Reviewer's report

Title: Evaluation of dose reduction vs. standard dosing for maintenance of remission in patients with spondyloarthritis and clinical remission with anti-TNF (REDES-TNF): study protocol for a randomized controlled trial

Version: 2
Date: 5 May 2015
Reviewer: Kent Johnson

Reviewer's report:

Major compulsory revision:

This is an important paper which should be published once the non-inferiority (NI) design is better defined and described. This would be aided by a biostatistical reviewer if not already done. A NI design requires, for credibility, assurance that the active control would have beat placebo, had a placebo arm been present. The manuscript notes that it is anticipated that no less than 87% of patients allocated to full-treatment will show clinical remission after one year. What is needed is a body of past studies in support of this 87% figure. The only study quoted is ref 30, a very small cohort. Short of this body of studies, justifying a NI design is difficult, as success can mean that both the test and active control were efficacious, or it can mean that the test and active control were both inefficacious. My concern is that, as written, the NI claim could be made even if the active control result was, say, 60% or even 40%. Would one make a NI claim if the full treatment result was 40% and the dose reduction result was, say, 30%?

One way out of this dilemma was used recently in the rituximab trial in ANCA-associated vasculitis trial (RAVE), a NI setting where there was virtually no literature on the effect size of the active control, cyclophosphamide. In that trial a claim of NI when the test result was numerically lower than the active control result could only be made if the active control result itself was above a certain threshold (40% in the case of the RAVE study). This design was pre-agreed upon and it provided a defence against a NI claim when, in fact, it would be likely that neither arm was efficacious (see U Specks, et al. The Open Arthritis Journal 2011.4:1-18).

I have additionally the following questions/comments:

1-In Study Objectives (p5) you say “patients with axial non-psoriatic spondyloarthritis” yet psoriasis is not an exclusion in Table 2. Please clarify.
2-Study design (p5) entry requires anti-TNF treatment for a minimum of 12 weeks then in remission for an additional 8 weeks, so 20 weeks treatment is needed. I assume all enrolees are still on anti-TNF therapy, yes? In other words, no patient has already been withdrawn from their TNF? Is this correct?
3-The proviso for three populations is confusing. One usually has the all randomized population (ITT population), and the per protocol population, and
with a NI trial both are important as is noted. If the difference between the RA and the FAS amounts to missing data, then you need a sensitivity analysis to demonstrate that the missing data are not informative.

4-You note that “in the event the model does not fit”. Please explain by what criterion this is to be made. You then say the Poisson link distribution function…will be used. Explain why.

5-There should be a “study has weaknesses” paragraph in the discussion.

6-In the discussion: Query the use of blinded assessors.

7-In the discussion: Discuss the underpowering for inferences about a specific TNF.

Stylistic suggestions

1-Avoid self-aggrandizement: E.g., in the abstract/discussion: The REDES-TNF study is a well designed and pragmatic …. I’d delete “well-designed”. Similarly throughout the manuscript.

2-Edit the entire manuscript by someone with extensive English experience. For example, The first sentence in the last paragraph is better written as: In summary, the REDES-TNF … aimed to answer the real need for evidence to support medical decisions now taken empirically.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.