Definition and Analysis of Endpoints in Clinical Trials for Visceral Leishmaniasis:

PhD Upgrade

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Presentation Outline

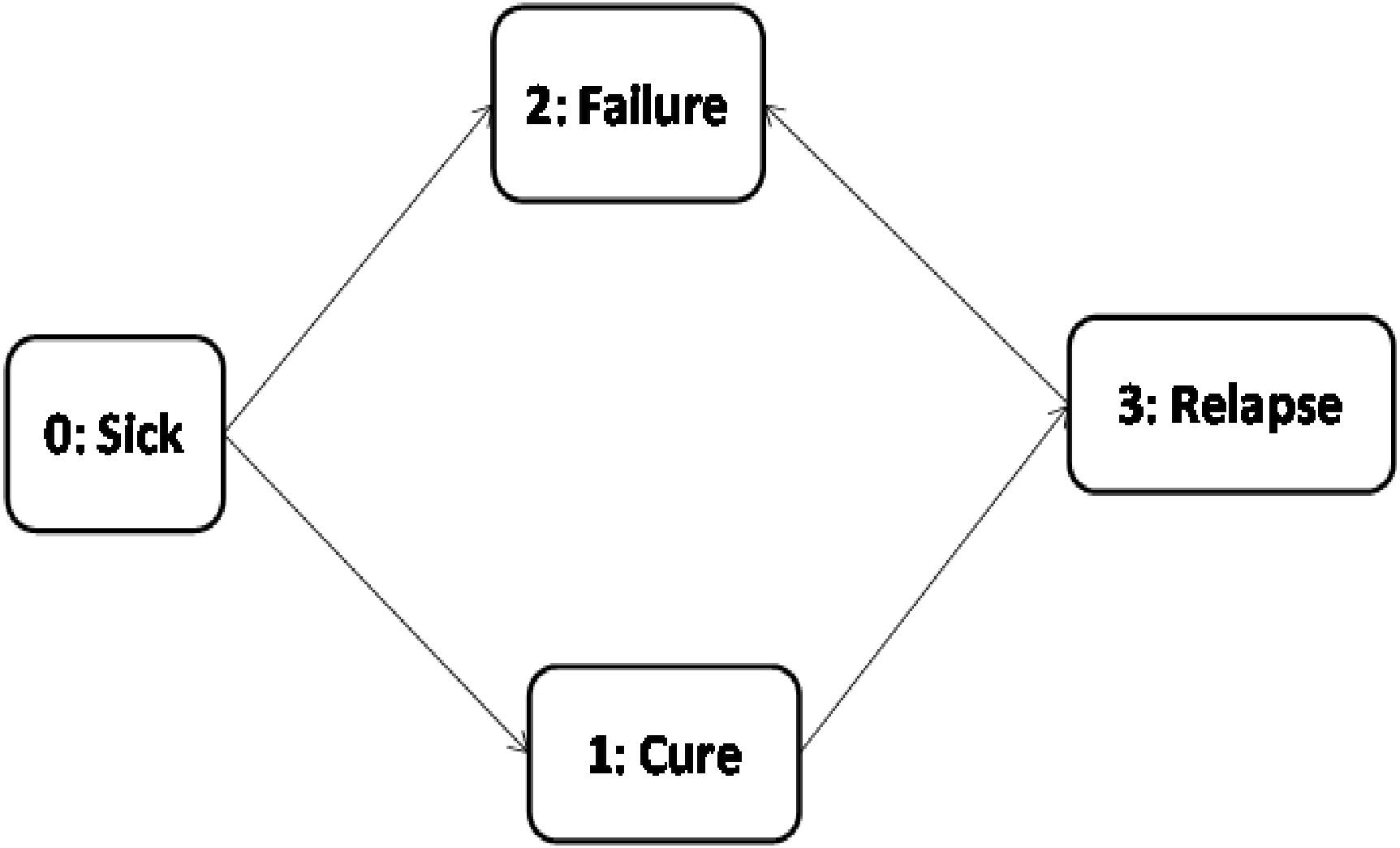
- Background
- Problem Statement
- Objectives
- Methodology
- Conclusion

