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# BMJ Open

## Host, parasite, and drug determinants of clinical outcomes following treatment of visceral leishmaniasis: a protocol for individual participant data meta-analysis

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6 2 following treatment of visceral leishmaniasis: a protocol for  
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8 3 individual participant data meta-analysis  
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## 21 **Abstract**

22 **Introduction:** Visceral leishmaniasis (VL) is a parasitic disease with an estimated 50,000 to  
23 90,000 new cases occurring annually. There is an observed variation in the efficacy of the  
24 current first line therapies across different regions. Such heterogeneity could be a function  
25 of host, parasite, and drug factors. An individual participant data meta-analysis (IPD-MA) is  
26 planned to explore the determinants of treatment outcomes.

27  
28 **Methods and analysis:** The Infectious Diseases Data Observatory (IDDO) VL living systematic  
29 review (IDDO VL LSR) library is an open-access resource of all published therapeutic studies  
30 in VL since 1980 (PROSPERO registration: CRD42021284622). Studies indexed in the IDDO VL  
31 LSR library were screened for eligibility for inclusion in this IPD-MA. Corresponding authors  
32 and principal investigators of the studies meeting the eligibility criteria for inclusion were  
33 invited to be part of the collaborative IPD-MA. Authors agreeing to participate in this  
34 collaborative research were requested to share the IPD using the IDDO (IDDO) VL data  
35 platform. The IDDO VL data platform currently holds datasets from clinical trials  
36 standardised to a common data format and provides a unique opportunity to identify host,  
37 parasite, and drug determinants of treatment outcomes. Multivariable regression models  
38 will be constructed to identify determinants of therapeutic outcomes using generalised  
39 linear mixed effects models accounting for within-study site clustering.

40  
41 **Ethics and dissemination:** The results of this IPD-MA will be disseminated at conferences,  
42 IDDO website and any peer-reviewed publications. All publications will be open source.  
43 Findings of this research will be critically important for the control programmes at  
44 regional/global levels, policy makers and groups developing new VL treatments.

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3 45 **PROSPERO registration:** The systematic review component of the IPD-MA has the following

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6 46 PROSPERO registration: CRD42021284622.

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#### 44 66 **Keywords**

45  
46 67 Visceral Leishmaniasis; Therapeutic Outcome; Statistical Analysis Plan, meta-analysis,

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48 68 individual participant data; relapse

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52 70 Word count: 3478 (main text); abstract (255)

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3 73 ***Strengths and limitations of this study***  
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6 74 • In any single Visceral Leishmaniasis clinical trial, only few relapses are observed which  
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9 75 limits the ability to identify predictors associated with it. An individual participant data  
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11 76 (IPD-MA) will increase the statistical power to detect the predictors and moderators of  
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14 77 treatment outcome.  
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18 79 • The identification of studies eligible for inclusion in the IPD-MA has been made through  
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21 80 a comprehensive literature search of all published studies since 1980 with pre-defined  
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24 81 inclusion-exclusion criteria. However, retrieval of data from trials published prior to  
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26 82 2000 can be a major challenge.  
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31 84 • This IPD-MA will utilise the VL repository of individual participant data hosted by  
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34 85 Infectious Diseases Data Observatory (IDDO VL data platform). A major strength of this  
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36 86 study is that data on the IDDO VL data platform is harmonised to a common standard  
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38 87 based on an extensive consultation with the VL research community.  
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43 89 • A particular scientific challenge is that distinction of relapse from re-infection is seldom  
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46 90 carried out in VL therapeutic trials and hence won't be considered in this analysis.  
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## 93 Introduction

94 Visceral leishmaniasis (VL), also known as kala-azar, is a parasitic disease with  
95 anthroponotic and zoonotic modes of transmission [1]. The disease is characterised by  
96 prolonged fever, cachexia, splenomegaly, hepatomegaly and anaemia. The annual global  
97 incidence of VL is estimated at 50,000 to 90,000 cases, with only 25-45% of the cases  
98 reported to the World Health Organization [2]. The disease has an outbreak potential and  
99 linked with war, conflicts and climate change, and if left untreated, the disease is fatal over  
100 95% of the cases [2-4].

101 The efficacy of antileishmanial regimens in VL varies across geographical regions. For  
102 example, single dose liposomal amphotericin B (L-AmB) has a demonstrated high efficacy  
103 ( $\geq 94\%$ ) in the Indian sub-continent while its efficacy is sub-optimal (58%) in East Africa [5,6].  
104 There are high levels of resistance against antimony-based drugs in India, although it  
105 continues to be used in a combination regimen with paromomycin as a first line therapy in  
106 East Africa [5,6]. The underlying reasons for such variation are not fully understood but the  
107 observed therapeutic response is likely multifactorial and may be a function of drug  
108 resistance, variation in the pharmacokinetic and pharmacodynamic properties of the drugs  
109 used and the underlying host immunity [7-10].

110 Several studies have reported on the determinants of therapeutic outcomes in  
111 studies conducted across different geographical regions and patient populations [11-16].  
112 Additionally, the heterogeneity introduced by variation in study design and conduct leads to  
113 challenges in reliably comparing the effect measures across the studies. A major challenge in  
114 reliably assessing risk factors of therapeutic outcomes is that at individual study level, the  
115 number of events is often small, which limits the precision of the estimated effect.



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3 116 Individual participant data (IPD) meta-analysis (IPD-MA) of existing studies can overcome  
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6 117 this limitation by increasing the effective sample size and allows for greater power in  
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8 118 detecting differential treatment effects across individuals in trials [17].  
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## 10 11 119 **Objectives**

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14 120 The objectives of this IPD-MA are:

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17 121 • To identify host, parasite, and drug determinants of initial cure after the  
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19 122 completion of treatment schedule
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23 123 • To identify host, parasite, and drug determinants of definitive cure at 6  
24  
25 124 months after treatment completion
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27  
28 125 • To identify host, parasite, and drug determinants of relapse at 6 months after  
29  
30 126 treatment completion
- 31  
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34 127 • To identify host, parasite, and drug determinants of mortality outcome at any  
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36 128 time point during the study

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39 129 Primary and secondary endpoints relating to these objectives are defined in the outcomes  
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42 130 section below.  
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3 131 **Methods and analysis: Patients, interventions and outcomes**  
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6 132 **PICOT statement**  
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9 133 *Population:* Any patient enrolled in an interventional study with a confirmed or suspected  
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11 134 diagnosis of VL defined by serological and/or parasitological testing.  
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14 135 *Interventions:* Any antileishmanial therapy  
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17 136 *Comparator:* Not restricted by the use of a comparator drug  
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20 137 *Outcome:* At least one of the following outcomes reported: initial cure, definitive cure,  
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22 138 relapse, or fatality  
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25 139 *Time:* Studies published on or after 1980  
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33 141 ***Criteria for study eligibility***  
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36 142 The following eligibility criteria must be fulfilled for study inclusion:  
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- 39 143 • Prospective clinical efficacy studies on patients with confirmed or suspected VL  
40  
41 144 either using microscopy/serology/molecular method (i.e. clinical diagnosis followed  
42  
43 145 by a confirmatory method)  
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45 146 • Information on constituent drug(s), dose and duration of treatment regimen is  
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47 147 available  
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49 148 • At least one of the following clinical outcomes are measured: initial cure, definitive  
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51 149 cure, relapse or mortality  
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3 151 **Criteria for patient eligibility**  
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6 152 The following minimum information are required for inclusion of a patient in the IPD meta-  
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9 153 analysis:

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12 154 • Details of antileishmanial treatment(s) administered  
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14 155 • Baseline information on age and gender  
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17 156 • Outcome is recorded  
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23 158 **Outcomes**  
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26 159 **Outcomes and definitions:**  
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29 160 **Primary endpoint**  
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32 161 The primary endpoint adopted is cure at 6-months following treatment completion. This is  
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35 162 commonly referred to as 'definitive' or 'final' cure. The precise definition and timing of  
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37 163 definitive cure will vary according to study design. As a minimum, it is expected that a  
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40 164 definitive cure is achieved if the patient remains alive and is no longer be manifesting  
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42 165 symptoms and/or signs of visceral leishmaniasis.  
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45 166 Further analysis of this endpoint will be carried out using a stricter definition of  
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48 167 definitive cure, defined as: achievement of initial cure (as defined below) and no subsequent  
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50 168 rescue treatment or evidence of clinical or parasitological relapse, and no death associated  
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53 169 with VL during the 6-months following treatment completion.  
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56 170 **Secondary endpoints:**  
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59 171 The following secondary endpoints are adopted:  
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3 172 **Initial cure:** Initial cure is defined at the time of initial assessment adopted in the original  
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6 173 study after completion of the therapy along with clinical improvement. The timing of initial  
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8 174 cure assessment would typically take place within 28 days of treatment completion but this  
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11 175 varies slightly across studies.

