Designing and Reporting Clinical Trials on Treatments for Cutaneous Leishmaniasis

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Cutaneous leishmaniasis is considered to be one of the most neglected and serious parasitic infectious skin diseases in many developing countries. We have assessed the design and reporting of randomized, controlled trials evaluating treatments included in 2 Cochrane systematic reviews on cutaneous leishmaniasis. The analysis of the methodological quality identified some potential bias that can make it difficult to determine whether truly effective therapies exist for this disease. We found important weaknesses in the adequacy and transparency of randomization, loss of participants, causative *Leishmania* species, outcome measures, and follow-up times. Given these distorting effects on the evidence base, we propose guidelines for authors who wish to conduct clinical trials aimed at the development of effective therapies in cutaneous leishmaniasis. The recommendations in this report will hopefully deserve the attention of the World Health Organization and assist in the planning and prioritization of global strategies for improving the interpretation and replication of clinical research on cutaneous leishmaniasis.

Cutaneous leishmaniasis (CL) is a current serious public health and social problem that is on the rise in many developing countries and is also increasingly seen in immigrants, military personnel, humanitarian aid workers, and travellers from endemic areas [1]. CL is a disfiguring and stigmatizing disease affecting the skin and mucous membranes and is caused by parasites (*Leishmania*) that are widespread in the Old World (Europe, Asia, and Africa) and America [2]. The World Health Organization has promoted global policies for its control [3] and is now prioritizing the delivery of drugs, which are currently available for the reduction of morbidity and disability in low-income countries [4]. However, to improve existing control of disease, evidence for the effectiveness of different treatment strategies is needed.

Many different treatments for CL have been described. Pentavalent antimonial drugs are the main first-line therapeutic agents worldwide, despite their toxicity. Although other drugs and treatment modalities have been used with varying success, the present and future strategies for the control of CL are centered in new treatments and their availability in rural and poorer areas [5]. Therefore, future trials of different anti-*Leishmania* drugs, compared with placebo, in self-healing forms of leishmaniasis or antimony-alternative treatments, compared with traditional first-line antimonials, in the complicated forms need to be designed in such a way to guarantee the discernment of efficacy between treatments.

The rise of evidence-based medicine has highlighted the use of systematic reviews of the best evidence as fundamental tools for health care. The quality of randomized clinical trials (RCTs) is essential to determine what therapeutic interventions work and are safe in people with CL. Special attention must be drawn to the design, conduct, analysis, clinical relevance, and reporting of the trials; otherwise, the conclusions derived from low quality and biased trials may remain elusive [6].

DESCRIPTION OF THE SOURCES OF BIAS FROM EXISTING RCTS ON TREATMENTS FOR CL

This article offers some guidelines based on the assessment of the quality of design and reporting of RCTs evaluating treatments for CL from 2 Cochrane systematic reviews on treatments for Old World and American CL (Table 1) [7, 8].

Selection bias. In RCTs, selection bias refers to the possible differences between baseline characteristics in the groups under comparison. Investigators should devote appropriate resources for allocating

Received 27 January 2010; accepted 11 May 2010; electronically published 12 July 2010.

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Clinical Infectious Diseases 2010; 51(4):409–419

1058-4838/2010/5104-0007$15.00
DOI: 10.1086/655134

Table 1. Sources of Risk for Bias in Randomized Clinical Trials Investigating Treatments for Cutaneous Leishmaniasis (CL)

Source	Percentage of trials	
	Old World CL	American CL
Sequence generation		
Adequate	35	33
Unclear	65	67
Allocation concealment		
Adequate	12	13
Unclear	88	87
Blinding		
Single blinded	8	13
Double blinded	40	38
Not blinded	27	33
Unclear	25	18
Withdrawals		
No dropouts	31	38
<10%	27	40
10%–25%	23	20
>25%	19	3
Original assigned group analyses		
Yes	42	47
No	58	53

interventions to participants on the basis of some chance (random) process and report their methods clearly [9], avoiding nonrandom methods of allocation. Adequate generation of the randomization sequence takes little effort and enhances scientific accuracy and credibility. However, randomization persists as the least-understood feature of trials. All RCTs included in the Cochrane reviews [10–102] stated or implied that treatment allocation was randomized; however, only 35% (18 of 52) and 33% (13 of 40) of studies in the Old World CL review and American CL review, respectively, clearly stated an adequate randomization method.

Proper randomization also rests on adequate allocation concealment, a process that keeps clinicians and participants unaware of upcoming assignments by preventing foreknowledge of the forthcoming allocations. Inadequate allocation concealment leads to either an underestimation or an overestimation of the treatment effect under investigation [103]. Even allocation concealment is an essential step to secure strict implementation of that schedule of random assignments; however, only 12% (6 of 52) of studies in the Old World CL review and 13% (5 of 40) of studies in the American CL review had an adequate reporting of the allocation concealment.

Blinding assessment. In clinical research, blinding is used to eliminate the risk of subjectivity in the assessment [104]. Success of blinding is a fundamental issue in many clinical trials. Forty percent (21 of 52) of RCTs included in the Old World CL review were double blinded. Thirty eight percent (15 of 40) of RCTs included in the American CL review were double blinded. Some interventions might be difficult to blind; however, 25% (13 of 52) and 18% (7 of 40) of studies in the Old World and American CL reviews, respectively, did not address blinding.

Attrition bias. Attrition bias is caused by a selective loss of participants (eg, withdrawals, dropouts, and protocol deviations) from the population that was initially selected. This bias can produce a deviation of the measure of the effect of intervention from its true value because of different rates of loss of participants between the intervention and the comparison group. To avoid attrition bias, an analysis assuming that missing data represent treatment failures is recommended [105].

Losses to follow-up were comparable in the Old World and American CL review, although in both cases, the majority of studies only assessed participants who completed treatment. Losses to follow-up occurred in 69% (36 of 52) of studies in the Old World CL review, and 83% (30 of 36) of studies did not carry out original assigned group analyses. Losses to follow-up occurred in 63% (25 of 40) of the studies in the American CL review, and 76% (19 of 25) of studies did not perform original group analyses.

A further important step in the study design is the calculation of the sample size; otherwise, the outcomes from studies with inadequate sample sizes are likely to be imprecise or provide false negatives. Only 25% (13 of 52) and 18% (7 of 40) of RCTs in the Old World and American CL review, respectively, calculated the sample size.

Overall, we found 3 trials in the Old World CL [12, 28, 29] and 2 trials in the American CL review [89, 99] that fulfilled randomization, allocation concealment, blinding, and group analyses adequately. In both Cochrane systematic reviews, additional information about the following 3 key elements of the study question that could influence the quality of the RCT was also analyzed: participants (Table 2), interventions (Tables 3 and 4), and outcomes (Table 5).

