Reviewer's report

Title: Botulinum neurotoxin type A in the treatment of classical trigeminal neuralgia (BoTN): study protocol for a randomized controlled trial.

Version: 3  Date: 20 July 2015

Reviewer: Joanna Zakrzewska

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This is a protocol for a randomised control trial of the use of Botulinum neurotoxin A (BT-A) in the treatment of trigeminal neuralgia (TN) which has already started.

Introduction
1. Minor: Although it is stated that BT-A has been shown to be effective it is not clear for how long this effect is present and whether it meant that other drug therapies were discontinued. Wu et al provide further details of the trial in response to a letter to the editor.
2. Major: The aim of the study should be clearly stated including whether this is a short or long term effect.

Methodology
3. Major: Given that the double blind phase starts at week 13 do the investigators estimate that the treatment effect will have worn off so patients will have had a return of pain? What if the patients are still pain free at week 12 therefore they are a responder would they receive further BT-A even though pain free?
4. Minor: Injection sites: very few of these in comparison to other studies, how are the upper branches of V3 covered? If patients have pain in all 3 divisions do they get all the injection points whereas if they have only one division pain do they get only injections for that site?
5. Major: How many investigators will be performing the injections? What experience have they had?
6. Minor: Primary outcome measure is number of pain attacks – why was this chosen rather than intensity?
7. Minor: Secondary outcomes please define HIT-6 and ADS which have never been used in TN studies and CGI. Why use SF12 – a very difficult scale to evaluate and would need to compare to population norms although is used in neuropathic pain scales. SF-36 only been used in a couple of surgical TN studies and not reported well.
8. Major: Concomitant drug therapy – the protocol states that this will be kept steady but surely the reason for use of BT-A is to reduce need for systemic drugs? How will the investigators prove that it is not the medication that has started to work or that the patients are going into a natural remission?
9. Major: Inclusion: at least an average of 3 paroxysms a day and a responder is defined as frequency reduction of 30% so how would this work in practice if a patient has only 4 paroxysms a day? What about severity as most trials suggest at least NRS of 4.

10. Major: Power calculation: the number needed for the trial is very small and it would be expected that more patients are needed in the open label phase to ensure enough are recruited even though a 20% drop out is anticipated. Would you recruit more if you cannot get enough for randomisation? A recent drug trial for TN needed around 60 in open label to get 29.

Discussion: this could include some potential problems in recruiting, whether the injections will be available after the end of the trial.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare I have no competing interests