METHODOLOGY OF CLINICAL TRIALS AIMED AT ASSESSING INTERVENTIONS FOR CUTANEOUS LEISHMANIASIS

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1st International Conference on Cutaneous Leishmaniasis,

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Lack of Standardization to conduct clinical trials

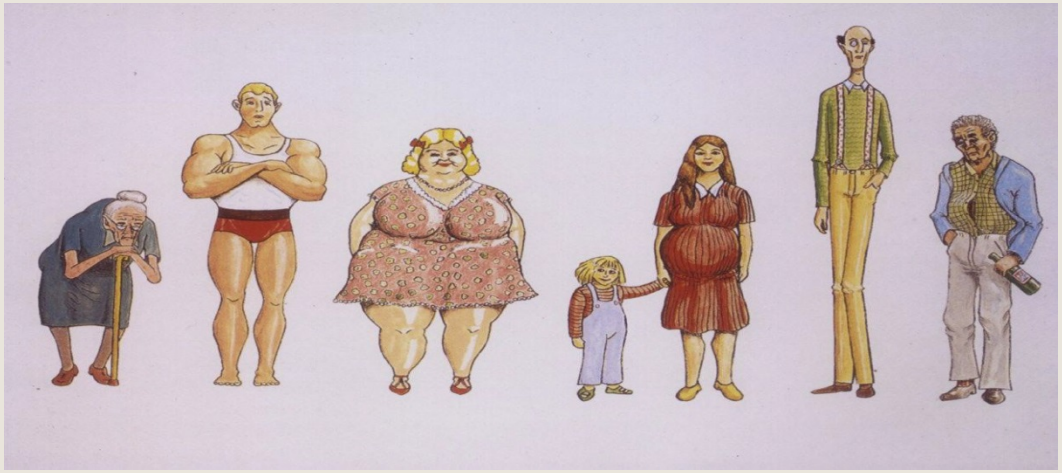
- The inadequacies of trials of different treatments of CL has been documented by two WHO-supported Cochrane systematic reviews in both NW and OW

- The systematic reviews revealed critical issues related to:
  - Adequacy of study design (Selection on appropriate controls, endpoints, outcome measures, follow-up times)
  - Trial execution (randomization, allocation concealment, blinding)
  - Analyses and reporting

Where are the challenges?

- Different *Leishmania* species
- Different clinical presentations
- Intrinsic differences in *Leishmania* species sensitivity to drugs
- Different natural history of the disease
- Variable treatment responses
- Variability in human subjects

One size don't fit all



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Why there is a need for a standard methodology to assess intervention for CL?

- T Improving the quality of studies and harmonizing protocols will make meta-analysis more informative and thus strengthen evidence for recommendations on treatment and case management
- High-quality clinical trials are essential to determine which therapeutic interventions can confidently be recommended for treating which form of CL.
- Improving the quality of studies and harmonizing protocols will make meta-analysis more informative and thus strengthen evidence for recommendations on treatment and case management.
- Conducting inadequate trials may lead to inappropriate conclusion, is both unethical and an inefficient use of the limited resources available for research into this neglected disease

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PLOS | NEGLECTED TROPICAL DISEASES

Methodology of Clinical Trials Aimed at Assessing Interventions for Cutaneous Leishmaniasis

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Objectives

- To provide clinical investigators with guidance for the design, conduct, analysis and report of clinical trials of treatments for CL, recognizing the complexity of the disease

- To enhance the capacity for high-quality trials that fulfil the requirements of Good Clinical Practice standards.

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Content:

- Defining trial participants
  - Inclusion / Exclusion criteria
- Endpoints – outcomes measures and therapeutic assessments
  - Efficacy parameters
  - Safety parameters
- Study design
- Study registration and reporting
- Complying with regulations

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Inclusion / exclusion criteria