Participants. Most of the RCTs recorded baseline characteristics of participants and defined the inclusion and exclusion criteria. In the American CL review, one-third of the included RCTs recruited male subjects only. None of the included RCTs in either of the reviews reported participants with immunodeficiency, coinfections with human immu-

Table 2. Description of Participants in Randomized Clinical Trials (RCTs) Investigating Treatments for Cutaneous Leishmaniasis (CL)

Descriptive criteria	Old World CL	American CL
Sex of participants		
RCTs describing sex, %	69	73
Male:female ratio	1.30:1	5.43:1
Only male participants, proportion (%) of RCTs	2/52 (4)	11/40 (28)
Duration of follow-up	3 weeks to 1 year	28 days to 7 years
Reported baseline characteristics of participants, proportion (%) of RCTs	42/52 (81)	39/40 (97)
Reported inclusion/exclusion criteria, proportion (%) of RCTs		
No/no	2/52 (4)	2/40 (5)
Yes/no	4/52 (8)	13/40 (33)
Yes/yes	46/52 (88)	25/40 (63)
Compliance assessment		
Stated compliance assessment, proportion (%) of RCTs	13/52 (25)	7/40 (18)
Reported compliance assessment, proportion (%) of RCTs	1/52 (2)	1/40 (4)
Reported *Leishmania* species involved, proportion (%) of RCTs		
Not mentioned	12/52 (23)	4/40 (10)
Assumed	20/50 (38)	9/40 (23)
Checked	20/52 (38)	27/40 (68)

nodeficiency virus, or use of immunosuppressants. In the Old World CL review, one-third of the included RCTs analyzed the species of *Leishmania* involved; the rest either assumed them or did not mention them at all. In the American CL review, the majority of RCTs analyzed *Leishmania* at a species level, and only one-third of them either assumed or did not report species at all. The RCTs included in the Old World CL review were mainly conducted in the Far or Middle East (especially in Iran), except for 3 that were conducted in Africa and 1 in Turkey. The species involved were *Leishmania major* or *Leishmania tropica*. None of the studies recruited participants infected with *Leishmania aethiopica* or *Leishmania infantum*, which are prevalent in Ethiopia and the Mediterranean, respectively. In the American CL review, RCTs were mainly conducted in Central and South America (especially in Brazil and Colombia), except for 2 that were conducted in United States and 1 in Edinburgh, United Kingdom. These latter 3 studies recruited active-duty military personnel that contracted leishmaniasis in endemic areas when deployed abroad.

Interventions. Few treatments for Old World and American CL have been well evaluated in RCTs. There was a complete absence of evidence on intramuscular pentamidine and topical amphotericin B in Old World CL, whereas there was no or little evidence for oral (antifungals and antibiotics) and local treatments, such as photodynamic therapy, laser, cryotherapy treatments, or alternative therapies, for American CL. In addition, there have been no trials involving the use of wound-healing management or alternative supportive therapies versus drug interventions for Old World and American CL.

Outcomes. It was not possible to find a general measure to define efficacy of an intervention. This resulted in heterogeneity of the outcome measures, which in turn hampered the possibility of a meta-analysis. The primary outcome for the Cochrane reviews was considered to be the percentage of participants "cured" at 3 months after the end of treatment, defined as the absence of all inflammatory signs (skin edema and/or hardening) and complete scarring or repair of ulcerative lesions [7, 8]. Only one-third of studies in the Old World CL review and over one-half in the American CL review reported this primary outcome. Outcomes were always recorded by physicians, and none of the included studies assessed degree of functional deterioration, quality-of-life, or aesthetic impairment, although some strains may cause extensive skin damage and disfigurement.

GUIDELINES FOR DESIGNING AND REPORTING RCTS ON TREATMENTS FOR CL

For the execution of a properly designed RCT aimed at the development of effective therapies in CL, it is necessary to establish standard clinical trial designs, rigorous peer review in journals, and to enhance the capacity for high quality trials. Given the gaps and potential bias found in the design and reporting of current clinical trials, we propose guidelines for authors who wish to conduct clinical trials on treatments for CL (Table 6). There are other valid and desirable reasons for conducting good RCTs on treatments for CL in developing countries because they can help with the development of local capacities and benefit populations with care

Table 3. Geographical Distribution and *Leishmania* Species in Randomized Clinical Trials on Treatments for Old World Cutaneous Leishmaniasis

Geographic area, country, species	Intervention	Year of publication and reference	Species determination
Africa			
Sudan: *Leishmania major*	PR plus urea vs placebo	1995 [19]	+++
Tunisia: *L. major*	Berelin vs Savlon	1992 [39]	++
	il MA vs placebo	1999 [20]	++
Far or Middle East			
Turkey: *Leishmania tropica*	Topical PR plus MBCL vs oral ketoconazole	1997 [52]	++
Iran			
L. major and *L. tropica*	Oral ketoconazole vs il MA	2001 [57]	+++
	Topical ketoconazole vs placebo	2003 [44]	+++
	PR plus urea vs placebo	1995 [14]	++
	Topical herbal extract Z-HE plus placebo vs im MA plus placebo	1999 [62]	++
	Oral azithromycin vs im MA	2007 [38]	++
L. major	Oral itraconazole vs placebo	1996 [42]	+++
	Topical garlic cream vs placebo	2000 [30]	+++
	Oral AL plus im MA vs im MA	2002 [43]	+++
	2-week vs 4-week topical PR	2003 [15]	+++
	Oral itraconazole vs placebo	2005 [47]	+++
	Topical PR vs im MA	2005 [61]	+++
	Topical PDT vs topical PR plus MBCL vs placebo	2006 [18]	+++
	Oral pentoxifylline plus im MA vs im MA plus placebo	2006 [54]	+++
	Oral miltefosine vs im MA	2007 [41]	+++
	Topical PR plus urea vs il MA	2003 [27]	++
	il zinc sulphate vs il MA	2004 [32]	++
	il zinc sulphate vs il MA	2005 [28]	++
	Topical PR vs placebo	2005 [33]	++
	il HSCS vs il MA	2006 [55]	++
NR	il MA plus cryotherapy vs il MA alone vs cryotherapy alone	2004 [16]	+
	CO_2 laser vs im MA	2004 [17]	+
	il MA vs combination triple therapy (PR plus urea cryotherapy and il MA)	2004 [48]	+
	Topical trichloroacetic acid vs il MA	2006 [49]	+
	Cryotherapy vs cryotherapy plus il MA vs il MA	2006 [58]	+
	Heating vs il MA	2007 [56]	+
	Topical honey plus il MA vs il MA	2007 [51]	+
L. tropica	Oral AL vs im MA vs Oral AL plus im MA	2002 [26]	++
	Topical imiquimod plus im MA vs im MA plus placebo	2006 [29]	++
Pakistan			
L. tropica	im MA vs im MA plus il MA vs no treatment	2008 [45]	+++
NR	Oral AL vs SSG injections	2001 [40]	+
	Weekly il MA vs fortnightly il MA	1999 [46]	+
Saudi Arabia			
L. major	Topical clotrimazole vs topical miconazole	1995 [37]	+++
	Oral fluconazole vs placebo	2002 [12]	+++
	il MA vs im MA	1997 [11]	++
NR	Oral rifampicin vs placebo	2006 [34]	+
India: *L. tropica*	Oral rifampicin vs placebo	2000 [35]	+++
	Oral rifampicin plus omeprazol vs placebo	2006 [36]	+++
	Oral itraconazole vs no treatment	1990 [22]	++
	Oral dapsone vs placebo	1991 [23]	++
	Oral itraconazole vs oral dapsone vs placebo	1992 [24]	++
	Oral itraconazole vs placebo	1996 [25]	++
Kuwait			
L. major and *L. tropica*	Oral itraconazole vs placebo	1991 [10]	++
NR	Ketoconazole 600 mg/6 weeks vs ketoconazole 800mg/6 weeks	1995 [13]	+
	il Zinc sulphate vs il HSCL vs il SSG vs no treatment	1997 [59]	++
	Doses of oral zinc sulphate 2.5, 5, and 10 mg/kg vs no treatment	2001 [60]	
	il MA vs il IFN-γ	1991 [31]	+++
	Oral fluconazole vs placebo	2005 [21]	
Afghanistan: *L. tropica*	il SSG vs im SSG vs thermotherapy	2005 [53]	+++

