REPORTING OF INFORMED CONSENT, STANDARD OF CARE AND POST-TRIAL OBLIGATIONS IN GLOBAL RANDOMIZED INTERVENTION TRIALS: A SYSTEMATIC SURVEY OF REGISTERED TRIALS

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Keywords
Africa, benefit sharing, bioethics, clinical trials, developing world, developing world bioethics, HIV/AIDS

ABSTRACT
Objective: Ethical guidelines are designed to ensure benefits, protection and respect of participants in clinical research. Clinical trials must now be registered on open-access databases and provide details on ethical considerations. This systematic survey aimed to determine the extent to which recently registered clinical trials report the use of standard of care and post-trial obligations in trial registries, and whether trial characteristics vary according to setting.

Methods: We selected global randomized trials registered on www.clinicaltrials.gov and www.controlled-trials.com. We searched for intervention trials of HIV/AIDS, malaria, and tuberculosis from 9 October 2004, the date of the most recent version of the Helsinki Declaration, to 10 April 2007.

Results: We collected data from 312 trials. Fifty-eight percent (58%, 95% CI = 53 to 64) of trial protocols report informed consent. Fifty-eight percent (58%, 95% CI = 53 to 64) of trials report active controls. Almost no trials (1%, 95% CI = 0.5 to 3) mention post-trial provisions. Most trials measure surrogate outcomes. Twenty percent (20%, 95% CI = 16 to 25) of trials measure patient-important outcomes, such as death; and the odds that these outcomes are in a low income country are five times greater than for a developed country (odds ratio (OR) 5.03, 95% CI = 2.70 to 9.35, p < 0.001). Pharmaceutical companies are involved in 28% (CI = 23 to 33) of trials and measure surrogate outcomes more often than nonpharmaceutical companies (OR 2.45, 95% CI = 1.18 to 5.09, p = 0.31).

Conclusion: We found a large discrepancy in the quality of reporting and approaches used in trials in developing settings compared to wealthier settings.

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INTRODUCTION

The ethics of conducting international randomized clinical trials (RCTs) remain contentious. Specifically, there is no consensus on obligations surrounding standard of care and post-trial obligations for care, or access to the interventions studied, if effective. The argument lies in the belief that participation in clinical trials should result in long-term care; whereas, more pragmatic researchers argue that they are not responsible for care after a trial.

International guidance documents address these issues. The Declaration of Helsinki, adopted by the World Medical Association (WMA) in 1964, is the pre-eminent ethics document, as it has arguably been ratified by all WMA member states. It has had seven revisions since 1964, indicating ability to adapt to ongoing ethical challenges. Clarifications on standard of care (Paragraph 30) were made in 2002. It states that when effective therapy exists, new interventions should be tested against the standard of care unless it is necessary to use placebo for safety and efficacy reasons, when there is no current proven prophylactic, diagnostic and therapeutic methods.\(^1\) The argument lies in the belief that participation in clinical trials should result in long-term care; whereas, more pragmatic researchers argue that they are not responsible for care after a trial.\(^2\)

We chose these disease categories because effective treatment available, or if the trial is studying a minor condition where there is little anticipated risk to the research participant.\(^6\) In October 2004, the WMA addressed obligations to the research participants at the conclusion of the trial.\(^7\) It states: ‘every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.’\(^8\) The WMA emphasizes that post-trial provisions to research participants should be identified as part of the planning process.\(^9\) The extent to which access to post-trial interventions exists, when proven effective, is largely unknown, suggesting that adherence to ethical standards may be suboptimal.

In 2004, the International Committee of Medical Journal Editors mandated that all randomized therapeutic trials must be registered on open-access trial registries.\(^10\) Subsequently, the United States (US) brought into law that all new intervention clinical trials must be registered.\(^11\) We aimed to determine the extent that trials registered on the publicly accessible databases report important ethical issues and whether trial characteristics vary according to settings. To date, no study has examined the reporting of ethical considerations in prospectively registered trials. We evaluated important ethical considerations using a systematic survey of the registries and address normative and ethical debate on arising issues.

METHODS

Study selection

Two members of our study team (E.C. and J.O.) independently reviewed the trials. Eligible studies met the following criteria: (1) were randomized trials; (2) were registered on open-access trial registries; (3) trial start date on or after 9 October 2004; and (4) were therapeutic trials addressing HIV/AIDS, malaria, and/or tuberculosis.

