Author’s response to reviews

Title: Treatment of Irritable Bowel Syndrome with diarrhoea using Titrated Ondansetron (TRITON): study protocol for a randomised control trial

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This is a very important study to evaluate the effectiveness and safety of ondansetron in patients with IBS-D. There are some questions need to be further clarified before final submission.

1. Please indicate why choose ondansetron as a potential drug for IBS-D. What is the main difference between currently used 5-HT3R for IBS.

Response: Alosetron was initially withdrawn and now is available in US only, through risk evaluation and mitigation strategy (REMS) and is not available in Europe. Cilansetron never came to market, while ramosetron only available in Japan, although licensed for IBS-D.

We now add to the text as shown highlighted on page 1 after the sentence
A previous meta-analysis [3] showed that the 5-hydroxytryptamine-3 receptor antagonists (5HT3RAs) alosetron and cilansetron benefitted such patients, improving stool consistency, and reducing both frequency and urgency of defaecation. However, these drugs had serious side effects, including constipation in 25% of patients and, rarely, ischaemic colitis (1 in 700). Alosetron was initially withdrawn and now is available in US only, through risk evaluation and mitigation strategy (REMS) and is not available in Europe. Cilansetron never came to market, while ramosetron, another 5-HT3 receptor antagonist is only available in Japan where it is licensed for IBS-D with several good quality trials confirming its benefit(Fukudo et al. 358-66; Fukudo et al. 953-59).

2. How to handle the side effects of ondansetron during the treatment such as constipation?

Response: This is dealt with in the section under heading Visit 3 but we agree it should be clearer.

We now add a separate sub-section headed Dose titration on page 12 under the heading intervention.

Dose titration

Since the optimum dose varies widely from 4mg alternate days up to 8mg t.d.s we will start all patients on 4mg daily and after 2 days contact them to adjust the dose, thus avoiding the complication of constipation. If stool consistency remains loose they will be asked to increase their dose in 4mg steps every 2 days up to the maximum of 8mg t.d.s. If stools become hard or there is no bowel movement on day 2 they will be asked to stop the drug for 1 day and recommence at a lower dose going from 4mg daily to 4mg alternate days. If stools still remain hard or infrequent they will be asked to reduce to 4mg every third day. In the unlikely event that their stool remains hard even at this low dose they will discontinue the trial.

3. Since it is a multiple centre study, how to allocate the patients (how many patients in each site) and the sequence of randomization should be further clarified.

Response: Thank you, we have now clarified this in the randomisation section as below:

Randomisation will be performed on a 1:1 basis to receive either ondansetron or placebo, and each patient will be allocated three bottles of trial medication, each with a unique IMP kit code. Minimisation will be used, in order to ensure treatment groups are well balanced. The stratification factors are registering site and whether the patient has undergone mechanistic assessments.
4. The methodology part should follow SPIRIT structure.

Response: Thank you we have followed the SPIRIT recommendations

5. Table one is not appropriate for publication and please follow SPIRIT style.

Response: Thank you we have revised following the SPIRIT recommendations

Reference List