NOTE. AL, allopurinol; IFN, interferon; il, intralesional; im, intramuscular; MA, meglumine antimoniate; MBCL, methylbenzethonium; NR, not reported; PDT, photodynamic therapy; PR, paromomycin; SSG, sodium stibogluconate; HSCS, hypertonic sodium chloride; +, no specification of *Leishmania* species; ++, assumed *Leishmania* species; +++, checked *Leishmania* species.

Table 4. Geographical Distribution and *Leishmania* Species in Randomized Clinical Trials on Treatments for American Cutaneous Leishmaniasis

Geographic area, country, species	Intervention	Year of publication and reference	Species determination
Deployed military personnel			
Belize (United Kingdom): *Leishmania braziliensis* and *Leishmania mexicana*	iv aminosidine vs iv SSG	1994 [77]	+++
Panama and Brazil (United States)			
L. braziliensis, Leishmania chagasi, and *L. mexicana*	Different doses and regimens of iv SSG	1985 [91]	+++
L. braziliensis and *L. chagasi*	10 mg/kg vs 20 mg/kg iv SSG	1987 [69]	+++
Central America			
Panama			
Leishmania panamensis	im SSG vs im MA	1987 [93]	+++
L. panamensis and *L. mexicana*	Oral ketoconazole vs im MA vs placebo	1990 [94]	+++
Guatemala			
L. braziliensis and *L. mexicana*	Heat vs im MA	1990 [84]	+++
	Oral ketoconazole vs iv SSG vs placebo	1992 [85]	+++
	IFN-γ plus iv MA vs iv MA plus placebo vs iv MA	1994 [65]	+++
	Oral miltefosine vs placebo	2004 [100]	+++
NR	Topical PR plus MBCL vs placebo	2001 [66]	+
Honduras: *L. chagasi* and *L. mexicana*	Topical PR vs placebo	1997 [89]	+++
El Salvador: *L. braziliensis*	Oral AL vs iv MA	1997 [73]	+++
South America			
Brazil			
L. braziliensis	im pentamidine isethionate vs im aminosidine sulphate vs im MA	1996 [72]	+++
	Different doses of iv MA	1997 [90]	+++
	GM-CSF plus iv SSG vs iv SSG plus placebo	1999 [63]	++
	sc vaccine plus im MA vs im MA plus placebo	2002 [84]	++
	GM-CSF plus iv MA vs iv MA plus placebo	2004 [95]	++
	Heat vs iv MA	2006 [81]	++
	Oral pentoxifylline plus iv SSG vs placebo plus iv SSG	2007 [83]	++
NR	Different doses of iv MA	1991 [74]	+
Peru			
L. braziliensis	28-day vs 40-day iv SSG	1994 [75]	+++
	iv pentamidine isethionate vs iv MA	2005 [64]	+++
	im aminosidine sulphate vs iv MA	2007 [80]	++
L. braziliensis, Leishmania peruviana, L. mexicana, and *Leishmania amazonensis*	Topical imiquimod vs topical imiquimod plus iv MA vs iv MA	2007 [67]	++
NR	Oral AL plus iv SSG vs iv SSG	1997 [79]	+
L. braziliensis and *L. peruviana*	Topical imiquimod plus im MA vs im MA plus placebo	2005 [82]	++
Venezuela: *L. braziliensis*	Vaccine vs im MA	1987 [70]	+++
	Vaccine vs im MA vs BCG alone	1989 [71]	+++
Colombia			
L. panamensis	Oral AL vs oral AL plus iv MA vs iv MA vs no treatment	1992 [85]	+++
	Different regimens iv or im aminosidine sulphate	1994 [96]	+++
	Oral AL plus iv SSG vs iv SSG	1997 [86]	+++
	Topical WR279396 vs placebo	2002 [98]	+++
	Generic and branded im SSG vs im MA	2004 [99]	+++
L. braziliensis and *L. panamensis*	Oral AL vs im MA vs placebo	1997 [102]	+++
	10-day vs 20-day im MA	2001 [92]	+++
L. braziliensis	Different regimens of topical PR-MBCL plus iv MA vs iv MA plus placebo vs iv MA alone	1998 [97]	+++
	Oral miltefosine vs im MA	2008 [101]	++
L. braziliensis and *L. mexicana*	Oral miltefosine vs placebo	2004 [100]	+++
Bolivia			
L. braziliensis	Oral miltefosine vs im MA	2008 [101]	++
L. panamensis	Generic and branded im SSG vs im MA	2004 [99]	+++
NR	Topical PR plus MBCL vs topical PR plus UR vs im MA	2004 [68]	+
Ecuador: *L. panamensis, Leishmania guyanensis, L. braziliensis,* and *L. mexicana*	Oral AL plus probenecid vs im SSG vs no treatment	1999 [76]	+++
Argentina: *L. braziliensis*	Oral azithromycin vs im MA	2007 [78]	+++

NOTE. AL, allopurinol; GM-CSF, granulocyte macrophage colony-stimulating factor; BCG, Bacille Calmette-Guérin; IFN, interferon; il, intralesional; im, intramuscular; iv, intravenous; MA, meglumine antimoniate; MBCL, methylbenzethonium; NR, not reported; PR, paromomycin; sc, subcutaneous; SSG, sodium stibogluconate. +, no specification of *Leishmania* species; ++, assumed *Leishmania* species; +++, checked *Leishmania* species.

Table 5. Reporting of Outcomes in Randomized Clinical Trials Investigating Treatments for Cutaneous Leishmaniasis (CL)

Outcomes	Proportion (%) of trials	
	Old World CL	American CL
Primary outcome: cure at 3 months of follow-up		
All	16/52 (31)	25/40 (63)
Reported primary outcome as percentage of lesions	3/52 (6)	NR
Secondary outcomes		
Speed of healing	7/52 (13)	10/40 (25)
Duration of remission and percentage of patients with treated lesions that recur within 6 months and 1, 2, and/or 3 years	13/52 (25)	16/40 (40)
Degree of functional and aesthetic impairment	NR	NR
Prevention of scarring	8/52 (15)	NR
Quality of life	2/52 (4)	NR
Adverse effects	48/52 (92)	34/40 (85)
Tertiary outcomes		
Change in ability to detect *Leishmania* through PCR or other methods	NR	NR
Emergence of resistance[a]	NR	NR
Microbiological or histopathological cure of skin lesions	12/52 (23)	3/40 (8)
Development of cell-mediated immunity	NR	2/40 (5)

NOTE. NR, not reported; PCR, polymerase chain reaction.

