Author's response to reviews

Title: High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial

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Responses to Reviewers’ comments

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Thank you for these helpful comments. We have amended the manuscript to take them into account and provide a list of changes below. The changes are highlighted in pink in the revised manuscript.

Reviewer Abubakar

1 We have found in previous trials that some patients have spontaneous resolution of their infection between recruitment and the administration of the first drug (usually an interval of several days). The study protocol made a provision for these children, and those with a possible bacterial contribution to the diarrhoea, to be excluded from the analysis. Dr Abubakar is right to point out that we failed to specify this in the trial registration as visible on the internet, though it is in the protocol. Although we were not asked, to our recollection, to provide details of how the analysis would be conducted for the trial registration, we agree that it would have been helpful and we will do this in future. In the event, neither ITT nor per-protocol analysis showed any effect. We have included a comment on this in the Discussion (p 9).

2 The sample size was indeed calculated on the basis of a large effect. We have always believed that only large treatment effects would justify major changes in drug policy in countries like Zambia, and have set the bar high for demonstration of efficacy in trials like this. In the event, there was no suggestion of effect, as Dr Abubakar noted. We have discussed this too (p9).

3 We did not define which species of Cryptosporidium and have amended the manuscript to Cryptosporidium spp.

Reviewer Tzipori

4 We have defined the dose more clearly in the Methods and the Abstract. It was not determined as mg/kg body weight, as the dose was determined by age, but we have given an average figure for the dose adjusted for weight.

5 Dr Tzipori is quite right that it would have been interesting to determine species, and in fact a PhD student was supposed to carry this out, but very few meaningful results were obtained and this aspect of the study was abandoned after we had waited too long for these data!

6 We accept this point which is the same as number 3 above.