data/outcomes
- Additional legitimate outputs from a TES
4. Method of analysis
5. Method of reporting results
- Inclusion of a flowchart
- Detail minimal standards by way of a checklist
- Frequency and nature of TES
6. Ethics and obtaining consent
7. Over-arching principles
- Consultation and stakeholder involvement
- General comments on TES and its reporting
- Sources of bias and generalisability
Minimum duration of a TES (100% agreement): It was agreed by consensus not to define this; nevertheless, the rationale for the length chosen should be stated in the pre-defined protocol with adequate justification.

Population for inclusion in a TES (96% agreement): Should include all patients included in the RCT, with the ability to separately report on patients who are of specific interest, for example, those in remission or with low disease activity.

The minimal information that should be collected and reported by a TES is listed in box 2. Minimum and maximum mean (SD) scores following the first Delphi exercise were 7.2 (2.72) and 9.9 (0.36) (refer to the online supplementary material for individual mean and median scores) with agreement by 100% of the task force in the second Delphi exercise.

The entire group also accepted the following statements relating to the nature of the initial RCT design following the first Delphi exercise:

The minimal data requirements for TES following placebo- and active comparator RCTs should be the same (93% agreement).

A TES that follows an active comparator RCT should follow all randomised patients for the same period of time (not only patients on the experimental treatment) and including patients who may switch to an active comparator treatment (analysed separately) (mean (SD) 7.9 (2.23), median (range) 8.5).2,10

Safety and efficacy outcomes

Evaluation of safety aspects includes several elements, some of which may not be feasible to capture within certain study designs. The following statements were agreed during the first Delphi exercise (minimum and maximum mean score of 7.0 and 8.4; refer to online supplementary material for individual scores) with 90% accepting all statements in the second round.

Safety

TES may identify new adverse effects that the original RCT was not able to detect due to greater cumulative drug exposure.

TES may identify whether the incidence of known adverse effects changes with longer-term drug exposure.

TES may confirm whether the nature of known adverse effects identified from the RCT changes with longer-term exposure.

TES are sub-optimal to detect rare safety events because they are not powered for this.

TES are sub-optimal to detect rare safety events because they include a selected population (responders with likely no previous serious adverse events).

Efficacy

Greater cumulative exposure to the active drug per patient in a TES might identify additional information on the drug's efficacy.

While definitions of relapse are currently not available and require further work, if/when validated, a TES might allow evaluation of relapse including time to relapse and therefore the sustainability of original disease control.

Additional data/outcomes

Economic evaluation of long-term treatment with the active drug may be possible if appropriate measures are recorded in the TES.

A TES could not accurately evaluate health-related quality of life.

Method of analysis

Following the second Delphi exercise, this section required further iterations to refine the initial Delphi statements. These are detailed in box 3. Minimum and maximum scores of agreement were 7.3 and 9.4 (refer to the online supplementary material for individual scores).

Method of reporting results

Inclusion of a flowchart

All TES reports should include a flowchart.

This was agreed as a minimal piece of information to accurately illustrate the treatment arms, and changes in treatment and in patient numbers during the course of the study (mean (SD) 9.9 (0.36)).

In particular, the absolute measure/count should be reported (with/without the percentage).

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Box 2 Minimal information to be included in a TES report

- Progress of subjects at each stage from RCT start to TES completion with:
  - A flow diagram detailing absolute numbers of subjects at each relevant time-point
  - Duration of active treatment
  - Time of last observation
- All drop-outs detailed
- The drop-out rates from each arm during the original RCT and the cross-over groups
- Reason for exclusion from the TES if the patient discontinues the drug
- Reason for cessation of follow-up
- Specification of reasons for cessation of follow-up other than adverse event or inefficacy as above, for example, geographical or doctor-related reasons
- Functional status at the time of inclusion in the TES if applicable
- Functional status at last observation if applicable
- Disease activity at the time of inclusion in the TES if applicable
- Disease activity at last observation if applicable
- For those patients entering the TES having achieved low disease activity or remission during the RCT, the sustainability of each disease state should be evaluated and reported
- For those subjects who enter a TES not having achieved remission/ an acceptable disease activity state following the RCT, the number who achieve this during the TES should be reported to determine whether longer drug exposure has the potential to improve the disease state of such subjects further
- Disease-related co-medication (DMARD, corticosteroid) at each stage from RCT start to TES completion
- Any serious adverse events and outcome related to safety at each stage from RCT start to TES completion DMARD, disease modifying anti-rheumatic drug; RCT, randomised controlled trial; TES, trial extension studies.
The null hypothesis should be stated at the start where appropriate.