[a] Defined as a decrease in the efficacy of a drug against a population of parasites previously susceptible to that compound.

that would otherwise be difficult to obtain [106, 107]. Investigators need to reinforce ethical practices because there is an impoverished reality of underresourced and understaffed health structures in most countries where CL is endemic [108, 109, 110].

The Study Question

Participants. Participants in RCT should be able to understand the nature and the purpose of the research and have a chance to have their queries answered. The informed consent process guarantees the free decision of participants on the basis of a good understanding of the information provided. Other treatment alternatives should be part of the information provided to all participants. Once the trial is completed, participants should have access to safe and beneficial therapies in environments where it is very difficult to access the public health services, as well as the results of the research.

Inclusion criteria are important to define the cases. Investigators should use parasitology to confirm the presence of lesions in eligible patients by direct smears and/or skin-punch biopsies of the active, infiltrated edge of a representative lesion. It is always important to specify criteria for exclusion, such as patients with multiple or disseminated lesions, pregnancy or potential for pregnancy, breast-feeding, chronic illness or concomitant disease, an immunologically compromised condition, and others.

The main selection biases in RCTs are found in the description of baseline characteristics, which need to be fully detailed to ensure homogeneity and comparability between groups. It is strongly recommended that investigators fully report baseline characteristics on a table describing age, sex, geographic area of residence, history of travel in an endemic area, duration of disease, number and morphology of lesions, sites and severity of lesions, previous treatment received, and past history of liver disease or characteristics such as infiltration, erythema, ulceration, and scaling.

There are several species of *Leishmania* involved in Old World and American CL. Thus, in CL it is especially relevant to analyze the infective species because it is well known that they respond differently to the same drug. There is also an urgent need for the standardized definition of clinical manifestations in clinical trials. The diagnostic tools for *Leishmania* identification are not always feasible or reliable, which delays the onset of treatment because of false negative results. Thus, there is a need to improve detection methods to avoid false negative results and to speed up the identification of the parasite at a species level, which will affect the choice and start of treatment.

Interventions. A placebo control group is not always feasible, not only because of the nature of some interventions, especially the systemic ones, which hamper the design of a placebo-controlled trial, but also because of specific situations where a placebo group may go against ethical principles and compromise a participant's well-being. The choice of active control or placebo treatment as the comparator within the context of developing countries must be determined in close consultation with local experts and health authorities and ideally be aligned with locally sustainable health care practice.

Compliance assessment is an important issue in RCTs conducted in developing countries. Compliance should be measured to ensure adherence to treatment and can be assessed using many standardized methods, such as requesting the return of unused medication, counts of remaining capsules/sachets/tablets, or patient interview. When possible, clinical trials could consider hospitalization to ensure compliance. However, the period of time and the best method to measure compliance remain unclear.

Outcome measures. Treatment duration and follow-up times should be clearly defined in the study protocol. Long-term efficacy of intervention and sustainability of responses may be determined with enough extended follow-up of patients after termination of therapy. However, the duration of follow-up may vary depending on the expected time of responses of well-known short- or long-acting drugs. The definition of the outcomes needs to be rigorous to make clinical sense and to be reproduced by others. It is preferable to analyze participants rather than lesions because it is more

Table 6. Summary of the Guidelines for Authors Who Wish to Conduct Randomized Clinical Trials (RCTs) on Treatments for Cutaneous Leishmaniasis

Study question	Level of description in reviewed RCTs
Participants	
Description of inclusion/exclusion criteria.	+++
Inclusion criteria: it is important to define the cases and the parasitological confirmation of cutaneous leishmaniasis.	
Exclusion criteria may include: previous treatment with anti-*Leishmania* therapy, any chronic or concomitant disease, pregnancy, potential for pregnancy or breast feeding females, immunodeficiency, coinfections with HIV, or use of immunosuppressants.	
Description of baseline characteristics of the participants by group: severity and duration of infection, number, size and site of lesions, age, sex, ethnicity.	+++
Analysis and report of the *Leishmania* species involved.	+
Study setting (eg, primary or secondary care, country, number of centers) .	+++
Interventions	
Adequate description of the intervention (name, trade mark, route of administration, doses and regimen schedule).	+++
Control arm (placebo arm only in limited infective species, *Leishmania major,* and *Leishmania mexicana,* but an active control is recommended for other species).	++
Adherence to treatment or compliance should be measurable, measured and reported.	+
Outcomes	
Adequate follow-up and frequency of data recording. We suggest a minimum time period of 3 months after the end of treatment. Extended times of follow-up may be useful in long-acting interventions and for evaluating recurrence.	++
Standardized definition of cure and measurements scales (especially for combination therapies).	+
Define primary and secondary outcomes.	+
Suggested primary outcome: percentage of participants with a complete cure at three months after the end of treatment).	
Suggested secondary outcomes: speed of healing (time taken to be 'cured'; recurrence (duration of remission and/or percentage of people with treated lesions that recur within six months, one, two and three years); degree of functional and aesthetic impairment; prevention of scarring; quality of life; adverse effects; change in ability to detect *Leishmania* by parasitological diagnostic methods (eg, smear, PCR, or culture); emergence of resistance; microbiological or histopathological cure of skin lesions; and development of cell-mediated immunity (ie, positive leishmanin skin test).	
Study design	
Criteria for adequate generation of randomization sequence: random numbers generated by computer or table of random numbers or other unbiased methods of allocation.	+
Criteria for adequate allocation concealment: participants and investigators enrolling participants cannot foresee assignment (ie, central allocation, including telephone, web-based or pharmacy-controlled randomization; a priori third-party sequentially numbered or coded drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or other descriptions that contain convincing elements of concealment).	+
Blinding (who and how they are blinded).	++
Calculation of the sample size.	+
Losses to follow-up per arm (when and why) and intention-to-treat analysis (analysis that include the total number of randomized participants, irrespective of what happened subsequently or how the original study authors analyzed the data).	++
Data reporting	
Follow CONSORT guidelines (authors, journals, and referees).	+

NOTE. HIV, human immunodeficiency virus; PCR, polymerase chain reaction. +, none or few described in reviewed RCTs; ++, fairly well described in reviewed RCTs; +++, mostly well described in reviewed RCTs.

clinically relevant to determine the proportion of participants who achieved the stipulated outcome. Outcomes should be reported in all groups to avoid selective bias. Because recurrence occurs frequently after the treatment of CL, outcome measures should be reported at regular intervals to provide documentation of whether a treatment demonstrates a gradual and sustained improvement or, rather, extensive fluctuations over the course of the study.