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\(^{4}\) Schüklank, op. cit. note 1; World Medical Association, op. cit. note 3.

\(^{5}\) World Medical Association, ibid. See ‘Note of Clarification on Paragraph 29 added by the WMA General Assembly.’ Available at: http://www.wma.net/e/policy/b3.htm#paragraphe29 [Accessed 2 Apr 2007].
therapeutic interventions exist for each, they contribute significantly to the disease burden of poor countries, and there are many research trials on these conditions. We based the eligibility requirement of a start date on or after 9 October 2004, the date of the most recent amendment to the Declaration of Helsinki.12

Search strategy
We systematically searched for registered clinical trials using www.clinicaltrials.gov (inception to March/April 2007) and www.controlled-trials.com (inception to April 2007). We searched these databases independently, in duplicate. We searched across multiple databases from the Controlled-trials.com website, including: National Health Service Research and Development Health Technology Assessment Programme (HTA), Action Medical Research, National Health Service Research and Development Programme ‘Time-Limited’ National Programmes, King’s College London (UK), National Health Service Research and Development Regional Programmes, Laxdale Ltd., National Institutes of Health (NIH) – randomized trial records held on NIH ClinicalTrials.gov website, Leukaemia Research Fund, Wellcome Trust, Medical Research Council (UK), UK Clinical Trials Register, NHS Trusts Clinical Trials Register. We searched for trials on HIV/AIDS, malaria, and tuberculosis.

We searched for trials by condition on the Clinicaltrials.gov website. Conditions included were: Acquired Immunodeficiency Syndrome/HIV Infections; AIDS Dementia Complex; AIDS-Associated Nephropathy; AIDS-Related Complex; AIDS-Related Opportunistic Infections; HIV Seropositivity; HIV Wasting Syndrome; HIV-Associated Candidiasis; HIV-Associated Lipodystrophy Syndrome; Malaria; Malaria, Cerebral; Malaria, Falciparum; Malaria, Vivax; Tuberculosis; Tuberculosis, Central Nervous System; Tuberculosis, Cutaneous; Tuberculosis, Meningeal; Tuberculosis, Multidrug-Resistant; Tuberculosis, Osteoarticular; Tuberculosis, Pleural; Tuberculosis, Pulmonary. We searched the Controlled-trials.com website using the terms: ‘HIV’, ‘AIDS’, ‘malaria’, and ‘tuberculosis’. Please see Supplementary Material for more details on the search strategy.

Data extraction
For each registered and eligible trial we recorded data on: trial start date, duration of trial, trial status, sponsoring institution, partner institution, funding source, country of residence of primary investigator (PI), research location(s), sample size, participants <18 years of age, primary outcome, intervention, informed consent/assent, standard of care in control arm, and post-trial provisions. We recorded trial locations and the country of the PI as high or low-to-middle income countries according to the World Bank country classifications.13 Primary outcomes such as death, HIV incidence, progression to AIDS, malaria, and tuberculosis were classified as clinical outcomes. We classified primary outcomes such as blood levels, viral load, CD4+ cells, and other common biomarkers as surrogate outcomes.

We independently extracted data and entered it into an Excel spreadsheet. Throughout the data extraction process we ensured consistency in search and retrieval processes through consensus. We merged our data sets on a weekly basis and verified there were no duplicate trial entries.

Statistical analysis
We used descriptive statistics to describe proportions. We calculated proportions and confidence intervals around proportions by first stabilizing the variances of the raw proportions (r/n) using a Freeman-Tukey type arcsine square root transformation:14 where, \( y = \arcsine(\sqrt{r/n + 1}) + \arcsine(\sqrt{r/(n + 1)}) \)

\[
\frac{y}{\sqrt{y^2 - 1}}\text{, with a variance of } 1/(n + 1), \text{ where } n \text{ is the denominator total sample size. We rounded confidence intervals to the nearest whole number. We conducted sensitivity analysis to determine if surrogate outcomes, country of primary investigator (PI), and involvement of pharmaceutical industry would result in differing outcomes using odds ratios (OR) and chi-squared. Finally, we evaluated how many studies were being conducted in settings with active oppression of the population (determined as the lower fifth of the Freedom House rankings).15 We used SPSS and StatsDirect (Version 2.1.4) for all analyses.}