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14 176 Further analysis of this endpoint will be carried out using a stricter definition of initial cure,  
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16 177 defined as: cure at day 28 or at time-point defined in the original study following treatment,  
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18 178 defined as clinical improvement of VL, absence of parasites in the spleen or bone marrow  
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20  
21 179 using microscopy) and no rescue therapy on or before day 28 or before the timepoint of  
22  
23  
24 180 initial cure assessment adopted in the original study.

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30 182 **Relapse:** Relapse is defined as recurrence of signs and symptoms of VL at any time point  
31  
32 183 during the study follow-up among those who achieved initial cure. The assessment typically  
33  
34 184 takes place at 6 months but this varies slightly across studies.

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37 185 Tissue aspirates for confirming parasitological presence are usually carried out based  
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39 186 on clinical suspicion of relapse during the follow-up [18,19]. Since tissue aspiration for  
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42 187 defining relapse won't be carried out in all the studies, further analysis of this endpoint will  
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44  
45 188 be restricted to studies that defined relapse based on parasitological demonstration.

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51 190 **Mortality:** This is defined as deaths reported as related to the study interventions or due to  
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53 191 the progressive worsening of the disease itself at any time during the study. Further analysis  
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56 192 of this endpoint will be carried out by considering all-cause mortality.

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3 194 ***Variation in time-points:***  
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6 195 The assessment of initial cure and definitive cure is usually undertaken at 1-month and 6-  
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8 196 months post treatment. However, the exact time of these assessment will vary across the  
9  
10 197 studies. Assessments undertaken between 15 to 60 days will be considered as time of initial  
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12 198 cure. For assessments of definitive cure and relapse, assessments made between 5 to 7  
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14 199 months will be considered as 6 months.  
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23 201 **Statistical methods**

24 202 **Identification of relevant studies**

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27 203 Eligible studies were identified from the infectious diseases data observatory (IDDO)  
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29 204 library of all prospective therapeutic studies that has systematically indexes all published  
30  
31 205 therapeutic efficacy studies in VL published from 1980 onwards [20,21]. The IDDO VL clinical  
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33 206 trials library is based on a living systematic review and the database is continually updated  
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35 207 every six months in accordance with the Preferred Reporting Items for Systematic-Reviews  
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37 208 and Meta-Analyses (PRISMA) guidelines [22]. The trial library indexes publications identified  
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39 209 from the following databases: PubMed, Embase, Scopus, Web of Science, Cochrane,  
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41 210 clinicaltrials.gov, WHO ICTRP, Global Index Medicus, IMEMR, IMSEAR, and LILACS. For this  
42  
43 211 current review, the search includes all clinical trials published between 1st of Jan 1980 and  
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45 212 2nd of May 2021. Details of the search strategy adopted is described elsewhere [22]. Studies  
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47 213 indexed in the IDDO VL library were eligible for inclusion in this review if they meet the  
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49 214 inclusion and exclusion criteria outlined above. This review is not limited by language.  
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## 215 **Collation of IPD**

216 Authors (principal investigators, corresponding authors) of the studies in the IDDO  
217 VL LSR library eligible for the inclusion in this IPD-MA were invited to be part of this  
218 collaborative research. Researchers agreeing to the terms and conditions of the submission  
219 were then requested to upload IPD to the IDDO VL data platform through a secured web  
220 portal [23]. Data in the IDDO VL platform are fully pseudonymised to protect personal  
221 information and patient privacy.

## 222 **Data management**

223 Raw data from individual studies shared with IDDO VL data platform are currently  
224 being standardised using the Clinical Data Interchange Standards Consortium (CDISC)  
225 compliant curation standards [24]. If required, investigators will be further contacted to  
226 clarify questions that arise during data curation and analysis, and individual study protocols  
227 will be requested. On standardisation, the data are stored in a relational database  
228 containing information on drug regimen, parasitological, clinical, and haematological  
229 assessments, and therapeutic outcomes.

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3 232 **Statistical methods for primary and secondary outcomes**  
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6 233 **Variables considered for regression modelling:** The following variables will be considered  
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9 234 for inclusion in the analysis of primary and secondary endpoints:  
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12 235 **Host variables:** The following host variables are considered: age, gender, body weight,  
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14 236 nutritional status, comorbidity status (such as HIV), and duration of illness prior to study  
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17 237 enrolment. The following baseline clinical measurements will be considered:  
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19 238 haemoglobin/anaemia status, spleen size, immunological biomarkers (CD4+ count), alanine  
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21 239 transaminase (ALT) and aspartate transaminase (AST), platelets and neutrophils. If data are  
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24 240 available, the following baseline characteristics will be considered: history of blood  
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27 241 transfusion, bilirubin, creatinine, urea, and albumin concentrations.  
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30 242 **Parasite variables:** The following parasite related baseline factors will be considered:  
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32 243 parasite load and information regarding the nature of infection (primary vs. previously  
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34 244 treated cases). Any cases described as previously untreated (or “fresh”) cases for  
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37 245 leishmaniasis will be considered as primary VL. The enumeration of parasite density is  
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40 246 usually carried out by evaluating bone marrow or splenic aspirates or through quantitation  
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42 247 of parasites in unit quantity of specimen or parasite DNA equivalence per PCR reaction  
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44 248 across studies[25–28]; the Chulay-Bryceson scale being the most commonly adopted [25].  
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47 249 The methodology used for parasite gradation will be considered in the analysis.  
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50 250 **Drug variables:** The following drug related variables will be considered for inclusion in  
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52 251 analysis: mg/kg total dose (or target dose) administered [29], treatment duration, whether  
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54 252 the regimen was monotherapy or a combination therapy, mode of drug administration  
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57 253 (intravenous, intramuscular or oral), administration of regimen either as a single dose or as  
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60 254 a multiple doses, direct or indirect observations of drug administration for oral medications.

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3 255 The dosage of antileishmanial interventions will be determined and expressed as dose per  
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6 256 unit body weight (e.g., total mg/kg dosage administered) and will be considered separately  
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8 257 for each drug regimens.  
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14 259 **Study level variables:** The following study or arm level variables will be considered in the  
15  
16 260 analysis of primary and secondary endpoints: geographical region, country, study site, and  
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18 261 calendar year of the study conduct.  
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## 21 22 262 **Statistical analysis and reporting**

### 23 24 25 263 **Descriptive summary:**

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28 264 A summary of included studies will be presented with respect to study location, year  
29  
30 265 of study conduct, characteristics of study population, duration of follow-up, details of drug  
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32 266 regimens including supervision of drug administration, and methodological details adopted  
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34 267 for disease confirmation and treatment outcomes.  
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39 268 Summary of baseline characteristics of the patients included in the analysis will be  
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41 269 presented by geographical region and overall. These include: age; weight; parasite grade at  
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43 270 enrolment; temperature; haemoglobin (or haematocrit) concentration; anaemia and severe  
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45 271 anaemia status, spleen size, description of severity of infection (severe  
46  
47 272 /mild/uncomplicated) if available, total mg/kg dose for each treatment, and supervision of  
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49 273 drug administration. The distribution of the baseline characteristics will be summarised  
50  
51 274 either as a proportion for categorical variables, as the mean (with standard deviation) or  
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53 275 median (with interquartile range) for continuous variables.  
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3 277 ***Analysis of the primary endpoint:***  
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6 278 A mixed effects logistic regression model will be used for identifying the risk factors  
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8 279 for definitive cure in a one-stage IPD-MA. Given a relatively low number of expected events  
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10 280 in each included study, to avoid imprecise estimates from small events and continuity  
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12 281 corrections, a one-stage IPD approach is preferred [30]. A random intercept regression  
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14 282 model will be considered with study sites specified as random effects to account for within-  
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16 283 site clustering of the patients (as some of the trials are multicentre studies).  
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21 284 If information regarding the time of occurrence of event is available, Kaplan-Meier  
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23 285 (K-M) method will be used to estimate the probability of definitive cure at the end of the  
24  
25 286 study follow-up, and a shared frailty Cox regression model will be considered with study site  
26  
27 287 fitted as a frailty term to account for between-study site heterogeneity. The following  
28  
29 288 outcomes will be censored in the survival analysis: lost to follow-up, death due to causes  
30  
31 289 adjudicated as unrelated to the study drug, voluntary withdrawal from the study.  
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37 290 ***Multivariable modelling***  
38  
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40 291 ***Core predictor set***  
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43 292 The following set of variables are the risk factors reported in clinical literature for  
44  
45 293 treatment outcomes in VL: age, sex, baseline parasite density, HIV co-infection, and  
46  
47 294 geographical region. These variables along with the drug regimen will form the minimal  
48  
49 295 adjustment set for assessment of other risk factors and will be kept in the regression model  
50  
51 296 regardless of statistical significance [31].  
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3 297 ***Assessment of other predictors and considerations for multivariable modelling***  
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6 298 The association between the remaining candidate predictors and therapeutic  
7  
8  
9 299 outcomes will be assessed by adjusting for the core predictor sets identified. Multivariable  
10  
11 300 model construction will follow the recommendations of Heinze et al (2017) [32]. Nested  
12  
13 301 models will be compared by assessing the change in log-likelihood estimates and Akaike's  
14  
15  
16 302 information criterion (AIC) will be used for comparing competing non-nested models. The  
17  
18 303 functional form of the continuous variables will be determined using multivariable fractional  
19  
20  
21 304 polynomials [33] or restricted cubic splines [31]. Stability investigations will be undertaken  
22  
23 305 to account for uncertainty introduced in multivariable modelling through bootstrap  
24  
25  
26 306 resampling [32].  
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28