We recommend the percentage of participants with a complete cure at 3 months after the end of treatment as the primary outcome for RCTs investigating treatments for CL. Reporting of adverse events is necessary in trials and at least some of the following secondary outcomes: degree of functional and aesthetic impairment; prevention of scarring; quality-of-life measured with validated scales; speed of healing (time taken to be "cured"); recurrence (duration of remission and/or percentage of participants with treated lesions that recur within 6 months and 1, 2, and 3 years, depending of the duration of the trial); change in ability to detect *Leishmania* by parasitological diagnostic methods (eg, smear, polymerase chain reaction, or culture); emergence of resistance (defined as a decrease in the efficacy of a drug against a population of parasites previously susceptible to that compound; the definition assumes that the original susceptibility of the population is known, which is not always the case for *Leishmania*); microbiological or histopathological cure of skin lesions; and development of cell-mediated immunity (ie, positive leishmanin skin test).

The Study Design

The main analysis of RCTs on treatments for CL should be focused on the primary outcome, which should also form the basis of the general conclusion of the study. Sample size needs to be calculated to ensure sufficient statistical power to appropriately evaluate the primary outcome measure. The fact that sample size, a source of potential imprecision, may lead to bias does not necessarily mean that small studies cannot provide some useful information about drug efficacy. The rationale used for the calculation of sample size should be specified in the study protocol.

Additionally, the statistical analysis should be based on full reporting of the reasons for withdrawal and the stage in which they occurred. Because a large proportion of missing data (ie, withdrawals) will diminish the credibility of a study, the best advice is to minimize the chance of withdrawals at the design stage or during the trial [111]. Secondary and tertiary outcomes may help to support the di-

rection and magnitude of the primary outcome. Finally, all outcomes need to be reported with the estimated effect of the intervention and the 95% confidence interval to allow further meta-analysis (ie, the mean and the standard deviation for each group) [112].

The methodology used for the generation of randomization sequence and the allocation concealment, as well as the blinding method, needs to be adequate and clearly described. Although some studies have chosen to randomize by lesions, typically for topical interventions, it may have made more clinical sense to randomize participants, especially in nonblinded trials.

The development of successful approaches for improving wound healing will lead to a reduced risk of developing scars in some lesions of CL and is likely to be a priority in the future. The investigation of specialized treatment strategies using patient satisfaction outcomes would be invaluable in future RCTs. The current evidence for different types of clinical management of Old World CL and for species such as *L. tropica* and *L. aethiopica* is lacking and emphasizes the need for more research. In American CL, clinical research on *Leishmania braziliensis* and *Leishmania panamensis* are the highest priority, because both species lead to the mucocutaneous form.

Reporting of Clinical Trials

Adequate reporting of RCTs improves transparency and enables the interpretation and replication of studies. Many journals require that trials conform to the guidelines in the Consolidated Standards of Reporting Trials (CONSORT) statement [113]. However, it is also important to ask for rigorous peer-review checks in journals.

Studies with more positive effects are more likely to be published than those with less conclusive results that normally remain unpublished, either because authors fail to write manuscripts and submit them to journals or because they are written in languages other than English [114]. Seemingly, the first study to be published on a particular intervention is more likely to show positive results. However, it is unethical to not publish RCTs with negative results. Fortunately, RCTs are currently registered in public databases, and unpublished studies can be easily detected.

CONCLUSIONS

A more evidence-based strategic approach based on the findings of 2 Cochrane systematic reviews of RCTs assessing treatments for CL may help to plan and prioritize global treatment recommendations and clinical research. There is much scope for improving the design and reporting of RCTs, and they can be improved by adopting general guidelines and rigorous peer-review checks in journals. There are other identified factors that have a particular effect on the validity of these trials, most notably the parasitological confirmation and determination of the causative *Leishmania* species, the use of longer duration designs, and clinically understandable and patient-orientated outcome measures.

Hopefully, the recommendations in this report will help in the process of overcoming the methodological challenges of RCTs investigating treatments for CL. We are aiming to create a World Health Organization CL clinical trials network with clinicians, health services, researchers, and patients throughout all affected countries. This concentration of resources may assist with the conduction of high-quality, multicenter RCTs that answer questions of importance to clinicians and patients.

Acknowledgments

We would like to thank the editorial team of the Cochrane Skin Group (Finola M. Delamere and Hywel C. Williams) for the help in the development of the Cochrane reviews, Marie-Charlotte Bouësseau for her helpful comments on ethical issues and Stuart Murray for the final copy-editing. This paper has been funded by a grant from the Office of Control of Neglected Tropical Diseases (WHO/CDS/NTD/IDM), Communicable Diseases Cluster, World Health Organization and the Spanish Agency for International Cooperation and Development (AECID). They have also been supported in part by the International Health Central American Institute Foundation, the Spanish Society of Dermato-Epidemiology and Evidence-based Dermatology (SEDEDBE), and the Hospital Plató, Barcelona, Spain.

Potential conflicts of interest. All authors: no conflicts.

References

1. Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. Trends Parasitol **2006**; 22:552–557.
2. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. Lancet Infect Dis **2007**; 7:581–596.
3. World Health Organization. Control of leishmaniasis. Report by the Secretariat. **2007**. http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_10-en.pdf. Accessed 7 July 2010.
4. Savioli L, Engels D, Daumerie D, et al. Response from Savioli and colleagues from the Department of Neglected Tropical Diseases, World Health Organization. PLoS Med **2006**; 3:e283.
5. World Health Organization (WHO). Report of the Fifth Consultatve Meeting on HIV-Leishmania Co-infection. Addis Ababa, 20–22 March 2007. WHO/CDS/NTD/IDM/2007. **2008**.
6. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled trials. BMJ **2001**; 323:42–46.
7. González U, Pinart M, Reveiz L, Alvar J. Interventions for Old World cutaneous leishmaniasis. Cochrane Database Syst Rev **2008**; 4:CD005067.
8. González U, Pinart M, Rengifo-Pardo M, Macaya A, Alvar J, Tweed J. Interventions for New World cutaneous and mucocutaneous leishmaniasis. Cochrane Database Syst Rev **2009**; 2:CD004834.
9. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. Lancet **2002**; 359:515–519.
10. Al-Fouzan AS, Al-Saleh QA, Najem NM, Rostom AI. Cutaneous Leishmaniasis in Kuwait. Int J Dermatol **1991**; 30:519–521.
11. Alkhawajah AM, Larbi E, Al-Gindan Y, Abahussein A, Jain S. Treatment of cutaneous leishmaniasis with antimony: intramuscular versus intralesional administration. Ann Trop Med Parasitol **1997**; 91:899–905.
12. Alrajhi AA, Ibrahim EA, de Vol EB, Khairat M, Faris RM, Maguire JH. Fluconazole for the treatment of cutaneous leishmaniasis caused by leishmania major. N Engl J Med **2002**; 346:891–895.
13. Alsaleh Qasem A, Dvorak R, Nanda A. Ketoconazole in the treatment of cutaneous leishmaniasis in Kuwait. Int J Dermatol **1995**; 34:495–497.
14. Asilian A, Jalayer T, Whitworth G, Ghasemi RL, Nilforooshzadeh M, Olliaro P. A randomized, placebo-controlled trial of a two-

