LB 5386

Re-analysis of a Sequential Three-arm Randomized Trial of AmBisome in Combination with Sodium Stibogluconate or Miltefosine, and Miltefosine Monotherapy, for African Visceral Leishmaniasis

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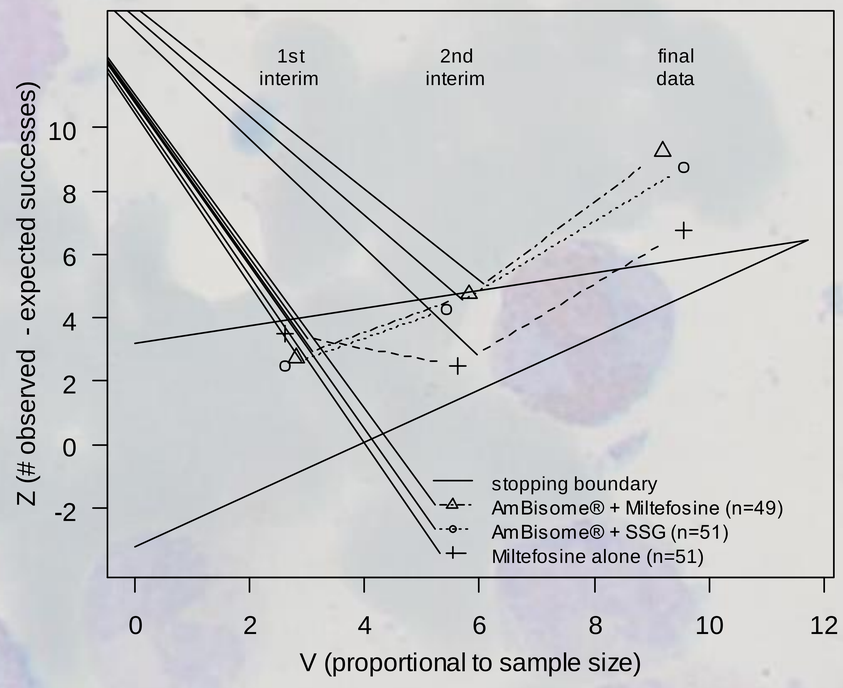
Objective: to compare alternative statistical estimation methods for the efficacy of drug regimens for visceral leishmaniasis in a sequential trial

Background: LEAP 0208 visceral leishmaniasis trial [1]

- Three arm non-comparative trial, in Kenya and Sudan
- Each arm subject to sequential stopping based on end of treatment (D28) clinical and parasitological status
- Data plotted till they cross the triangular stopping region
- Crossing upper boundary favours, crossing lower boundary does not (**Figure 1**)
- Primary endpoint was at day 28. Day 210 efficacy estimated from probability tree estimator [2]

Figure 1 Sequential stopping in the LEAP 0208 trial [1]



Analysis methods (**Table 1**) and point and interval estimates for day 210 definitive cure (**Figure 2**)

Method	Description
Maximum likelihood (ML)	Simple proportion: number cured / total Biased because does not take into account the tendency to stop on extremes
Whitehead 1st edn [3], results published [1]	Based on stochastic process theory. Pulls the ML estimates back towards the null hypothesis value (0.75) No allowance for 'over-run' or 'over-shoot' Can be calculated from the book's appendices
Liu [4]	Piecewise linear approximation to sigmoid bias function Allows for 'over-run' and 'over-shoot' Facilitates explicit calculation
Shrinkage [2]	Based on a Bayesian probit model, draws together the estimates from the different arms Rather than adjusting towards the null, this method can adjust the opposite way

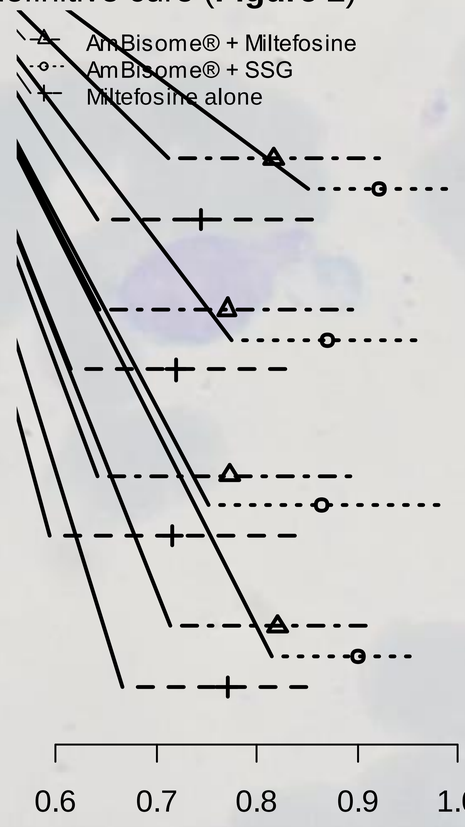


Table 2 Further methods (not in Figure 2)

Whitehead 2nd edn [5]	Takes into account non-continuous monitoring Relies on the PEST software which is not supported for current Windows versions
Jovic & Whitehead [6]	Originally designed for non-sequential multistage designs Will be applied to the 0208 trial in future work.

Conclusions

- The Liu method is favoured because it takes account of over-run and over-shoot, and is accessible
- For the 0208 trial, the Liu method gives similar results to those published based on Whitehead 1st edn

References [1] Wasunna *et al.* 2016 *PLoS NTDs,* [2] Allison *et al. Trials* 2015, [3] Whitehead J 1983 *The Design and Analysis of Sequential Clinical Trials*, Ellis Horwood, Chichester, [4] Liu 2003 in *Crossing boundaries: Statistical Essays in Honor of Jack Hall*, IMS, Beachwood, [5] Whitehead 2nd edn 1997 [6] Jovic & Whitehead 2010 *Stat Med*. Background image: Paulo Henrique Orlandi Mourao, *Leishmania* in bone marrow aspirate from liver transplant recipient.