29 307 ***Missing data***  
30  
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32 308 The proportion of missing observation for each of the variables considered in the  
33  
34 309 analysis will be summarised and any missingness patterns will be explored. Multiple  
35  
36  
37 310 imputation [34], which assumes missing at random mechanism for missingness, will be  
38  
39 311 undertaken to handle missing observations. Construction of the imputation model will  
40  
41  
42 312 include all the variables in the target analysis (i.e., all included exposures, outcome in the  
43  
44 313 target analysis), and additional auxiliary variables including any interaction terms and  
45  
46  
47 314 nonlinear associations. The number of imputations will be determined based on the fraction  
48  
49 315 of missing information. The target analysis will then be carried out in each of the completed  
50  
51 316 (observed plus imputed values) datasets and the estimates will be combined across the  
52  
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54 317 imputed datasets using Rubin's combination rules [34].  
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3 319 ***Subgroup analyses***  
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6 320 The following two analyses are planned:  
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- 9 321 • There is a known regional variation in treatment response in VL [5]. Therefore,  
10  
11 322 interaction between treatment and geographical region will be investigated. A separate  
12  
13 323 analysis could be undertaken for each of the geographical regions.  
14  
15  
16 324 • Patients living with HIV who are treated for VL typically have worse outcomes and higher  
17  
18 325 mortality risk than those who are not living with HIV [20,35]. Although, usually an  
19  
20 326 exclusion criterion of therapeutic trials, a separate sub-group analysis will be carried out  
21  
22 327 among patients with defined VL-HIV coinfections (data permitting). An interaction  
23  
24 328 between treatment and HIV status (treatment-covariate interaction) will therefore be  
25  
26 329 considered; within-study interaction will be separated from the between-study  
27  
28 330 interaction by centering the covariates [36].  
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43 332 ***Sensitivity analyses***  
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46 333 Stability investigations will be undertaken to account for uncertainty introduced in  
47  
48 334 multivariable modelling through bootstrap resampling. The robustness of the derived  
49  
50 335 estimates and their variance will be summarised using the recommendations in Heinze et al  
51  
52 336 (2017) [32]. The influence of each of the studies towards the estimated regression  
53  
54 337 coefficients will be assessed by removing each study at a time and estimating the coefficient  
55  
56 338 of variation for the parameter estimates.  
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3 339 **Analysis of secondary endpoints**  
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6 340 **Initial cure:** Proportion of patients achieving initial cure (as defined previously) in each of  
7  
8 341 the studies will be presented. The construction of univariable and multivariable regression  
9  
10 342 models will follow the same approach as for the primary endpoint.  
11  
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13  
14 343 **Relapse:** Proportion of patients achieving relapse (as defined previously) in each of the  
15  
16 344 studies will be presented. The construction of univariable and multivariable regression  
17  
18 345 models will follow the same approach as for the primary endpoint.  
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21  
22 346 **Mortality:** Proportion of deaths reported in each of the studies will be presented. The  
23  
24 347 construction of univariable and multivariable regression models will follow the same  
25  
26 348 approach as for the primary endpoint.  
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30 349 **Software**  
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33 350 All analyses will be carried out using R software or Stata 17 software [37,38]. Use of any  
34  
35 351 other data analysis tools will not change the statistical analysis plan.  
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42 353 **Risk of bias assessment in included studies and in the IPD-MA**  
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45 354 To examine the risk of bias in included studies, the Cochrane risk of bias tool (RoB 2)  
46  
47 355 for randomised studies [39]. Risk of bias in non-randomised studies will be carried out by  
48  
49 356 assessing the pre-intervention, at intervention and post-intervention domains as outlined in  
50  
51 357 using ROBINS-I tool [40].  
52  
53

54  
55 358 To examine the risk of bias in IPD-MA, the first four domains of the quality In  
56  
57 359 prognosis studies (QUIPS) tool and the first three domains of the prediction model risk of  
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3 360 bias assessment tool (PROBAST) will be considered as recommended in Riley et al (2021)  
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5  
6 361 [31]. The relevant domains from the QUIPS checklist are study participation, study attrition,  
7  
8 362 prognostic factor measurement, and outcome measurement, and the relevant domains  
9  
10 363 from PROBAST checklist are patient selection, prognostic factors, and outcomes. Two  
11  
12  
13 364 reviewers will independently assess the risk of bias in the studies included in the analysis.  
14  
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16 365

### 19 366 **Assessment of risk of potential bias in missing studies**

22 367 Despite best possible efforts, it is anticipated that raw data from all the identified  
23  
24 368 studies will not be available. The characteristics of patient population and study meta-data  
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26  
27 369 from the missing studies will be summarised to explore if the missing studies are  
28  
29  
30 370 systematically different from the studies that are included in the meta-analysis. A two-stage  
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32 371 IPD may be conducted if sufficient details (or any covariate adjustment) are reported in the  
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34 372 original studies.  
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3 373 **Dissemination plans**  
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6 374 ***Ethics and dissemination***  
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9 375 This IPD-MA meets the criteria for waiver of ethical review as defined by the Oxford  
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11  
12 376 Tropical Research Ethics Committee (OxTREC) granted to IDDO, as the research consists of  
13  
14 377 secondary analysis of existing anonymised data. Ethical approval was granted to each study  
15  
16  
17 378 included in this pooled analysis by their respective ethics committees. This IPD-MA will  
18  
19 379 address research questions similar to that of included studies. Findings of this IPD-MA will  
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21  
22 380 be reported in open-access, peer-reviewed journals following the PRISMA-IPD guidelines  
23  
24 381 [41].  
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27 382 ***Patient and public involvement***  
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30 383 The research questions considered in this IPD-MA is based on a research agenda  
31  
32  
33 384 developed by the global VL research community [42]. The design and development of this  
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35 385 IPD-MA were done by the study authors only and no patient was involved at any stage.  
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42 387 **Further development of statistical analysis plan**  
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45 388 Major statistical analyses have been included in this plan. Amendments to the  
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47 389 current plan or additional statistical analyses may be required as data accrual is in progress.  
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## 390 Discussion

391 Global commitment over the past few decades has led to significant progress in the  
392 control and elimination of VL. In the Indian subcontinent (ISC) the VL burden has greatly  
393 reduced in the past 15 years [43,44]. Availability of effective antileishmanial treatment is  
394 the cornerstone for achieving and sustaining elimination in the ISC. As the overall incidence  
395 of VL is falling, a growing proportion of the total reported cases in the region is attributed to  
396 relapses [44]. Similarly, a recent report assessing long-term epidemiological trend in South  
397 Sudan has also indicated increasing incidence of relapses over the past two decades [45].  
398 This is an important public health concern as patients with relapse are predisposed to  
399 further relapse, especially in those with HIV co-infections, [12] and thus can fuel the  
400 onwards transmission the disease. Therefore, identification of host, parasite or drug related  
401 characteristics remain crucial for effective case management.