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…

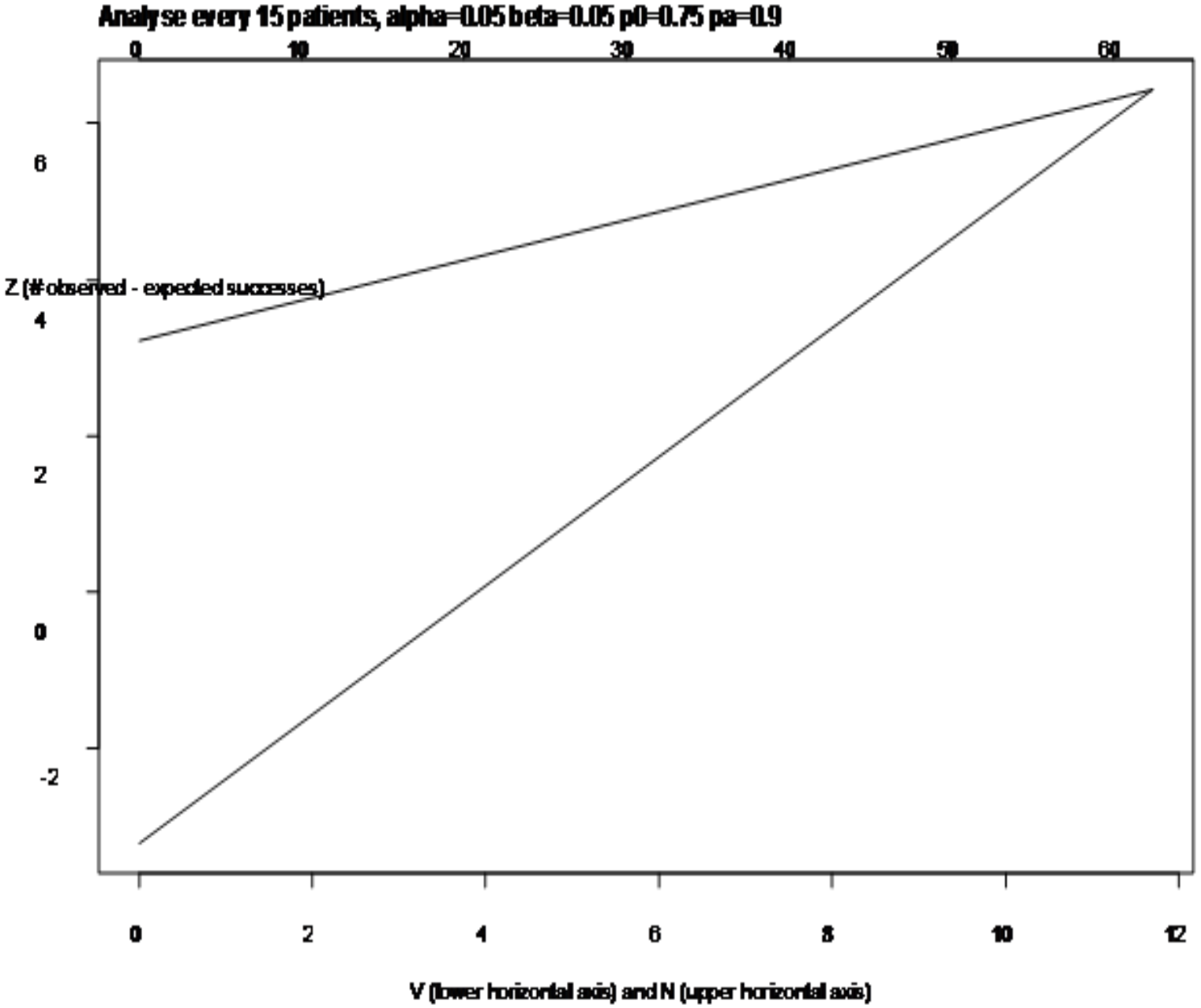
- Clinical Trials
  - Experiments conducted in humans to compare the effect and value of intervention(s)
  - The intervention could be a therapeutic agent, devise, diagnostic, regimens or procedures
- End points
  - the clinical outcome time point which provides evidence sufficient to fully categorize 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

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


Analyse every 15 patients, alpha=0.05 beta=0.05 p0=0.75 pa=0.9
0
10
20
30
40
50
60
6
4
2
0
-2
Z (# observed - expected successes)
0
2
4
6
8
10
12
V (lower horizontal axis) and N (upper horizontal axis)

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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