Study Phase	Topical Treatment			Systemic Treatment		
Criteria	**Phase II**	**Phase III**	**Phase IV**	**Phase II**	**Phase III**	**Phase IV**
Gender	Male & Female	Male & Female	Male & Female	Male & Female	Male & Female	Male & Female
Women of child-bearing age[1]	No	Yes/No	Yes	No	No	Yes/No
pregnant or breastfeeding[2]	No	No	Yes	No	No	Yes/No
Age	Adults	>5 YO	>2 YO[3]	Adults	>5 YO	All
Type of lesion[4]	Ulcers	All	All	Ulcers	All	All
Number of lesions	1-2	1-5[5]	1-5[5]	1-2	All	All
Size of lesions[6]	≤30 mm	≤30 mm	≤30 mm	≤30 mm	All	All
Localization	Trunk, arms, legs	Trunk, arms, legs, face[7]	Trunk, arms, legs, face[7]	Trunk, arms, legs	All	All
Duration of lesion[8]	≤3 months	≤6 months	≤6 months	≤6 months	≤6 months	≤6 months
Parasitological confirmation	Yes	Yes	Yes	Yes	Yes	Yes
Baseline lab tests, ECG, etc[9].	Yes/No	No	No	Yes	Yes	No
Informed consent	Yes	Yes	Yes	Yes	Yes	Yes

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Endpoint - outcome measures and therapeutic assessment

The protocol must clearly identify primary and secondary endpoints for efficacy and safety

Endpoint must be both accurate and robust

When cure is defined (Time frame)

Avoid multiple, diffuse endpoints

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Efficacy parameters

- Parasitological examination at the end of therapy correlates poorly with the final treatment outcome
- Cure should be defined on clinical parameters
- *Ideally*, a clinically accurate definition would include five parameters:
    1. area of ulceration when present
    2. area of induration
    3. thickness of induration
    4. colour of infiltrated border
    5. degree of scaring as a proxy for patient's quality of life.
- Ulcer surface area should be the primary efficacy endpoint whenever possible
- For non-ulcerated lesions induration area should be used to measure treatment efficacy