402 Several clinical trials and meta-analyses have highlighted the therapeutic efficacy  
403 and safety of one or more antileishmanial therapies [5,11–13,16,46]. However, risk factors  
404 determining the undesirable therapeutic outcomes remain poorly understood. Underlying  
405 heterogeneities in the published studies in terms of study population, treatment regimen,  
406 outcome definitions, and study designs render difficulties in drawing a comprehensive  
407 conclusion regarding drug efficacy. Some of these difficulties can be ameliorated through an  
408 IPD-MA [17]. We hope that this IPD-MA will provide evidence for the efficacy of different  
409 treatments in VL that can be further considered by policy makers at regional and global  
410 levels.

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3 412 The identification of studies eligible for inclusion in the IPD-MA has been made  
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6 413 through a comprehensive literature search of all published studies since 1980 with pre-  
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8 414 defined inclusion-exclusion criteria. A major strength of this study is that data from several  
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10 415 studies will be harmonised to a common standard based on an extensive consultation with  
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13 416 the VL research community [24], thus allowing us to address some of the methodological  
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15 417 sources of heterogeneity.

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18 418 A major challenge is that a substantial proportion of the studies in the IDDO library  
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20 419 were conducted prior to the year 2000; the retrieval of data from historical trials is a major  
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23 420 challenge. A particular scientific challenge is that misclassification of re-infection as “true”  
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25  
26 421 relapse can potentially introduce bias in relapse estimates. A distinction of relapse and re-  
27  
28 422 infection is seldom carried out in VL therapeutic trials and hence won’t be considered in this  
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31 423 analysis. Evidence from a study conducted in Nepal that used parasite genotyping suggested  
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33 424 late relapses were less likely to be new infections [18], but generalisability to other settings  
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36 425 remains unclear. Finally, the determinants of therapeutic outcomes in this IPD-MA would be  
37  
38 426 limited to the commonly assessed and available clinical-laboratory parameters across VL  
39  
40  
41 427 drug trials.

## 42 43 44 428 **Conclusion**

45  
46 429 This IPD-MA will combine IPD from therapeutic studies from the IDDO VL data platform to  
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49 430 identify the determinants of therapeutic outcomes. Findings of this research will generate  
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51 431 important information for the control programmes at regional and global levels, policy  
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54 432 makers and groups developing new VL treatments.  
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3 433 **Authors' contributions**  
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6 434 All authors listed were responsible for the study conceptualisation. RK, PD, KP, PJG, KS  
7  
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9 435 wrote the first draft of the manuscript. All authors were involved in reading, revising it  
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11 436 critically, editing and approving the final manuscript.  
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18  
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21  
22  
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26 441  
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29 442 **Conflict of Interest**  
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32 443 None  
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38 445 **Data Availability**  
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41 446 N/A as this is an analysis protocol.  
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# BMJ Open

## Host, parasite, and drug determinants of clinical outcomes following treatment of visceral leishmaniasis: a protocol for individual participant data meta-analysis

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<b>Primary Subject Heading</b>:	Global health



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Manuscripts

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6 2 following treatment of visceral leishmaniasis: a protocol for  
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## 21 **Abstract**

22 **Introduction:** Visceral leishmaniasis (VL) is a parasitic disease with an estimated 30,000 new  
23 cases occurring annually. There is an observed variation in the efficacy of the current first  
24 line therapies across different regions. Such heterogeneity could be a function of host,  
25 parasite, and drug factors. An individual participant data meta-analysis (IPD-MA) is planned  
26 to explore the determinants of treatment outcomes.

27  
28 **Methods and analysis:** The Infectious Diseases Data Observatory (IDDO) VL living systematic  
29 review (IDDO VL LSR) library is an open-access resource of all published therapeutic studies  
30 in VL since 1980 (PROSPERO registration: CRD42021284622). For this current review, the  
31 search includes all clinical trials published between 1st of Jan 1980 and 2nd of May 2021.  
32 Studies indexed in the IDDO VL LSR library were screened for eligibility for inclusion in this  
33 IPD-MA. Corresponding authors and principal investigators of the studies meeting the  
34 eligibility criteria for inclusion were invited to be part of the collaborative IPD-MA. Authors  
35 agreeing to participate in this collaborative research were requested to share the IPD using  
36 the IDDO (IDDO) VL data platform. The IDDO VL data platform currently holds datasets from  
37 clinical trials standardised to a common data format and provides a unique opportunity to  
38 identify host, parasite, and drug determinants of treatment outcomes. Multivariable  
39 regression models will be constructed to identify determinants of therapeutic outcomes  
40 using generalised linear mixed effects models accounting for within-study site clustering.

41  
42 **Ethics and dissemination:** This IPD-MA meets the criteria for waiver of ethical review as  
43 defined by the Oxford Tropical Research Ethics Committee (OxTREC) granted to IDDO, as the  
44 research consists of secondary analysis of existing anonymised data (Exempt granted on 29<sup>th</sup>

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3 45 March 2023, OxTREC REF: Infectious Diseases Data Observatory (IDDO)). The results of this  
4  
5 46 IPD-MA will be disseminated at conferences, IDDO website and any peer-reviewed  
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7  
8 47 publications. All publications will be open source. Findings of this research will be critically  
9  
10 48 important for the control programmes at regional/global levels, policy makers and groups  
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12  
13 49 developing new VL treatments.  
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18 51 **PROSPERO registration:** The systematic review component of the IPD-MA has the following  
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20 52 PROSPERO registration: CRD42021284622.  
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58

59 72 **Keywords**  
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3 73 Visceral Leishmaniasis; Therapeutic Outcomes; Statistical Analysis Plan, meta-analysis,  
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6 74 individual participant data; IPD meta-analysis; relapse  
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10 76 Word count: 3478 (main text); abstract (255)  
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13 77 ***Strengths and limitations of this study***  
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- 16 78 • In any single Visceral Leishmaniasis clinical trial, only few relapses are observed which  
17  
18 79 limits the ability to identify predictors associated with it. An individual participant data  
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21 80 meta-analysis (IPD-MA) will increase the statistical power to detect the predictors and  
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24 81 moderators of treatment outcome.  
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28 83 • The identification of studies eligible for inclusion in the IPD-MA has been made through  
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31 84 a comprehensive literature search of all published studies since 1980 with pre-defined  
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33 85 inclusion-exclusion criteria. However, retrieval of data from trials published prior to  
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36 86 2000 can be a major challenge.  
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40 88 • This IPD-MA will utilise the VL repository of individual participant data hosted by  
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43 89 Infectious Diseases Data Observatory (The IDDO VL data platform). A major strength of  
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46 90 this study is that data on the IDDO VL data platform is harmonised to a common  
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48 91 standard based on an extensive consultation with the VL research community.  
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52 93 • A particular scientific challenge is that distinction of relapse from re-infection is seldom  
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55 94 carried out in VL therapeutic trials and hence won't be considered in this analysis.  
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For peer review only

## 97 Introduction

98 Visceral leishmaniasis (VL), also known as kala-azar, is a parasitic disease with  
99 anthroponotic and zoonotic modes of transmission [1]. The disease is characterised by  
100 prolonged fever, cachexia, splenomegaly, hepatomegaly and anaemia. The annual global  
101 incidence of VL is estimated at 30,000 cases, with only 25-45% of the cases reported to the  
102 World Health Organization [2]. The disease has an outbreak potential and linked with war,  
103 conflicts and climate change, and if left untreated, the disease is fatal in over 95% of the  
104 cases [2–4].

105 The efficacy of antileishmanial regimens in VL varies across geographical regions. For  
106 example, single dose liposomal amphotericin B (L-AmB) has a demonstrated high efficacy  
107 ( $\geq 94\%$ ) in the Indian sub-continent while its efficacy is sub-optimal (58%) in East Africa [5,6].  
108 There are high levels of resistance against antimony-based drugs in India, although it  
109 continues to be used in a combination regimen with paromomycin as a first line therapy in  
110 East Africa [5,6]. The underlying reasons for such variation are not fully understood but the  
111 observed therapeutic response is likely multifactorial and may be a function of drug  
112 resistance, variation in the pharmacokinetic and pharmacodynamic properties of the drugs  
113 used and the underlying host immunity [7–10].

