METHODOLOGY OF CLINICAL TRIALS AIMED AT ASSESSING INTERVENTIONS FOR 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
Why there is a need for a standard methodology to assess intervention for 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.

- 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.
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.
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
<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Topical Treatment</th>
<th>Systemic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td>Gender</td>
<td>Male &amp; Female</td>
<td>Male &amp; Female</td>
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<tr>
<td>Women of child-bearing age&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
<td>Yes/No</td>
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<tr>
<td>pregnant or breastfeeding&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Age</td>
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<td>&gt;2 YO&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Type of lesion&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Ulcers</td>
<td>All</td>
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<tr>
<td>Number of lesions</td>
<td>1-2</td>
<td>1-5&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Size of lesions&lt;sup&gt;6&lt;/sup&gt;</td>
<td>≤30 mm</td>
<td>≤30 mm</td>
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<td>Localization</td>
<td>Trunk, arms, legs</td>
<td>Trunk, arms, legs, face&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>Duration of lesion&lt;sup&gt;8&lt;/sup&gt;</td>
<td>≤3 months</td>
<td>≤6 months</td>
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<td>Parasitological confirmation</td>
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<td>Yes</td>
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<td>Baseline lab tests, ECG, etc&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Yes/No</td>
<td>No</td>
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<td>Informed consent</td>
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</table>
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.
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 scarring 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.
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

Drugs for Neglected Diseases initiative
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

**Induration area**
Skin area with increased

- Calculated area: product of two induration diameters measured by the ball-pen technique
- Less objective and reproducible

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

- 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/
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.
Thank you