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Efficacy Assessment

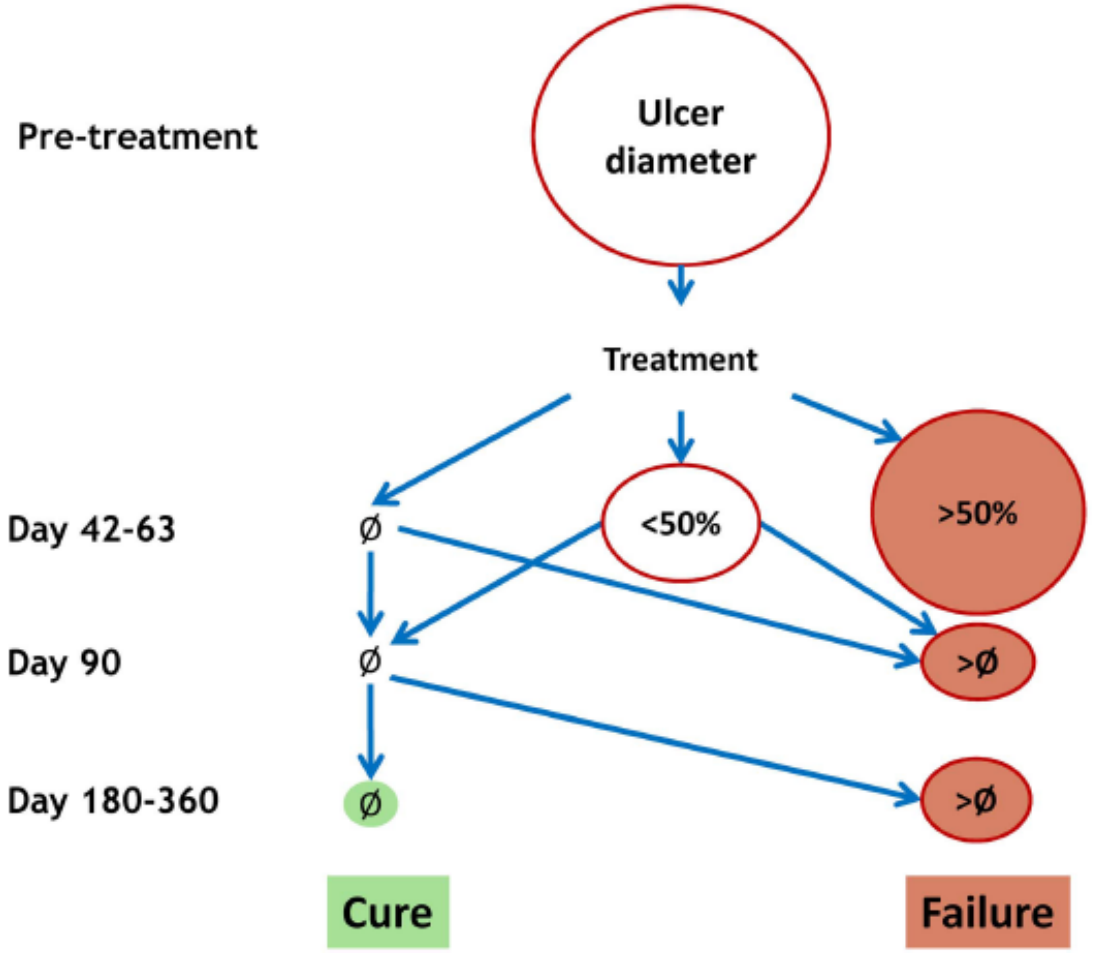

Figure 3. Decision tree for the assessment of treatment outcome. Ø = complete re-epithelialisation; <50% = less than 50% of the initial size; >50% = greater than 50% of the initial size.
doi:10.1371/journal.pntd.0002130.g003

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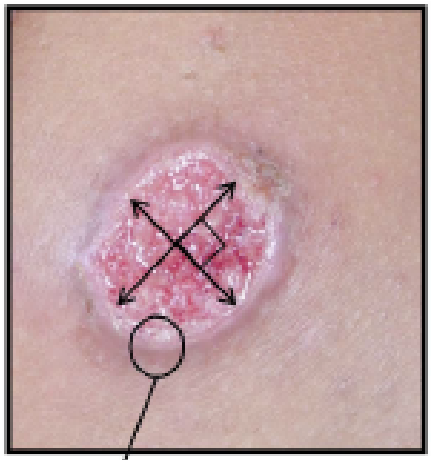
How to measure a lesion

Ulceration area
Skin area devoid of epidermis and part of the dermis

Calculated area: product of ulcer 2 longest diameters measured using a ruler or caliper

Fairly objective and reproducible

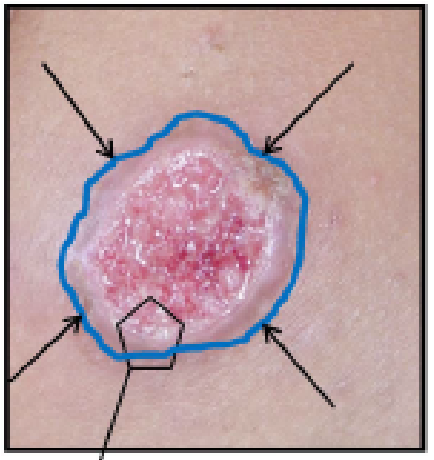


Color of the border
Highly clinically informative (on light-colored skin)
Highly subjective

Induration area
Skin area with increased

Calculated area: product of two induration diameters measured by the ball-pen technique

Less objective and reproducible



Height of the induration (z)
Highly clinically informative
No appropriate tool to measure it

Figure 2. Measuring lesions.
doi:10.1371/journal.pntd.0002130.g002

Safety parameters

- In a clinical trial, all events, whether considered drug-related or not, should be reported
- It is important to report and grade events using standard nomenclature and criteria of severity
- Definitions
  - Adverse Event (AE)
  - Adverse Drug Reaction (ADR)
  - Treatment-Emergent Adverse Event (TEAE)
  - Serious Adverse Event (SAE)
- Grading
  - For grading intensity of events (mild, moderate, severe, very severe), use standardised criteria, e.g. the Common Terminology Criteria for Adverse Events

Study registration and reporting

- All trials should be registered (see: the WHO International Clinical Trials Registration Platform (WHO-ICTRP) and reported, whether the results are favourable, unfavourable or inconclusive both for ethical and scientific reasons.

- Traditionally, the importance of negative results has been underestimated both by researchers and publishers

- The Consolidated Standards of Reporting Trials (CONSORT) checklist (study design, analysis and interpretation) and flow diagram (patient attrition throughout the study) should be followed.

- All major journals today do not publish papers on trials that have not been registered and do not follow the CONSORT guidelines. http://www.consort-statement.org/

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Complying with regulations

- Clinical trials must be conducted in accordance with current international standards of Good Clinical Practices.
- GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.
- Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
- When GCP standards are followed, the quality of data from clinical trials is adequate to make informed clinical and policy decisions.

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Thank you

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