Multiple comparisons should be taken into account when determining the level of statistical significance.

The null hypothesis should take account of the results of the original RCT. Depending on the research question, the results of an RCT should be accommodated in the TES.

The report should comment on cumulative outcome analysis (beneficial and adverse events) maintaining the original trial groups, that is, from RCT start not TES start, to avoid reporting of only the sub-selected patient group that proceeds to the TES.

The selection bias associated with a TES population means meaningful non-inferiority/superiority analysis would not be reliable. The report should focus on how data for sustained effect from the start to the end of the TES period, within a single group or the difference between groups was analysed and whether there was any suggestion of increased effect (although this could not be subject to formal statistical testing).

The plan for subjects that drop out of a TES should be specified to demonstrate sustained effect from the start to the end of the TES period. With reducing number of participants (the denominator), the proportion responding will artificially increase if/when the number of patients (numerator) responding stays the same.

The analysis should include survival/retention rates on therapy explicitly reporting the number of patients at each milestone with reasons for change detailed.

A plan on how to analyse this should be included with both intent-to-treat (ITT) (denominator as the original number entering the RCT) and completer (those entering TES only) population analyses reported. A completer analysis should always be reported together with an ITT analysis.

The repeated measures analysis of the data from a TES in rheumatology should include the area under the curve of absolute disease activity (ie, not dichotomous response/change) preferentially expressed as a score (eg, DAS, SDAI, etc).

A TES should preferably include hard endpoints (eg, death, work disability, joint replacement surgery, hospital admission) from the TES with or without linkages with other data sources.

RCT, randomised controlled trial; TES, trial extension studies. The agreement scores were recorded after Delphi round 1.

Reporting frequency should not be specified for all TES since this depends on the research question.

However, the protocol of each TES should pre-specify the minimum frequency of reports to be written and the basis for them (purpose, outcomes, length of RCT).

The efficacy and safety results of a TES should generally be reported together; abstract selection committees and journal editors should carefully consider reporting of efficacy alone before acceptance.

Consent

The recommendations related to obtaining consent are detailed below; this item in particular required specific input from the patient representative (refer to the online supplementary material for individual scores on additional questions that had means scores of between 6.2–9.4).

All of the subjects undergoing an RCT should be informed of the importance of long-term surveillance and be given the opportunity of entering in the long-term follow-up (mean (SD) 9.4 (0.85)).

Subjects should sign a new consent form both for continuation of the drug and for data collection at that time point (mean (SD) 7.6 (2.87)).

Annual updates for consent are not recommended (mean (SD) 3.7 (4.4)).

Over-arching principles

The report of a TES should be consistent with and consolidate existing established guidelines including CONSORT20 28 and STROBE29 (mean (SD) score 9.4 (0.85)).

The report of a TES should be consistent with the ACR/ EULAR recommendations on the reporting of clinical trials in RA21 (mean (SD) score 8.9 (1.88)).

General comments on TES and its reporting

All the following statements were accepted by 95% of the group in the second Delphi exercise, agreement with the individual statements having been established as part of the initial Delphi exercise (agreement score out of 10):

While data linkage is important for long-term observation, access may be difficult as pharmaceutical companies conduct most TES; this may in turn limit the overall benefit of such studies (mean (SD) 7.1 (2.06)).

TES, by definition, comprise a sub-selected population, not reflective of routine care; hence, even if all patients in an RCT were entered into a TES, such a study is generalisable only to patients with similar disease characteristics (mean (SD) 7.9 (1.76)).

The absence of a clear null hypothesis may make the definition of comparator groups in a TES difficult (mean (SD) 7.4 (1.74)) and should therefore be stated where appropriate (see table 3 for details on method of data analysis).

Potential sources of bias or lack of generalisability

Several factors were identified as possibly influencing the inclusion of patients in a TES following completion of an RCT, which could introduce sources of bias and lack of generalisability (80% agreement to include all the following statements):

The requirement of a certain level of response (mean (SD) 7.9 (2.67))

The stage of the disease of the patient (mean (SD) 7 (2.18)).

The fact that the investigator is remunerated for each patient recruited or that the patients may also receive financial...
compensation and that the drug is free of charge could be of importance in some health systems (mean (SD) 7.4 (1.7)).

- Geographical differences in practice/approach (leading to differences in the number and nature of patients included) (mean (SD) 7.5 (2.45)).
- Unwanted heterogeneity from countries where treatment options may be more limited (eg, patients with higher levels of disease activity recruited where otherwise only patients in remission/with low disease activity would be included) (mean (SD) 7.6 (1.45)).