12 World Medical Association, op. cit. note 3.
RESULTS

In total, we included data from 312 RCTs. Two hundred and twenty-two (222) of these trials were HIV/AIDS trials, 67 were malaria trials, and 23 were tuberculosis trials. Forty-one (41) of the 312 trials (13%) were multistate trials. Six (6) of the 312 trials (1.9%) did not indicate the trial location. One hundred and sixteen (116) trial locations were being conducted within the United States. Other research sites included: Argentina (n = 3), Australia (n = 10), Bangladesh (n = 1), Belgium (n = 7), Benin (n = 3), Bolivia (n = 1), Botswana (n = 5), Brazil (n = 9), Burkina Faso (n = 3), Cambodia (n = 3), Cameroon (n = 5), Canada (n = 16), China (n = 2), Colombia (n = 2), Denmark (n = 2), Dominican Republic (n = 1), France (n = 21), Gabon (n = 2), Gambia (n = 3), Germany (n = 11), Ghana (n = 7), Greece (n = 2), Guinea (n = 2), Haiti (n = 3), Hungary (n = 1), India (n = 11), Indonesia (n = 2), Ireland (n = 1), Israel (n = 2), Italy (n = 9), Jamaica (n = 1), Japan (n = 1), Kenya (n = 13), Republic of Korea (n = 1), Madagascar (n = 1), Malawi (n = 6), Malaysia (n = 1), Mali (n = 5), Mexico (n = 4), Mozambique (n = 5), Netherlands (n = 11), Nigeria (n = 2), Peru (n = 2), Philippines (n = 1), Poland (n = 1), Portugal (n = 1), Puerto Rico (n = 14), Romania (n = 2), Russia (n = 1), Rwanda (n = 2), Senegal (n = 2), South Africa (n = 28), Spain (n = 17), Switzerland (n = 4), Tanzania (n = 13), Thailand (n = 22), Uganda (n = 15), United Kingdom (n = 13), Vietnam (n = 2), Zambia (n = 4), and Zimbabwe (n = 1). Table 1 displays the main findings of these trials.

Most trials occur in high income countries (56%, 95% CI = 51 to 62). Seventy-five percent of PIs involved in these trials are from high income countries, compared to 13% from low-to-middle income countries. Five percent of trials have co-PIs from either high and low income or high and middle income countries. The odds ratio that low-to-middle income countries use placebo controls is 1.26 (95% CI = 0.78 to 2.03, p = 0.4116). Thirteen (13) trial locations (4.2%, 95% CI = 2 to 6) were among the lowest one-fifth of Freedom House ranking of countries: Russia, Ethiopia, Gambia, Zimbabwe, Vietnam, China, Iran, Rwanda and Guinea.

Informed consent and child assent

Informed consent is reported in the majority of trials (59%, 95% CI = 53 to 64). In total, 27% (95% CI = 22 to 32) of trials include child participants. Fifteen percent (15%, 95% CI = 11 to 19) of trials with children less than 18 years old state that informed consent is obtained from a parent or guardian. Ninety percent (90%) of trials with children do not report obtaining assent from the child (95% CI = 82 to 95).