114 Several studies have reported on the determinants of therapeutic outcomes in  
115 studies conducted across different geographical regions and patient populations [11–16].  
116 Additionally, the heterogeneity introduced by variation in study design and conduct leads to  
117 challenges in reliably comparing the effect measures across the studies. A major challenge in  
118 reliably assessing risk factors of therapeutic outcomes is that at individual study level, the  
119 number of relapses is often small [17], which limits the precision of the estimated effect.

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3 120 Individual participant data (IPD) meta-analysis (IPD-MA) of existing studies can overcome  
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6 121 this limitation by increasing the effective sample size and allows for greater power in  
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8 122 detecting differential treatment effects across individuals in trials [18].  
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## 10 11 123 **Objectives** 12

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14 124 The objectives of this IPD-MA are:  
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17 125 • To identify host, parasite, and drug determinants of initial cure after the  
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19 126 completion of treatment schedule  
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23 127 • To identify host, parasite, and drug determinants of definitive cure at 6  
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25 128 months after treatment completion  
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29 129 • To identify host, parasite, and drug determinants of relapse at 6 months after  
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31 130 treatment completion  
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34 131 • To identify host, parasite, and drug determinants of mortality outcome at any  
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36 132 time point during the study  
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40 133 Primary and secondary endpoints relating to these objectives are defined in the outcomes  
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42 134 section.  
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3 135 **Methods and analysis: Patients, interventions and outcomes**  
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6 136 **PICOT statement**  
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9 137 *Population:* Any patient enrolled in an interventional study with a confirmed or suspected  
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11 138 diagnosis of VL defined by serological and/or parasitological testing.  
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15 139 *Interventions:* Any antileishmanial therapy  
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18 140 *Comparator:* Not restricted by the use of a comparator drug  
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21 141 *Outcome:* At least one of the following outcomes reported: initial cure, definitive cure,  
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23 142 relapse, or mortality  
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26 143 *Time:* Studies published on or after 1980  
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29 144 **Criteria for study eligibility**  
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33 145 The following eligibility criteria must be fulfilled for study inclusion:  
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36 146 • Prospective clinical efficacy studies on patients with confirmed or suspected VL  
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38 147 either using microscopy/serology/molecular method (i.e. clinical diagnosis followed  
39  
40 148 by a confirmatory method)  
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43 149 • Information on constituent drug(s), dose and duration of treatment regimen is  
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45 150 available  
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48 151 • At least one of the following clinical outcomes are measured: initial cure, definitive  
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50 152 cure, relapse or mortality  
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3 154 **Criteria for patient eligibility**  
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6 155 The following minimum information are required for inclusion of a patient in the IPD meta-  
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9 156 analysis:

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12 157 • Details of antileishmanial treatment(s) administered  
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14 158 • Baseline information on age and gender  
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17 159 • Outcome is recorded  
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20 160 **Outcomes**  
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23 161 **Outcomes and definitions:**  
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26 162 **Primary endpoint**  
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29 163 The primary endpoint adopted is cure at 6-months following treatment completion. This is  
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31  
32 164 commonly referred to as 'definitive' or 'final' cure. The precise definition and timing of  
33  
34 165 definitive cure will vary according to study design. As a minimum, it is expected that a  
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37 166 definitive cure is achieved if the patient remains alive and is no longer be manifesting  
38  
39 167 symptoms and/or signs of visceral leishmaniasis.  
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42 168 Further analysis of this endpoint will be carried out using a stricter definition of  
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45 169 definitive cure, defined as: achievement of initial cure (as defined below) and no subsequent  
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47 170 rescue treatment or evidence of clinical or parasitological relapse, and no death associated  
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49  
50 171 with VL during the 6-months following treatment completion.  
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53 172 **Secondary endpoints:**  
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56 173 The following secondary endpoints are adopted:  
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3 175 **Initial cure**  
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6 176 Initial cure is defined at the time of initial assessment adopted in the original study  
7  
8 177 after completion of the therapy along with clinical improvement. The timing of initial cure  
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10 178 assessment would typically take place within 28 days of treatment completion but this  
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12 179 varies slightly across studies.  
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16 180 Further analysis of this endpoint will be carried out using a stricter definition of initial  
17  
18 181 cure, defined as: cure at day 28 or at time-point defined in the original study following  
19  
20 182 treatment, defined as clinical improvement of VL, absence of parasites in the spleen or bone  
21  
22 183 marrow using microscopy) and no rescue therapy on or before day 28 or before the  
23  
24 184 timepoint of initial cure assessment adopted in the original study.  
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29 185 **Relapse**  
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32 186 Relapse is defined as the recurrence of signs and symptoms of VL at any time point  
33  
34 187 during the study follow-up among those who had achieved initial cure. The assessment  
35  
36 188 typically takes place at 6 months but this varies slightly across studies.  
37  
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40 189 Tissue aspirates for confirming parasitological presence are usually carried out based  
41  
42 190 on clinical suspicion of relapse during the follow-up [19,20]. Since tissue aspiration for  
43  
44 191 defining relapse won't be carried out in all the studies, further analysis of this endpoint will  
45  
46 192 be undertaken by considering the methodology used to define relapse.  
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51 193 **Mortality**  
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54 194 This is defined as deaths reported as related to the study interventions or due to the  
55  
56 195 progressive worsening of the disease itself at any time during the study. Further analysis of  
57  
58 196 this endpoint will be carried out by considering all-cause mortality.  
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### 197 **Variation in time-points**

198           The assessment of initial cure and definitive cure is usually undertaken at 28-days  
199 and 180-days post treatment. However, the exact time of these assessment will vary across  
200 the studies. Assessments undertaken between 15 to 60 days will be considered as time of  
201 initial cure. For assessments of definitive cure and relapse, assessments made between 150  
202 to 210 days will be considered as 180 days.

203

## 204 **Statistical methods**

### 205 **Identification of relevant studies**

206           Eligible studies were identified from the infectious diseases data observatory (IDDO)  
207 library of all prospective therapeutic studies that has systematically indexes all published  
208 therapeutic efficacy studies in VL published from 1980 onwards [21]. The IDDO VL clinical  
209 trials library is based on a living systematic review and the database is continually updated  
210 every six months in accordance with the Preferred Reporting Items for Systematic-Reviews  
211 and Meta-Analyses (PRISMA) guidelines. The trial library indexes publications identified  
212 from the following databases: PubMed, Embase, Scopus, Web of Science, Cochrane,  
213 clinicaltrials.gov, WHO ICTRP, Global Index Medicus, IMEMR, IMSEAR, and LILACS. For this  
214 current review, the search includes all clinical trials published between 1st of Jan 1980 and  
215 2nd of May 2021. Details of the search strategy adopted is described elsewhere [21]. The  
216 search details are presented in a online supplemental file S1. Studies indexed in the IDDO VL  
217 library were eligible for inclusion in this review if they meet the inclusion and exclusion  
218 criteria outlined above. This review is not limited by language.

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3 219 **Collation of IPD**  
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5

6 220 Authors (principal investigators, corresponding authors) of the studies in the IDDO  
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9 221 VL LSR library eligible for the inclusion in this IPD-MA were invited to be part of this  
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11 222 collaborative research. Researchers agreeing to the terms and conditions of the submission  
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13  
14 223 were then requested to upload IPD to the IDDO VL data platform through a secured web  
15  
16 224 portal [22]. Data in the IDDO VL platform are fully pseudonymised to protect personal  
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19 225 information and patient privacy.  
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21  
22 226 **Data management**  
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25 227 Raw data from individual studies shared with IDDO VL data platform are currently  
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27 228 being standardised using the Clinical Data Interchange Standards Consortium (CDISC)  
28  
29  
30 229 compliant curation standards [23]. If required, investigators will be further contacted to  
31  
32 230 clarify questions that arise during data curation and analysis, and individual study protocols  
33  
34  
35 231 will be requested. On standardisation, the data are stored in a relational database  
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37 232 containing information on drug regimen, parasitological, clinical, and haematological  
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40 233 assessments, and therapeutic outcomes.  
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3 236 **Statistical methods for primary and secondary outcomes**  
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6 237 **Variables considered for regression modelling:** The following variables will be considered  
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9 238 for inclusion in the analysis of primary and secondary endpoints:  
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11  
12 239 **Host variables**  
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15 240 The following host variables are considered: age, gender, body weight, nutritional  
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17 241 status, comorbidity status (such as HIV), and duration of illness prior to study enrolment.  
18

