Author’s response to reviews

Title: Zinc for Infection Prevention in Sickle Cell Anemia (ZIPS): Study Protocol for a Randomized Placebo-Controlled Trial in Ugandan children with Sickle Cell Anemia

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Reviewer #1: This trial protocol describes a RCT to compare oral zinc supplementation with placebo in children with sickle cell anaemia in Uganda, in order to prevent severe infections. This is a well written protocol and the details of the study are clearly articulated. The authors have written the protocol in accordance with the SPIRIT guidelines, and have provided the relevant checklist. The study addresses an important topic, with potential significant benefit for patients. Overall there were no major concerns that I identified and any comments are brief and relatively minor

1. The study will use blood cultures to identify severe invasive infections / bacteraemia and and Biofire panel for viral / atypical bacterial respiratory infections - it was not 100% clear if these were being performed at site (ie in Uganda) and used for patient treatment in real time, or were being shipped back for testing in the US laboratories, or tested at local research facility or within the hospital’s own laboratories? This level of sophisticated lab testing seems unusual for a hospital in regional Uganda
Response:

Thank you for this comment. Blood cultures will be done on site, in Jinja, Uganda, for children in the study with a measured fever temperature of ≥38°C. The Jinja Regional Referral Hospital Lab has been equipped to incorporate blood culture in routine clinical care – included here is a publication detailing the capacity available within Uganda (Lamorde et al. 2018). We are able to obtain culture information within 24 hours and these can be used to confirm bacteremia to inform treatment, as needed.

Reference:

Lamorde, M., et al. (2018), 'A Cross-Cutting Approach to Surveillance and Laboratory Capacity as a Platform to Improve Health Security in Uganda', Health Secur, 16 (S1), S76-S86.

PCR testing of Nasopharyngeal (NP) swab specimens, however, for analysis of C. pneumoniae, M. pneumoniae, B pertussis and 17 viral URI pathogens, using the FilmArray™ Respiratory Panel (RP; BioFire Diagnostics, Salt Lake City, UT) – will be done on stored samples at the future time at Indiana University Health Pathology Laboratory (IUHPL) in Indianapolis, IN.

2. Stool samples were planned to be collected for possible future 'microbiome testing' - any details of at which time points these might be collected? Also at baseline at 12 months? I presume these will then be frozen?

Response:

Stool samples will be collected and cryopreserved at baseline and at 12 months and shipping to Indiana University in Indianapolis, IN for microbiome testing. We have clarified this information on Page 13, Line 321-322 – “Stool samples will also be collected at enrollment and 12-month follow-up from children who are able to provide them, and stored for future microbiome testing.”

3. Line 253: "Chlamydia pneumoniae or Mycoplasma pneumoniae" species should be italicised

Response:

Page 10, Line 253 has been revised with species names italicized