Table 1. Trial Information: Variables, Frequencies and Percentages

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percent</th>
<th>Number of Trials in Developed Settings</th>
<th>Number of Trials in Developing Countries</th>
<th>Odds Ratio of Trials in Developed and Developing Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials reporting informed consent</td>
<td>183</td>
<td>58.6</td>
<td>99</td>
<td>83</td>
<td>1.37 (CI = 0.86 to 2.19)</td>
</tr>
<tr>
<td>Research location in low-to-middle income countries</td>
<td>130</td>
<td>41.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Research location in high income countries</td>
<td>159</td>
<td>51</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Primary investigator in high income countries</td>
<td>234</td>
<td>75</td>
<td>166</td>
<td>82</td>
<td>76.93 (CI = 10.38 to 570.22)</td>
</tr>
<tr>
<td>Primary investigator in low income countries</td>
<td>39</td>
<td>12.5</td>
<td>1</td>
<td>38</td>
<td>76.93 (CI = 10.38 to 570.22)</td>
</tr>
<tr>
<td>Trials using active controls</td>
<td>182</td>
<td>58.4</td>
<td>97</td>
<td>82</td>
<td>0.79 (CI = 0.49 to 1.28)</td>
</tr>
<tr>
<td>Trials using placebos</td>
<td>114</td>
<td>36.5</td>
<td>67</td>
<td>45</td>
<td>1.26 (CI = 0.78 to 2.03)</td>
</tr>
<tr>
<td>Trials without mention of post-trial obligations and provisions</td>
<td>308</td>
<td>98.7</td>
<td>174</td>
<td>128</td>
<td>0.74 (CI = 0.10 to 5.29)</td>
</tr>
<tr>
<td>Trials measuring surrogate outcomes</td>
<td>237</td>
<td>76</td>
<td>152</td>
<td>80</td>
<td>5.03 (CI = 2.71 to 9.35)</td>
</tr>
<tr>
<td>Trials measuring clinical outcomes</td>
<td>63</td>
<td>20.2</td>
<td>17</td>
<td>45</td>
<td>0.20 (CI = 0.11 to 0.37)</td>
</tr>
<tr>
<td>Trials involving pharmaceutical companies</td>
<td>87</td>
<td>27.9</td>
<td>59</td>
<td>23</td>
<td>2.35 (CI = 1.36 to 4.06)</td>
</tr>
<tr>
<td>Trials involving child participants</td>
<td>83</td>
<td>26.6</td>
<td>20</td>
<td>62</td>
<td>0.13 (CI = 0.07 to 0.23)</td>
</tr>
</tbody>
</table>


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We define the p value as the probability of observing results such as these or more extreme supposing that the null hypothesis is true. It is really the area of the distribution beyond which the null hypothesis of no difference between interventions is rejected. A p value equal to or less than .05 is considered statistically significant since there is only a 5% probability the event occurred due to chance alone.
Standard of care
Fifty-eight percent (58%, 95% CI = 53 to 64) of trials use an active control\textsuperscript{17} and 37% (95% CI = 31 to 42) of trials use a placebo control. The remaining trials did not indicate the type of control.

Post-trial provisions
The vast majority of trials make no mention of post-trial provisions in their protocol (99%, 95% CI = 97 to 100). A small number of trials (4 out of 312) mention some form of post-trial provision including treatment follow-up for a specified time period.

Trial outcomes
Twenty percent (20%, 95% CI = 11 to 37) of trials measure clinical events as their primary outcomes. The odds that a trial measuring a clinical outcome is located in a low-to-middle income country is 5.03 (95% CI = 2.70 to 9.35, \(p < 0.001\)) compared to developed settings. Principle investigators from developed settings conducting research in developing settings are more likely to evaluate clinical event trials than their lower income counterparts (\(p = 0.027\)). The odds ratio for clinical events versus surrogate outcomes, by setting of PI, is 1.67 (95% CI = 0.77 to 3.59, \(p = 0.33\)).

Funding
The majority of trials (72%, 95% CI = 67 to 77) are publicly funded. Pharmaceutical companies are involved in only 28% (95% CI = 23 to 33) of the trials. Pharmaceutical companies are more often involved in trials measuring surrogate outcomes (OR 2.45, 95% CI = 1.18 to 5.09, \(p = 0.03\)).

DISCUSSION
The findings of our review should be of interest to ethicists, trialists and the public alike. Reporting on standards relevant to the ethical conduct of research is suboptimal. This does not mean that such trials were conducted unethically, but a reader cannot determine this because of the lack of requirement that such issues be reported. Arguably, issues such as informed consent, justified use of a placebo, and management of post-trial obligations are as essential to understanding research as the main outcome measure, study design, and method of statistical analysis. Generally, the principle of informed consent is accepted by most trial investigators.\textsuperscript{19} Whereas, standard of care and post-trial obligations are controversial with quite nuanced arguments on many positions, informed consent is a \textit{sina qua non} in human experimental research and is in every guideline and code of ethics and enshrined in human rights and law. In our investigation, almost 60% of researchers reported obtaining informed consent from trial participants. Other important considerations for protecting participants and ensuring their benefit are less likely to be reported or, presumably, conducted. Trials conducted in developing settings appear to use a different quality of care than those conducted in comparatively wealthier settings.