week regimen of aminosidine (paramomycin) ointment for treatment of cutaneous leishmaniasis in Iran. Am J Trop Med Hyg **1995**; 53:648–651.
15. Asilian A, Jalayer T, Nilforoosshzadeh M, et al. Treatment of cutaneous leishmaniasis with aminosidine (paromomycin) ointment: double-blind, randomized trial in the Islamic Republic of Iran. Bull World Health Organ **2003**; 81:353–359.
16. Asilian A, Sadeghinia A, Faghihi G, Momeni A. Comparative study of the efficacy of combined cryotherapy and intralesional meglumine antimoniate (glucantime) vs. cryotherapy and intralesional meglumine antimoniate (glucantime) alone for the treatment of cutaneous leishmaniasis. Int J Dermatol **2004**; 43:281–283.
17. Asilian A, Sharif A, Faghihi G, Enshaeieh SH, Shariati F, Siadat AH. Evaluation of CO_2 laser efficacy in the treatment of cutaneous leishmaniasis. Int J Dermatol **2004**; 43:736–738.
18. Asilian A, Davami M. Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. Clin Exp Dermatol **2006**; 31:634–637.
19. Ben Salah A, Zakraoui H, Zaatour A, et al. A randomized, placebo-controlled trial in Tunisia treating cutaneous leishmaniasis with paromomycin ointment. Am J Trop Med Hyg **1995**; 53:162–166.
20. Chahed MK, Ben Salah A, Louzir H, et al. Efficacy of intra-lesional glucantime in the treatment of zoonotic cutaneous leishmaniasis in basic health care conditions [in French]. Arch Inst Pasteur Tunis **1999**; 76: 13–18.
21. Dandashi A. Treatment of cutaneous leishmaniasis with fluconazole: a randomized double-blind, placebo-controlled trial. JEADV **2005**; 19(suppl 2):43.
22. Dogra J, Aneja N, Lal Behari B, Mishra SN. Cutaneous Leishmaniasis in India: Clinical Experience with Itraconazole. Int J Dermatol **1990**; 29:661–662.
23. Dogra J. A double-blind study on the efficacy of oral dapsone in cutaneous leishmaniasis. Trans R Soc Trop Med Hyg **1991**; 85:212–213.
24. Dogra J. Cutaneous leishmaniasis in India: evaluation of oral drugs (dapsone versus itraconazole). Eur J Dermatol **1992**; 2:568–569.
25. Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. Int J Parasitol **1996**; 26: 1413–1415.
26. Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (glucantime) in the treatment of cutaneous leishmaniasis. Int J Dermatol **2002**; 41:521–524.
27. Faghihi G, Tavakoli-kia R. Topical paromomycin vs intralesional meglumine antimoniate in cutaneous leishmaniasis. Clin Exp Dermatol **2003**; 28:13–16.
28. Firooz A, Khatami A, Khamesipour A, et al. Intralesional injection of 2% zinc sulphate solution in the treatment of acute Old World cutaneous leishmaniasis: a randomized, double-blind, controlled clinical trial. J Drugs Dermatol **2005**; 4:73–79.
29. Firooz A, Khamesipour A, Ghoorchi MH, et al. Imiquimod in combination with meglumine antimoniate for cutaneous leishmaniasis: a randomized assessor-blind controlled trial. Arch Dermatol **2006**; 142:1575–1579.
30. Gholami A, Khamesipour A, Momeni A, et al. Treatment of cutaneous leishmaniasis with 5% garlic cream: a randomized, double-blind study. Iranian J Dermatol **2000**; 3:2–6.
31. Harms G, Chehade AK, Douba M, et al. A randomized trial comparing a pentavalent antimonial drug and recombinant interferon in the local treatment of cutaneous leishmaniasis. Trans R Soc Trop Med Hyg **1991**; 85: 214–216.
32. Iraji F, Vali A, Asilian A, Shahtalebi M, Momeni AZ. Comparison of intralesionally injected Zinc sulphate with meglumine antimoniate in the treatment of acute cutaneous leishmaniasis. Dermatology **2004**; 209:46–49.
33. Iraji F, Sadeghinia A. Efficacy of paromomycin ointment in the treatment of cutaneous leishmaniasis: results of a double-blind, randomized trial in Isfahan, Iran. Ann Trop Med Parasitol **2005**; 99:3–9.
34. Jaffar H. Rifampicin in cutaneous leishmaniasis- a therapeutic trial in Saudi Arabia. J Pakistan Assoc Dermatol **2006**; 16:4–9.
35. Kochar DK, Aseri S, Sharma BV, Bumb RA, Mehta RD, Purohit SK. The role of rifampicin in the management of cutaneous leishmaniasis. QJM **2000**; 93:733–737.
36. Kochar DK, Saini G, Kochar SK, et al. A double blind, randomised placebo controlled trial of rifampicin with omeprazole in the treatment of human cutaneous leishmaniasis. J Vector Borne Dis **2006**; 43:161–167.
37. Larbi EB, Al-Khawajah A, Al-gindan Y, Jain S, Abahusain A, Al-Zayer A. A randomized, double-blind, clinical trial of topical clotrimazole versus mizonazole for treatment of cutaneous leishmaniasis in the eastern province of Saudi Arabia. Am J Trop Med Hyg **1995**; 52:166–168.
38. Layegh P, Yazdanpanah M J, Vosugh EM, Pezeshkpoor F, Shakeri M T, Moghiman T. Efficacy of azithromycin versus systemic meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. Am J Trop Med Hyg **2007**; 77:99–101.
39. Lynen L, Van Damme W. Local application of Diminazene aceturate: an effective treatment for cutaneous leishmaniasis? Ann Soc Belg Med Trop **1992**; 72:13–19.
40. Mashood AA, Hussain K. Efficacy of allopurinol compared with pentostam in the treatment of old world cutaneous leishmaniasis. J Coll Physicians Surg Pak **2001**; 11: 367–370.
41. Mohebali M, Fotouhi A, Hooshmand B, et al. Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomized clinical trial in Iran. Acta Trop **2007**; 103:33–40.
42. Momeni AZ, Jalayer T, Emamjomeh M, et al. Treatment of cutaneous leishmaniasis with itraconazole. Randomized double-blind study. Arch Dermatol **1996**; 132:784–786.
43. Momeni AZ, Reiszadae MR, Aminjavaheri M. Treatment of cutaneous leishmaniasis with a combination of allopurinol and low-dose meglumine antimoniate. Int J Dermatol **2002**; 41:441–443.
44. Momeni AZ, Aminjavaheri M, Omidghaemi MR. Treatment of cutaneous leishmaniasis with ketoconazole cream. J Dermatolog Treat **2003**; 14:26–29.
45. Munir A, Janjua SA, Hussain I. Clinical efficacy of intramuscular meglumine antimoniate alone and in combination with intralesional meglumine antimoniate in the treatment of old world cutaneous leishmaniasis. Acta Dermatovenerol Croat **2008**; 16:60–64.
46. Mutjaba G, Khalid M. Weekly versus fortnightly intralesional meglumine antimoniate in cutaneous leishmaniasis. Int J Dermatol **1999**; 38:607–609.
47. Nassiri-Kashani M, Firooz A, Khamesipour A, et al. A randomized, double-blind, placebo-controlled clinical trial of itraconazole in the treatment of cutaneous leishmaniasis. JEADV **2005**; 19:80–83.
48. Nilforoushzadeh MA. Efficacy of combined triple therapy (paromomycin ointment, cryotherapy and intralesional glucantime) in comparison with intralesional glucantime for treatment of acute cutaneous leishmaniasis. Iranian J Dermatol **2004**; 3:136–139.
49. Nilforoushzadeh MA, Jaffary F, Reiszadeh MR. Comparative effect of topical trichloroacetic and intralesional meglumine antimoniate in the treatment of acute cutaneous leishmaniasis. Int J Pharmacol **2006**; 2:633–636.
50. Nilforoushzadeh MA, Reiszadeh MR, Jafari F. Topical trichloroacetic A compared with intralesional glucantime injection in the treatment of acute wet cutaneous leishmaniasis: an open clinical trial. Iranian J Dermatol **2003**; 2:34–39.
51. Nilforoushzadeh MA, Jaffary F, Moradi S, Derakhshan R, Haftbaradaran E. Effect of topical honey application along with intralesional injection of glucantime in the treatment of cutaneous leishmaniasis. BMC Complement Altern Med **2007**; 7:13.
52. Özgöztasi O, Baydar I. A randomized clinical trial of topical paromomycin versus oral ketoconazole for treating cutaneous leishmaniasis in Turkey. Int J Dermatol **1997**; 36: 61–63.
53. Reithinger R, Mohsen M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania* tropica in Kabul, Afghanistan: a randomized, controlled trial. Clin Infect Dis **2005**; 40:1148–1154.
54. Sadeghian G, Nilforoushzadeh MA. Effect