Consultation on recommendations and stakeholder involvement

The Delphi process established whether input from relevant stakeholder organisations, namely, industry, regulatory authorities (Food and Drug Administration (FDA), European Medicines Agency (EMA)) and contract research organisations (CRO) should be sought. In the initial Delphi exercise, 75% voted in favour of some level of industry input, 94% for regulatory authorities and 81% for CRO.

The second Delphi exercise asked for agreement that each of these organisations be included in the initiative:

- Industry and regulatory authority input into the final recommendations was recommended, with mean (SD) scores out of 10 of 7.2 (2.48), 8.3 (1.77) and 4.9 (2.85) recorded for the FDA, EMA and CRO, respectively.
- Key industry companies that have been associated with new drugs in the RA arena were therefore approached (refer to online supplementary material for details of the companies represented).

DISCUSSION

We present a series of pragmatic recommendations on the design and reporting of TES in rheumatological conditions (mainly inflammatory arthritis, although the basic principles are generally applicable), based on a high degree of expert consensus. Our EULAR task force comprised a group of experts encompassing a range of expertise including clinical trialists, clinicians experienced in RA treatment, and clinical epidemiologists as well as patient representatives. A wide range of countries...
and health systems were represented, albeit with some omissions (e.g. absence of individuals from Asia), although the opportunity to evaluate these recommendations in the wider community in the future should highlight any differing perspectives. With a generally accepted methodology for prospective observational studies, we felt an additional systematic review was not necessary and decided to use our expert opinion to formulate guidance for TES. These recommendations complement those established for clinical trials and registries.1-3

Central to the recommendations was the principle that a TES report should focus on cumulative outcome analysis, maintaining the original trial groups to avoid reporting of only the sub-selected patient group that proceeds to the TES, and thereby achieve better generalisability of results. Furthermore, the task force was clear that absolute numbers and not just percentage response rates should be reported. To facilitate this, we recommend a flow diagram detailing absolute numbers of subjects at each relevant time point, with clear illustration of drop-outs and the reason for cessation and/or exclusion at each relevant stage. While it was agreed that a TES might elaborate on the incidence and nature of adverse events over time, they are not designed to capture rare safety signals. TES reports may also have the potential to inform on the durability of response and the dynamics of achieving pre-determined targets of treatment (low disease activity and remission). It was agreed that any analysis should be prespecified in the protocol but should always include an intention-to-treat in addition to a completer approach. We acknowledge there are elements that may in particular be the subject of further discussion in the wider community, for example, the issue of split reporting. While the task force discouraged this, each case should be considered individually as there may be instances when there is utility in this approach to ensure relevant data that is of interest is disseminated within the public domain.

The recommendations were actively commented on by several industry companies (see the ‘Consultation of recommendations and stakeholder involvement’ section) and include their specific feedback (which has been indicated directly in the results where appropriate in the online supplementary material) and as such, gained the approval of the participating stakeholders. While EMA representation did not suggest changes to the recommendations, it acknowledged the importance of standardisation. The interaction also highlighted how regulatory expectations may drive the industry approach on whether and how TES should be undertaken.

While we acknowledge that the working group was perhaps relatively small for a consensus exercise, following dissemination of these recommendations, we would anticipate a subsequent exercise to capture how they have been received in the wider rheumatology, trial and industry communities. In future, it will be important for journal reviewers and editors to measure future TES reports against the standard set by these recommendations. The future research agenda will include a systematic review of forthcoming TES to evaluate how well this document is utilised, with further refinement based on the nature of outcomes observed. In addition, regulatory agencies may wish to consider the recommendations and associated issues and how these may influence their expectations from industry. This initiative and the interactive session at EULAR, Madrid 2013 with relevant stakeholders will hopefully be a springboard for further action (the outcome of the EULAR meeting is summarised in the online supplementary material).

In summary, there is a clear unmet need for a reliable approach to the reporting of TES to maximise our understanding of drug effects in chronic conditions. This initiative, its principles and resulting recommendations apply to TES for any drug in RA as well as for drugs used to treat other chronic rheumatological conditions. This document provides much needed first recommendations to ensure a transparent and standardised approach to the reporting of future TES.

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Contributors
MH, LS-F, LC and MB contributed substantially to the design, implementation and data collection of the Delphi exercises. LS-F analysed the DELPHI data. MH, LS-F, LC and MB reviewed the DELPHI data analysis before dissemination to the task force. MH wrote the paper and the supplementary materials. All authors discussed the summaries presented in the Delphi exercises, results and implications and commented on the manuscript at all stages.

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REFERENCES


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