Presentation Outline

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Background

• Visceral Leishmaniasis (VL) also known as kala-azar, is a vector-borne parasitic disease
  – Characterized by fever, substantial weight loss, swelling of the spleen and liver, and anemia

• The diagnosis and assessment of cure in VL is primarily through internal tissues aspiration
  – Painful and Invasive

• VL clinical trials generally take long to conclude
  – Patient recruitment
  – Evidence for complete cure made at least 6 months after treatment completion
Background cont...

• Clinical Trials
  – Experiments conducted in humans to compare the effect and value of intervention(s)
  – The intervention could be a therapeutic agent, devise, diagnostic, regimens or procedures

• End points
  – the clinical outcome time point which provides evidence sufficient to fully categorize clinically the effect of a treatment that would support a regulatory claim for that treatment
  – Its choice and timing is crucial to the success of any clinical trial
Model of events following VL treatment

- 0: Sick
- 1: Cure
- 2: Failure
- 3: Relapse
Background cont...

• Safety Data
  – Include both adverse events and laboratory measurements
  – Collected as part of patient monitoring to detect any safety or efficacy problems

• Group sequential designs like the triangular test (TT) have become useful in the conduct of phase II clinical trials
  – Also useful in the case of HIV-VL coinfection
  – Timely decision on whether a treatment is sufficiently effective to warrant further evaluation in phase III need to be made
Problem Statement

• Involvement in the LEAP trials and discussions with the Investigators led to interest in the research questions and need to address them for future trials;
  – Diagnosis and assessment of VL final cure
  – Timing for final cure assessment in VL
  – Analysis of final cure following TT
  – Reporting & Analysis of safety data for VL
Objectives

• Develop a predictive model based on clinical signs & symptoms of VL in assessment of final cure as an alternative to parasitology

• Estimate the optimal timing for final cure assessment post end of treatment in VL patients

• Develop alternative analysis approach for final cure (secondary endpoint) following the TT design

• Devise new methods for the design, analysis and reporting of secondary endpoint markers for VL
Methodology

• Multi-state models
• Logistic regression
• Analysis following TT
• Repeated measures analysis
• Survival Analysis
Timing for Final Cure

• Look at the different event outcomes in VL after treatment administration
  – Cure, failure and relapse considered as transient states.
  – Death is also an event but for purposes of this analysis will be excluded as it is an absorbing state.

• We will follow a Markov model with statistical model specification via transition intensities and likelihood inference as in Andersen et al
Final Cure Assessment

• Tabulate signs and symptoms of VL by final cure status
• Logistic regression to build a multivariate model
• Prepare sensitivity, specificity, positive predictive value (PPV) & negative predictive value (NPV) tables based on this approach
• Validate the algorithm proposed by Rahmen et al on the LEAP data
Analysis following TT

- Use LEAP 0208 data set to validate what is proposed by Omollo et al for final cure
  - Error rate and power
- Simulate trial data sets under variable assumptions for parameters $p_0$ & $p_a$ for both approaches.
  - Omollo et al & Liu et al
- Estimate final cure, standard error and the confidence intervals.
Markers for Efficacy

• Use repeated measures analysis techniques based on the assumptions of normality, random selection and homogeneity of variance

• Model the change during hospitalization for each parameter

• Survival analysis techniques
  – Frailty models for competing risks if any
Analyses Soft wares

• STATA
• R
• Familiar with both soft wares
• Strengthen statistical computing skills using both
Conclusion

• Overall
  – Improve knowledge and the application of statistical rigor in the methods for design and analysis of VL trials

• Come up with a suitable model in the assessment of final cure in the absence of parasitology.

• Estimate the optimal timing for final cure assessment post end of treatment in VL patients
Conclusion cont...

• A better understanding of the methodological issues in sequential designs particularly the TT in phase II trials;
  – Analysis of final cure in VL.

• Improved methods for the design, analysis and reporting of secondary endpoint markers for VL
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• LEAP
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