19  
20 242 The following baseline clinical measurements will be considered: haemoglobin/anaemia  
21  
22 243 status, spleen size, immunological biomarkers (CD4+ count), alanine transaminase (ALT) and  
23  
24 244 aspartate transaminase (AST), platelets and neutrophils. If data are available, the following  
25  
26 245 baseline characteristics will be considered: history of blood transfusion, bilirubin, creatinine,  
27  
28 246 urea, and albumin concentrations.  
29  
30

31  
32  
33 247 **Parasite variables**  
34

35  
36 248 The following parasite related baseline factors will be considered: parasite load and  
37  
38 249 information regarding the nature of infection (primary vs. previously treated cases). Any  
39  
40 250 cases described as previously untreated (or “fresh”) cases for leishmaniasis will be  
41  
42 251 considered as primary VL. The enumeration of parasite density is usually carried out by  
43  
44 252 evaluating bone marrow or splenic aspirates or through quantitation of parasites in unit  
45  
46 253 quantity of specimen or parasite DNA equivalence per PCR reaction across studies [24–27];  
47  
48 254 the Chulay-Bryceson scale being the most commonly adopted [24]. The methodology used  
49  
50 255 for parasite gradation will be considered in the analysis.  
51  
52

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55  
56 256 **Drug variables**  
57  
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3 257 The following drug related variables will be considered for inclusion in analysis:  
4  
5  
6 258 mg/kg total dose (or target dose) administered [28], treatment duration, whether the  
7  
8 259 regimen was monotherapy or a combination therapy, mode of drug administration  
9  
10 260 (intravenous, intramuscular or oral), administration of regimen either as a single dose or as  
11  
12  
13 261 a multiple doses, direct or indirect observations of drug administration for oral medications.  
14  
15 262 The dosage of antileishmanial interventions will be determined and expressed as dose per  
16  
17 263 unit body weight (e.g., total mg/kg dosage administered) and will be considered separately  
18  
19  
20 264 for each drug regimens.

### 23 265 **Study level variables**

26 266 The following study or arm level variables will be considered in the analysis of  
27  
28  
29 267 primary and secondary endpoints: country, study site, and calendar year of the study  
30  
31 268 conduct.

### 34 269 **Geographical variation in treatment response**

37 270 There is a known regional variation in treatment response in VL [5], along with  
38  
39  
40 271 differences in patient characteristics and treatment guidelines. Therefore, a separate  
41  
42 272 analysis will be undertaken within each geographical region to construct the univariable and  
43  
44  
45 273 multivariable regression models for the primary and secondary outcomes.

### 48 274 **Statistical analysis and reporting**

#### 51 275 **Descriptive summary**

54 276 A summary of included studies will be presented with respect to study design, study  
55  
56  
57 277 location, year of study conduct, characteristics of study population, duration of follow-up,  
58  
59  
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2  
3 278 details of drug regimens including supervision of drug administration, and methodological  
4  
5  
6 279 details adopted for disease confirmation and treatment outcomes.  
7  
8

9 280 Summary of baseline characteristics of the patients included in the analysis will be  
10  
11 281 presented by geographical region and overall. These include: age, weight, parasite grade at  
12  
13 282 enrolment, temperature, haemoglobin (or haematocrit) concentration, anaemia and severe  
14  
15 283 anaemia status, spleen size, description of severity of infection (severe/mild/uncomplicated)  
16  
17 284 if available, total mg/kg dose for each treatment, and supervision of drug administration.  
18  
19 285 The distribution of the baseline characteristics will be summarised either as a proportion for  
20  
21 286 categorical variables, as mean (with standard deviation) or median (with interquartile range)  
22  
23 287 for continuous variables.  
24  
25  
26  
27  
28  
29 288  
30  
31

32 289 ***Analysis of the primary endpoint:***  
33  
34

35 290 A mixed effects logistic regression model will be used for identifying the risk factors  
36  
37 291 for definitive cure in a one-stage IPD-MA. Given a relatively low number of expected events  
38  
39 292 (for relapse) in each included study [17], to avoid imprecise estimates from small events and  
40  
41 293 continuity corrections, a one-stage IPD approach is preferred [29]. A random intercept  
42  
43 294 regression model will be considered with study sites specified as random effects to account  
44  
45 295 for within-site clustering of the patients (as some of the trials are multicentre studies).  
46  
47  
48  
49

50 296 If information regarding the time of occurrence of event is available, Kaplan-Meier  
51  
52 297 (K-M) method will be used to estimate the probability of definitive cure at the end of the  
53  
54 298 study follow-up, and a Cox regression model will be considered with study sites fitted as a  
55  
56 299 frailty term to account for between-study site heterogeneity. The following outcomes will  
57  
58  
59  
60



1  
2  
3 300 be censored in the survival analysis: lost to follow-up, death due to causes adjudicated as  
4  
5  
6 301 unrelated to the study drug, voluntary withdrawal from the study.  
7

## 8 302 ***Multivariable modelling***

### 9 303 ***Core predictor set***

10  
11  
12  
13  
14  
15 304 The following set of variables are the risk factors reported in clinical literature for  
16  
17 305 treatment outcomes in VL: age, sex, baseline parasite density, and HIV co-infection. These  
18  
19  
20 306 variables along with the drug regimen will form the minimal adjustment set for assessment  
21  
22 307 of other risk factors and will be kept in the regression model regardless of statistical  
23  
24  
25 308 significance [30].  
26  
27

### 28 309 ***Assessment of other predictors and considerations for multivariable modelling***

29  
30  
31 310 The association between the remaining candidate predictors and therapeutic  
32  
33 311 outcomes will be assessed by adjusting for the core predictor sets identified. Multivariable  
34  
35  
36 312 model construction will follow the recommendations of Heinze et al (2017) [31]. Nested  
37  
38 313 models will be compared by assessing the change in log-likelihood estimates and Akaike's  
39  
40  
41 314 information criterion (AIC) will be used for comparing competing non-nested models. The  
42  
43 315 functional form of the continuous variables will be determined using multivariable fractional  
44  
45  
46 316 polynomials [32] or restricted cubic splines [30]. Stability investigations will be undertaken  
47  
48 317 to account for uncertainty introduced in multivariable modelling through bootstrap  
49  
50  
51 318 resampling [31].  
52

### 53 319 ***Missing data***

54  
55  
56  
57 320 The proportion of missing observation for each of the variables considered in the  
58  
59 321 analysis will be summarised and any missingness patterns will be explored. Multiple  
60

1  
2  
3 322 imputation [33], which assumes missing at random mechanism for missingness, will be  
4  
5  
6 323 undertaken to handle missing observations. Construction of the imputation model will  
7  
8 324 include all the variables in the target analysis (i.e., all included exposures, outcome in the  
9  
10 325 target analysis), and additional auxiliary variables including any interaction terms and  
11  
12  
13 326 nonlinear associations. The number of imputations will be determined based on the fraction  
14  
15 327 of missing information. The target analysis will then be carried out in each of the completed  
16  
17  
18 328 (observed plus imputed values) datasets and the estimates will be combined across the  
19  
20 329 imputed datasets using Rubin's combination rules [33].  
21  
22

### 23 330 ***Subgroup analysis***

24  
25  
26 331 Patients living with HIV who are treated for VL typically have worse outcomes and  
27  
28  
29 332 higher mortality risk than those who are not living with HIV [34,35]. Although, usually an  
30  
31 333 exclusion criterion of therapeutic trials, a separate sub-group analysis will be carried out  
32  
33  
34 334 among patients with defined VL-HIV coinfections (data permitting). An interaction between  
35  
36 335 treatment and HIV status (treatment-covariate interaction) will therefore be considered;  
37  
38  
39 336 within-study interaction will be separated from the between-study interaction by centering  
40  
41 337 the covariates [36].  
42  
43

### 44 338 ***Sensitivity analyses***

45  
46  
47 339 Stability investigations will be undertaken to account for uncertainty introduced in  
48  
49  
50 340 multivariable modelling through bootstrap resampling. The robustness of the derived  
51  
52 341 estimates and their variance will be summarised using the recommendations in Heinze et al  
53  
54 342 (2017) [31]. The influence of each of the studies towards the estimated regression  
55  
56  
57 343 coefficients will be assessed by removing each study at a time and estimating the coefficient  
58  
59 344 of variation for the parameter estimates.  
60

## 345 **Analysis of secondary endpoints**

### 346 ***Initial cure***

347 The proportion of patients achieving initial cure (as defined previously) in each of  
348 the studies will be presented. The construction of univariable and multivariable regression  
349 models will follow the same approach as for the primary endpoint.