of combination therapy with systemic glucantime and pentoxifylline in the treatment of cutaneous leishmaniasis. Int J Dermatol **2006**; 45:819–821.
55. Sadeghian G, Nilfroushzadeh MA, Siadat AH. A comparison between intralesional hypertonic sodium chloride solution and meglumine antimoniate in the treatment of cutaneous leishmaniasis. Egyptian Dermatol Online **2006**; 1:8.
56. Sadeghian G, Nilfroushzadeh MA, Iraji F. Efficacy of local heat therapy by radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate. Clin Exp Dermatol **2007**; 32:371–374.
57. Salmanpour R, Handjani F, Noupisheh MK. Comparative study of the efficacy of oral ketoconazole with intra-lesional meglumine antimoniate (glucantime) for the treatment of cutaneous leishmaniasis. J Dermatolog Treat **2001**; 12:159–162.
58. Salmanpour R, Razmavar MR, Abtahi N. Comparison of intralesional meglumine antimoniate, cryotherapy and their combination in the treatment of cutaneous leishmaniasis. Int J Dermatol **2006**; 45:1115–1116.
59. Sharquie KE, Najim RA, Farjou IB. A comparative controlled trial of intralesionally- administered zinc sulphate, hypertonic sodium chloride and pentavalent antimony compound against cutaneous leishmaniasis. Clin Exp Dermatol **1997**; 22:169–173.
60. Sharquie KE, Najim RA, Farjou IB, Al-timimit DJ. Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. Clin Exp Dermatol **2001**; 26:21–26.
61. Shazad B, Abbaszadeh B, Khamesipour A. Comparison of topical paromomycin sulfate (twice/day) with intralesional meglumine antimoniate for the treatment of cutaneous leishmaniasis caused by *L. major.* Eur J Dermatol **2005**; 15:85–87.
62. Zerehsaz F, Salmanpour R, Farhad H, et al. A double-blind randomized clinical trial of a topical herbal extract (Z-HE) vs. systemic meglumine antimoniate for the treatment of cutaneous leishmaniasis in Iran. Int J Dermatol **1999**; 38:610–612.
63. Almeida R, D'Oliveira A Jr, Machado P, et al. Randomized, double-blind study of stibogluconate plus human granulocyte macrophage colony stimulating factor versus stibogluconate alone in the treatment of cutaneous leishmaniasis. J Infect Dis **1999**; 180: 1735–1737.
64. Andersen EM, Cruz-Saldarriaga M, LLanos-Cuentas A, et al. Comparison of meglumine and pentamidine for peruvian cutaneous leishmaniasis. Am J Trop Med Hyg **2005**; 72: 133–137.
65. Arana BA, Navin TR, Arana FE, Berman JD, Rosenkaimer F. Efficacy of a short course (10 days) of high-dose meglumine antimoniate with or without interferon-gamma in treating cutaneous leishmaniasis in Guatemala. Clin Infect Dis **1994**; 18:381–384.
66. Arana BA, Mendoza CE, Rizzo NR, Kroeger A. Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with the paromomycin plus methylbenzethonium chloride ointment in Guatemala. Am J Trop Med Hyg **2001**; 65:466–470.
67. Arevalo I, Tulliano G, Quispe A, et al. Role of imiquimod and parenteral meglumine antimoniate in the intitial treatment of cutaneous lesihmaniasis. Clin Infect Dis **2007**; 44: 1549–1554.
68. Armijos RX, Weigel MM, Calvopiña M, Mancheno M, Rodriguez R. Comparison of the effectiveness of two topical paromomycin treatments versus meglumine antimoniate for New World cutaneous leishmaniasis. Acta Trop **2004**; 91:153–160.
69. Ballou WR, McClain JB, Gordon DM, et al. Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. Lancet **1987**; 2:13–16.
70. Convit J, Castellanos PL, Rondon A, et al. Immunotherapy versus chemotherapy in localised cutaneous leishmaniasis. Lancet **1987**; 1:401–405.
71. Convit J, Castellanos PL, Ulrich M, et al. Immunotherapy of localized, intermediate, and diffuse forms of american cutaneous leishmaniasis. J Infect Dis **1989**; 160:104–114.
72. Correia D, Macêdo VO, Carvalho EM, et al. Comparative study of meglumine antimoniate, pentamidine isothionate and aminosidine sulphate in the treatment of primary skin lesions caused by *Leishmania* (viannia) braziliensis. Rev Soc Bras Med Trop **1996**; 29:447–453.
73. D'Oliveira A Jr, Machado PR, Carvalho EM. Evaluating the efficacy of allopurinol for treatment of cutaneous leishmaniasis. Int J Dermatol **1997**; 36:938–940.
74. Figueiredo Kopke LF, Siviero do Vale EC, Grossi Araujo M, Araújo Magalhâes P, Furtado T. Treatment of american tegumentary leishmaniasis with N-methyl-glucamine: double-blind study with doses of 14 mg/kg/day and 28 mg/kg/day of antimoniate. An Bras Dermatol **1991**; 66:87–94.
75. Franke ED, LLanos-Cuentas A, Echevarria J, et al. Efficacy of 28-day and 40-day regimens of sodium stibogluconate (pentostam) in the treatment of mucosal leishmaniasis. Am J Trop Med Hyg **1994**; 51:77–82.
76. Guderian RH, Chico ME, Rogers MD, Pattishall KM, Grogl M, Berman JD. Placebo controlled treatment of Ecuadorian cutaneous leishmaniasis. Am J Trop Med Hyg **1991**; 45:92–97.
77. Hepburn NC, Tidman MJ, Hunter JAA. Aminosidine (paromomycin) versus sodium stibogluconate for the treatment of American cutaneous leishmaniasis. Trans R Soc Trop Med Hyg **1994**; 88:700–703.
78. Krolewiecki AJ, Romero HD, Cajal SP, et al. A randomized clinical trial comparing oral azithromycin and meglumine antimoniate for the treatment of American cutaneous leishmaniasis caused by *Leishmania* (Viannia) braziliensis. Am J Trop Med Hyg **2007**; 77:640–646.
79. Llanos-Cuentas A, Echevarria J, Cruz M, et al. Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. Clin Infect Dis **1997**; 25:677–684.
80. Llanos-Cuentas A, Echevarria J, Seas C, et al Parenteral aminosidine is not effective for Peruvian mucocutaneous leishmaniasis. Am J Trop Med Hyg **2007**; 76:1128–1131.
81. Lobo IM, Soares MB, Correia TM, et al. Heat therapy for cutaneous leishmaniasis elicits a systemic cytokine response similar to that of antimonial (Glucantime) therapy. Trans R Soc Trop Med Hyg **2006**; 100:642–649.
82. Miranda-Verástegui C, LLanos-Cuentas A, Arévalo I, Ward BJ, Matlashewski G. Randomized, double-blind clinical trial of topical imiquimod 5% with parenteral meglumine antimoniate in the treatment of cutaneous leishmaniasis in Peru. Clin Infect Dis **2005**; 40:1395–1403.
83. Machado PR, Lessa H, Lessa M, et al. Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. Clin Infect Dis **2007**; 44:788–793.
84. Machado-Pinto J, Pinto J, da Costa CA, et al Immunochemotherapy for cutaneous leishmaniasis: a controlled trial using killed *Leishmania* (*Leishmania*) *amazonensis* vaccine plus antimonial. Int J Dermatol **2002**; 41:73–78.
85. Martinez S, Marr J. Allopurinol in the treatment of American cutaneous leishmaniasis. N Engl J Med **1992**; 326:741–744.
86. Martinez S, Gonzalez M, Vernaza ME. Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. Clin Infect Dis **1997**; 24:165–169.
87. Navin TR, Arana BA, Arana FE, de Mérida AM, Castillo AL, Pozuelos JL. Placebo-controlled clinical trial of meglumine antimoniate (glucantime) versus localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. Am J Trop Med Hyg **1990**; 42:43–50.
88. Navin TR, Aran BA, Arana FE, Berman JD, Chajón JF. Placebo-controlled clinical trial of sodium stibogluconate (pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. J Infect Dis **1992**; 165:528–534.
89. Neva FA, Ponce C, Ponce E, Kreutzer R, Modabber F, Olliaro P. Non-ulcerative cutaneous leishmaniasis in Honduras fails to respond to topical paromomycin. Trans R Soc Trop Med Hyg **1997**; 91:473–475.
90. Oliveira-Neto MP, Schubach A, Mattos M, Gonçalves-Costa SC, Pirmez C. Treatment of american cutaneous leishmaniasis: a comparison between low dosage (5 mg/kg/day) and high dosage (20 mg/kg/day) antimony regimens. Pathol Biol (Paris) **1997**; 45:496–499.