The majority of trials had control arms using active controls, dose comparisons, or parallel assignments, but almost 37% of trials used a placebo for the control group. There was no difference in the likelihood that a placebo is used in clinical event trials (measuring such patient and policy relevant outcomes as morbidity and mortality) or surrogate outcome trials (such as changes in biological parameters, for example, CD4 counts) (OR 1.13, 95% CI = 0.64 to 2.01). Placebo based trials with clinical outcomes where standards of care exist are controversial.\textsuperscript{19} The use of placebo is considered permissible when there is equipoise as to whether a standard of care exists. For all of the conditions we examined, consensus guidelines exist on standards of care, casting doubt on the legitimacy of the need for a placebo.\textsuperscript{20} The justification for a placebo should be made publicly available in the research protocol particularly when effective agents are available.\textsuperscript{21}

Almost all trials registered with the databases failed to report if post-trial provisions would be available to trial participants upon completion of the trial. Post-trial provisions were listed in only 4 of 312 trials and the provisions were vague. One study mentioned that post-trial medication would be provided by the governments of the participating countries. Another study reported that participants who become infected with HIV during the trial

\textsuperscript{17} ‘Active control’ implies that the control group receives a treatment that is known to be effective. More information is available at: http://www.pre.ethics.gc.ca/English/policystatement/section7.cfm#7D [Accessed 21 Feb 2008].


\textsuperscript{21} Lurie & Wolfe, op. cit. note 19.
will receive ongoing supportive counselling, CD4 and viral load monitoring, education about HIV infection/disease, and access to HIV care including free antiretrovirals when clinically indicated. There was no mention of who will provide these provisions and who will ensure that these are provided. It is possible that this is due to the fact that most trials are funded by the US government, which has thus far failed to ratify the International Covenant on Economic, Social and Cultural Rights;\(^{22}\) where access to health care is guaranteed.

Only 13% (95% CI = 0.01 to 0.17) of PIs are from low-to-middle income countries whereas 42% (95% CI = 36 to 47) of trials occur in these countries. Seventy-five percent (75%, 95% CI = 70 to 80) of PIs are from high income countries. Investigators from high income countries are more likely to measure clinical outcomes than investigators from low-to-middle income countries. Moreover, clinical outcomes are five times more likely to occur in low-to-middle income countries than in high income countries. Clinical outcomes measure such outcomes as death, incidence of infection and other serious outcomes; whereas, surrogate markers, more likely to be used in developed settings, measure prognostic markers prior to full-blown disease or mortality. We believe that the likelihood of clinical outcomes being higher in developing settings is linked to an acceptance that disease and poor mortality outcomes are rife in these populations anyway. We can think of no other justification for this discrepancy.

The majority of trials were funded by non-pharmaceutical organizations. Pharmaceutical companies were involved in only 28% of trials. Non-pharmaceutical companies are almost 2.5 times more likely than a pharmaceutical company to be involved in a trial measuring clinical outcomes (OR 2.45). The tendency to demand greater accountability from pharmaceutical companies is thus important but narrowly focussed.\(^{23}\) Similarly, accountability must be demanded from other sponsoring and funding institutions that are measuring clinical outcomes among research participants.

This study should be interpreted once aware of the strengths and limitations of our analysis. There are several strengths to consider about our analysis. Firstly, this is the first study to assess whether publicly available trial protocols report important ethical considerations. We searched publicly available trial registries since the last amendment to the Declaration of Helsinki, a declaration that is non-binding, but arguably represents customary law and has been used successfully in legal cases in developing and developed settings.\(^{24}\) Our searches were extensive and were conducted in duplicate. Finally, our study is the first to examine ethical issues comparing high with low-to-middle income settings, allowing for inferences about the differences between these settings.