### 350 ***Relapse***

351 The proportion of patients achieving relapse (as defined previously) in each of the  
352 studies will be presented. The construction of univariable and multivariable regression  
353 models will follow the same approach as for the primary endpoint.

### 354 ***Mortality***

355 The proportion of deaths reported in each of the studies will be presented. The construction  
356 of univariable and multivariable regression models will follow the same approach as for the  
357 primary endpoint.

## 358 **Software**

359 All analyses will be carried out using R software or Stata 17 software [37,38]. Use of  
360 any other data analysis tools will not change the statistical analysis plan.

## 361 **Risk of bias assessment in included studies and in the IPD-MA**

362 To examine the risk of bias in included studies, the Cochrane risk of bias tool (RoB 2)  
363 for randomised studies [39]. Risk of bias in non-randomised studies will be carried out by  
364 assessing the pre-intervention, at intervention and post-intervention domains as outlined in  
365 using ROBINS-I tool [40].

1  
2  
3 366 To examine the risk of bias in IPD-MA, the first four domains of the quality In  
4  
5  
6 367 prognosis studies (QUIPS) tool and the first three domains of the prediction model risk of  
7  
8 368 bias assessment tool (PROBAST) will be considered as recommended in Riley et al (2021)  
9  
10 369 [30]. The relevant domains from the QUIPS checklist are study participation, study attrition,  
11  
12  
13 370 prognostic factor measurement, and outcome measurement, and the relevant domains  
14  
15 371 from PROBAST checklist are patient selection, prognostic factors, and outcomes. Two  
16  
17  
18 372 reviewers will independently assess the risk of bias in the studies included in the analysis.  
19  
20

### 21 373 **Assessment of risk of potential bias in missing studies**

22  
23  
24 374 Despite best possible efforts, it is anticipated that raw data from all the identified  
25  
26 375 studies will not be available. The characteristics of patient population and study meta-data  
27  
28  
29 376 from the missing studies will be summarised to explore if the missing studies are  
30  
31 377 systematically different from the studies that are included in the meta-analysis. A two-stage  
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33  
34 378 IPD may be conducted if sufficient details (or any covariate adjustment) are reported in the  
35  
36 379 original studies.  
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## 380 **Dissemination plans**

### 381 ***Ethics and dissemination***

382 This IPD-MA meets the criteria for waiver of ethical review as defined by the Oxford  
383 Tropical Research Ethics Committee (OxTREC) granted to IDDO, as the research consists of  
384 secondary analysis of existing anonymised data (Exempt granted on 29<sup>th</sup> March 2023,  
385 OxTREC REF: Infectious Diseases Data Observatory (IDDO)). Ethical approval was granted to  
386 each study included in this pooled analysis by their respective ethics committees. This IPD-  
387 MA will address research questions similar to that of included studies. Findings of this IPD-  
388 MA will be reported in open-access, peer-reviewed journals following the PRISMA-IPD  
389 guidelines [41].

### 390 ***Patient and public involvement***

391 The research questions considered in this IPD-MA is based on a research agenda  
392 developed by the global VL research community [42]. The design and development of this  
393 IPD-MA were done by the study authors only and no patient was involved at any stage.

### 394 **Further development of statistical analysis plan**

395 Major statistical analyses have been included in this plan. Amendments to the  
396 current plan or additional statistical analyses may be required as data accrual is in progress  
397 and will be transparently reported in subsequent reports of the results.

## 398 Discussion

399 Global commitment over the past few decades has led to significant progress in the  
400 control and elimination of VL. In the Indian subcontinent (ISC) the VL burden has greatly  
401 reduced in the past 15 years [43,44]. Availability of effective antileishmanial treatment is the  
402 cornerstone for achieving and sustaining elimination in the ISC. As the overall incidence of  
403 VL is falling, a growing proportion of the total reported cases in the region is attributed to  
404 relapses [44]. A recent report from South Sudan has also indicated increasing incidence of  
405 relapses over the past two decades [45]. This is an important public health concern as  
406 patients with relapse are predisposed to further relapse, especially among those with HIV  
407 co-infections [12]. Increasingly large proportion of VL patients have been found to present  
408 with HIV co-infections in Brazil (0.7% in 2001 to 8.5% in 2012), India (0.88% in 2000 to 4.19%  
409 in 2020) and Northern Ethiopia (15-35%)[35]. A study in India found that over half of those  
410 with HIV co-infections were unaware of their status [46]. This presents an important  
411 challenge to the ongoing control and elimination efforts as patients with VL-HIV co-  
412 infections typically have worse outcomes and higher mortality risk than those who are not  
413 living with HIV [34,35]. VL-HIV patients are also recognised as an important reservoir of  
414 transmission as the co-infected patients are predisposed to multiple relapses, and have a  
415 high potential for infectiousness to sand-flies due to the generally high parasite loads and  
416 poses threat to the control and elimination efforts [47,48]. Therefore, the identification of  
417 host, parasite or drug related characteristics remain crucial not only for effective case  
418 management but also for disease control and elimination.

419 Several clinical trials and meta-analyses have highlighted the therapeutic efficacy  
420 and safety of one or more antileishmanial therapies [5,11–13,16,34]. However, risk factors

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3 421 determining the undesirable therapeutic outcomes remain poorly understood. Underlying  
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5 422 heterogeneities in the published studies in terms of study population, treatment regimen,  
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8 423 outcome definitions, and study designs render difficulties in drawing a comprehensive  
9  
10 424 conclusion regarding drug efficacy. In addition, the national treatment guidelines differ in  
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12  
13 425 terms of practices and approaches for case management. Some of these limitations could be  
14  
15 426 addressed through a well-designed prospective study, which will incur a substantial  
16  
17 427 logistical and financial costs to reach a critical mass required for robust investigation of the  
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19 428 predictors of treatment relapse and remains unfeasible to achieve within short period of  
20  
21 429 time. Utilising the existing datasets and undertaking a carefully planned IPD-MA can  
22  
23 430 ameliorate some of these limitations [18]. We hope that this IPD-MA will provide evidence  
24  
25 431 for the efficacy of different treatments in VL that can be further considered by policy makers  
26  
27 432 at regional and global levels.  
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33 433 The identification of studies eligible for inclusion in the IPD-MA has been made  
34  
35 434 through a comprehensive literature search of all published studies since 1980 with pre-  
36  
37 435 defined inclusion-exclusion criteria. A major strength of this study is that data from several  
38  
39 436 studies will be harmonised to a common standard based on an extensive consultation with  
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41 437 the VL research community [23], thus allowing us to address some of the methodological  
42  
43 438 sources of heterogeneity.  
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48 439 A major challenge is that a substantial proportion of the studies in the IDDO library  
49  
50 440 were conducted prior to the year 2000; the retrieval of data from historical trials is a major  
51  
52 441 challenge. A particular scientific challenge is that misclassification of re-infection as “true”  
53  
54 442 relapse can potentially introduce bias in relapse estimates. A distinction of relapse and re-  
55  
56 443 infection is seldom carried out in VL therapeutic trials and hence won’t be considered in this  
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3 444 IPD-MA. Evidence from a study in Nepal suggested late relapses were less likely to be new  
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6 445 infections [19], but generalisability to other settings remains unclear. Finally, the  
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8 446 determinants of therapeutic outcomes in this IPD-MA would be limited to the commonly  
9  
10 447 assessed and available clinical-laboratory parameters across VL drug trials. Similarly, the  
11  
12  
13 448 exploration of parasitic factors is limited to parasite gradation and the nature of the  
14  
15 449 infection (primary vs previously treated cases). Other important parasite factors such as *in*  
16  
17 450 *vitro* status of drug susceptibility, their virulence, and the underlying genomic plasticity  
18  
19 451 allowing parasites to undergo mutation under drug pressure[49,50] are not routinely  
20  
21  
22 452 collected in clinical trials and hence remains beyond the scope of this IPD-MA.  
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26 453 This IPD-MA will combine data from the studies in the IDDO VL data platform to  
27  
28 454 identify the determinants of therapeutic outcomes. Findings of this research will generate  
29  
30 455 important information for the control programmes at regional and global levels, policy  
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33 456 makers and groups developing new VL treatments.  
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3 457 **Authors' contributions**  
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5

6 458 Study Conception: RK, PD, SSP, NAS, AM, CN, JW, GB, MR, PM, FA, SS, KR, KS, PJG and KP.  
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8  
9 459 Project supervision: SSP, MR, KP, PJG.  
10