91. Oster CN, Chulay JD, Hendricks LD, et al. American cutaneous leishmaniasis: a comparison of three sodium stibogluconate treatment schedules. Am J Trop Med Hyg **1985**; 34:856–860.
92. Palacios R, Osorio LE, Grajales LF, Ochoa MT. Treatment failure in children in a randomized clinical trial with 10 and 20 days of meglumine antimoniate for cutaneous leishmaniasis due to *Leishmania viannia* species. Am J Trop Med Hyg **2001**; 64:187–193.
93. Saenz RE, Paz HM, Johnson CM, Narvaez E, de Vasquez AM. Evaluation of the effectiveness and toxicity of pentostam and glucantime in the treatment of cutaneous leishmaniasis. Rev Med Panama **1987**; 12:148–157.
94. Saenz RE, Paz H. Efficacy of ketoconazole against *Leishmania braziliensis panamensis* cutaneous leishmaniasis. Am J Med **1990**; 89: 147–155.
95. Santos JB, de Jesus AR, Machado PR, et al Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low doses enhances healing of cutaneous leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. J Infect Dis **2004**; 190:1793–1796.
96. Soto J, Grogl M, Berman J, Olliaro P. Limited efficacy of injectable aminosidine as single-agent therapy for Colombian cutaneous leishmaniasis. Trans R Soc Trop Med Hyg **1994**; 88:695–698.
97. Soto J, Fuya P, Herrera R, Berman J. Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimoniate as treatment for American cutaneous leishmaniasis: controlled study. Clin Infect Dis **1998**; 26:56–58.
98. Soto JM, Toledo JT, Gutierrez P, et al. Treatment of cutaneous leishmaniasis with a topical antileishmanial drug (WR279396): phase 2 pilot study. Am J Trop Med Hyg **2002**; 66: 147–151.
99. Soto J, Valda-Rodriguez L, Toledo J, et al. Comparison of generic to branded pentavalent antimony for treatment of new world cutaneous leishmaniasis. Am J Trop Med Hyg **2004**; 71:577–581.
100. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. Clin Infect Dis **2004**; 38:1266–1272.
101. Soto J, Rea J, Balderrama M, et al. Efficacy of miltefosine for Bolivian cutaneous leishmaniasis. Am J Trop Med Hyg **2008**; 78:210–211.
102. Velez I, Agudelo S, Hendrickx E, et al. Inefficacy of allopurinol as monotherapy for colombian cutaneous leishmaniasis: a randomized, controlled trial. Ann Int Med **1997**; 126:232–236.
103. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet **2002**; 359:614–618.
104. Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. BMJ **2000**; 321:504.
105. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.0.0. Cochrane Collaboration, **2008**. http://www.cochrane-handbook.org/. Accessed 7 July 2010.
106. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. Lancet Infect Dis **2008**; 8:458; author reply, 458–459.
107. Benatar SR, Fleischer TE. Ethical issues in research in low-income countries. Int J Tuberc Lung Dis **2007**; 11:617–623.
108. Cutts FT, Enwere G, Zaman SM, Yallop FG. Operational challenges in large clinical trials: examples and lessons learned from the Gambia pneumococcal vaccine trial. PLoS Clin Trials **2006**; 1:e16.
109. White NJ. Editorial: clinical trials in tropical diseases: a politically incorrect view. Trop Med Int Health **2006**; 11:1483–1184.
110. Owens S, Stokes E, Mueller J. Re: Clinical trials in tropical diseases: a politically incorrect view. Trop Med Int Health **2007**; 12:472.
111. Shih WJ. Problems in dealing with missing data and informative censoring in clinical trials. Curr Control Trials Cardiovasc Med **2002**; 3:4.
112. Simon R. Confidence intervals for reporting results of clinical trials. Ann Intern Med **1986**; 105:429–435.
113. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ **2010**; 340: c869.
114. Bigby M, Williams H. Appraising systematic reviews and meta-analyses. Arch Dermatol **2003**; 139:795–798.