There are also several limitations to consider. We searched publicly available protocols, now mandated by law\(^{25}\) and by medical journals before a randomized trial can be published.\(^{26}\) It is possible that other randomized trials exist that may differ in quality and it is indeed likely that registered trials are of a higher quality than non-registered. Publicly accessible databases do not provide the complete protocols for trials, so it is possible that these issues are considered in the full protocol, but not reported in the online databases. However, National Institutes of Health guidelines on registering clinical trials require reporting ethical issues.\(^{27}\) Further, our findings are consistent with previous studies of published manuscripts, so the inferences made about inadequate reporting of these ethical standards remains strong.\(^{28}\) We examined only three major diseases. It is possible, though unlikely, that other diseases would have improved reporting of ethical issues. Finally, because we were limited to the information reported online, we are unaware of the extent ethical principles are adhered to in the field. However, we cannot think of a compelling reason that researchers would withhold this information.

The debate on consensus around international standards of care in clinical trials in developing settings is a heated one and addresses a difficult conundrum for trialists and ethicists alike.\(^{29}\) International guidelines recommend the best standard of care for research participants (Paragraph 29); however, in most developing settings standards of care for non-research participants are very different than standards for non-research participants in

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\(^{25}\) Department of Health and Human Services (HHS). US Food and Drug Administration, op. cit. note 11.

\(^{26}\) Lott, op. cit. note 10; Gold & Studdert, op. cit. note 10.

\(^{27}\) Lott, ibid.


\(^{29}\) Schüklken, op. cit. note 1.
developed settings. The debate is focused on whether research participants should receive the local standard of care or the international standard of care. Ironically, it seems that United Nations agencies now support the sub-optimal standard of care for research participants and permit withholding effective treatment from the control arm of a clinical trial.

The extent to which ethical considerations should be mandatory is an important debate. Certain ethical requirements, such as voluntary participation and informed consent, are considered *jus cojens* requirements in clinical trials and recent court cases and rulings have used international declarations as customary law. Other issues such as standard of care and standards of post-trial access have received considerably less attention, but may indeed receive legal standing. Recent trial closures in Cambodia, Nigeria, Cameroon, and difficulties in Thailand with HIV prophylaxis trials and Nepal with hepatitis E vaccines, indicate that participant communities and activist groups are demanding improved access to care.

Funding sources have emerged as an important ethical dimension, especially in conflict of interest discourse. As clinical research becomes more globalized we are faced with ethical and legal considerations that challenge the research community. Unless clinical trialists pre-empt trial difficulties, we can expect further trial closures and perhaps difficulties in recruiting populations.

**CONCLUSION**

In conclusion, important ethical aspects of clinical trials are under-reported in publicly available trial registries.

Trials intended for developing settings have consistently poorer reporting of ethical considerations than more developed settings. Most trials in developing settings are funded by developed nations and are led by developed nation investigators, underscoring the importance of discussing obligations around standard of care and post-trial obligations. Could the same trial be conducted in a developed nation setting? Will provisions be available to participants at the completion of a successful trial? Since the Declaration of Helsinki and the WMA have not listed different criteria for different research locations, we would not expect to find different outcomes depending on the locations. It is imperative that we resolve the debate as to whether ethical obligations are indeed obligations or simply considerations.

**Supplementary material**

Trials were searched ‘by condition’ from the ClinicalTrials.gov website. Conditions included were: Acquired Immunodeficiency Syndrome/HIV Infections (2505 studies); AIDS Dementia Complex (12 studies); AIDS-Associated Nephropathy (5 studies); AIDS-Related Complex (277 studies); AIDS-Related Opportunistic Infections (160 studies); HIV Seropositivity (38 studies); HIV Wasting Syndrome (14 studies); HIV-Associated Candidiasis (1 study); HIV-Associated Lipodystrophy Syndrome (14 studies); Malaria (216 studies); Malaria, Cerebral (5 studies); Malaria, Falciparum (74 studies); Malaria, Vivax (7 studies); Tuberculosis (146 studies); Tuberculosis, Central Nervous System (1 study); Tuberculosis, Cutaneous (7 studies); Tuberculosis, Meningeal (1 study); Tuberculosis, Multidrug-Resistant (1 study); Tuberculosis, Osteoarticular (1 study); Tuberculosis, Pleural (2 studies); Tuberculosis, Pulmonary (17 studies).

Trials were searched on the Controlled-trials.com website using the terms: ‘HIV’ (3201 studies), ‘AIDS’ (1086 studies), ‘malaria’ (257 studies), and ‘tuberculosis’ (528 studies).

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