11  
12 460 Methodology: PD, NAS, SSP, SS, KR, JW, FA, PJG, KS  
13

14  
15 461 Data curation: AM, SSP, PM, JW, PD, GB  
16

17  
18 462 Project administration: SSP, CN  
19

20  
21 463 Funding acquisition: PJG  
22

23  
24 464 Resources: SSP, FA, PJG  
25

26  
27 465 Writing-original draft: RK, PD, KP, PJG, KS  
28

29  
30 466 Writing- review and editing: All authors were involved in reading and critical revision of the  
31  
32 467 initial draft and approved the final manuscript.  
33  
34

35  
36 468  
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40

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43

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46

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48  
49

50 473 **Conflict of Interest**  
51

52  
53 474 None  
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55  
56 475 **Data Availability**  
57

58  
59 476 N/A as this is an analysis protocol.  
60

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## Example of Search Strategies: The dates will be different for future searches

### Pubmed

((((((((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))) AND Clinical Trial[ptyp])) AND (((("Leishmaniasis, Visceral"[Mesh]) OR visceral leishmaniasis[Title/Abstract]) OR kala azar[Title/Abstract]) OR black fever[Title/Abstract])) OR (((((((((((("Pentamidine"[Mesh]) OR "liposomal amphotericin B" [Supplementary Concept]) OR "Amphotericin B"[Mesh]) OR "Paromomycin"[Mesh]) OR "miltefosine" [Supplementary Concept]) OR "Sodium"[Mesh]) OR "8-aminoquinoline" [Supplementary Concept]) OR "Ketoconazole"[Mesh]) OR "Azoles"[Mesh]) OR "Allopurinol"[Mesh]) OR ( "Atovaquone"[Mesh] OR "atovaquone, proguanil drug combination" [Supplementary Concept] ))) OR ((pentamidine[Title/Abstract] OR ambisome[Title/Abstract] OR amphotericin[Title/Abstract] OR paromomycin[Title/Abstract] OR miltefosine[Title/Abstract] OR pentavalent[Title/Abstract] OR sodium[Title/Abstract] OR sitamaquine[Title/Abstract] OR azole\*[Title/Abstract] OR allopurinol[Title/Abstract] OR atovaquone[Title/Abstract] OR ketoconazole[Title/Abstract] OR fluconazole[Title/Abstract] OR metronidazole[Title/Abstract]))) AND (((("Leishmaniasis, Visceral"[Mesh]) OR visceral leishmaniasis[Title/Abstract]) OR kala azar[Title/Abstract]) OR black fever[Title/Abstract])))) NOT (((animals not humans)))  
 Filters activated: Publication date from 2016/01/01 to 2020/12/31.

- This search strategy uses the PubMed RCT filter for sensitivity- and precision-maximising version (2008). <https://work.cochrane.org/pubmed>

### Database: Embase 1974 to present

#### Search Strategy:

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- 1 exp visceral leishmaniasis/ (9675)
- 2 "black fever".ti,ab. (17)
- 3 "kala azar".ti,ab. (2227)
- 4 "visceral leishmaniasis".ti,ab. (9360)
- 5 1 or 2 or 3 or 4 (12383)
- 6 exp randomized controlled trial/ (603493)
- 7 Controlled clinical study/ (464274)
- 8 Random\$.ti,ab. (1531396)
- 9 randomization/ (86779)
- 10 intermethod comparison/ (260073)
- 11 placebo.ti,ab. (305154)
- 12 (compare or compared or comparison).ti. (507638)
- 13 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2100417)
- 14 (open adj label).ti,ab. (78868)
- 15 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (231216)
- 16 double blind procedure/ (172220)
- 17 parallel group\$.ti,ab. (25399)
- 18 (crossover or cross over).ti,ab. (104779)

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3 19 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or  
4 subject\$1 or participant\$1)).ti,ab. (328145)  
5 20 (assigned or allocated).ti,ab. (386517)  
6 21 (controlled adj7 (study or design or trial)).ti,ab. (346624)  
7 22 (volunteer or volunteers).ti,ab. (245818)  
8 23 trial.ti. (298535)  
9 24 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23  
10 (4650673)  
11 25 5 and 24 (1506)  
12 26 (pentamidine or ambisome or amphotericin or paromomycin or miltefosine or pentavalent or sodium or  
13 sitamaquine or azole\* or allopurinol or atovaquone or ketoconazole or fluconazole or metronidazole).mp.  
14 (1012481)  
15 27 5 and 26 (3701)  
16 28 25 or 27 (4786)  
17 29 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)  
18 (6396469)  
19 30 28 not 29 (3730)  
20 31 30 (3730)  
21 32 limit 31 to yr="2016 -Current" (774)

- This search strategy uses the Cochrane RCT filter for Embase.

<https://www.cochranelibrary.com/central/central-creation>

## Scopus

(( TITLE-ABS-KEY ( "visceral leishmaniasis" OR "kala azar" OR "black fever" )) AND (( TITLE-ABS-KEY ( random\* OR rct OR placebo OR allocat\* OR crossover\* OR "cross over" OR trial OR ( doubl\* W/1 blind\* ) OR ( singl\* W/1 blind\* )) ) OR ( TITLE-ABS-KEY ( control\* W/1 trial\* )) OR ( TITLE-ABS-KEY ( cohort\* )) ) ) OR (( TITLE-ABS-KEY ( "visceral leishmaniasis" OR "kala azar" OR "black fever" )) AND ( TITLE-ABS-KEY ( pentamidine OR ambisome OR amphotericin OR paromomycin OR miltefosine OR pentavalent OR sodium OR sitamaquine OR azole\* OR allopurinol OR atovaquone OR ketoconazole OR fluconazole OR metronidazole )) ) AND ( EXCLUDE ( EXACTKEYWORD , "Animals" ) OR EXCLUDE ( EXACTKEYWORD , "Animal" ) OR EXCLUDE ( EXACTKEYWORD , "Animal Experiment" ) OR EXCLUDE ( EXACTKEYWORD , "Mouse" ) OR EXCLUDE ( EXACTKEYWORD , "Mice" ) OR EXCLUDE ( EXACTKEYWORD , "Dogs" )) AND ( LIMIT-TO ( LIMIT-TO ( PUBYEAR , 2020 ) OR ( PUBYEAR , 2019 ) OR LIMIT-TO ( PUBYEAR , 2018 ) OR LIMIT-TO ( PUBYEAR , 2017 ) OR LIMIT-TO ( PUBYEAR , 2016 ) )

## Web of Science Core Collection

1. TOPIC: ("visceral leishmaniasis" OR "kala azar" OR "black fever")
2. TOPIC: (random\* OR rct OR placebo OR allocat\* OR crossover\* OR "cross over" OR trial OR (doubl\* near/1 blind\*) OR (singl\* near/1 blind\*))
3. TOPIC: (control\* near/1 trial\*)
4. TOPIC: (cohort\*)
5. #4 OR #3 OR #2
6. #5 AND #1
7. TOPIC: (pentamidine OR ambisome OR amphotericin OR paromomycin OR miltefosine OR pentavalent OR sodium OR sitamaquine OR azole\* OR allopurinol OR atovaquone OR ketoconazole OR fluconazole OR metronidazole)

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- 3 8. #7 AND #1
- 4 9. #8 OR #6
- 5 10. #8 OR #6
- 6 11. Refined by: PUBLICATION YEARS: ( 2020 OR 2019 OR 2018 OR 2017 OR 2016 )
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### Cochrane Central Register of Controlled Trials

Issue 5 of 12, May 2020

#1 MeSH descriptor: [Leishmaniasis, Visceral] explode all trees 39

#2 "black fever" 1

#3 "kala azar" 119

#4 "visceral leishmaniasis" 242

#5 #1 or #2 or #3 or #4 283

Custom Range: 2016 to 2020

World Health Organization Global Index Medicus <https://www.globalindexmedicus.net/>

tw:(tw:(("visceral leishmaniasis" OR "kala azar" OR "black fever") ) AND (instance:"ghl") AND ( year\_cluster("2016" OR "2017" OR "2018" OR "2019" OR "2020")))) AND (instance:"ghl")

ClinicalTrials.gov Advanced Search <https://clinicaltrials.gov/ct2/search/advanced?>

Condition or disease: visceral leishmaniasis OR kala azar OR black fever

WHO International Clinical Trials Registry Platform <http://apps.who.int/trialsearch/>

visceral leishmaniasis OR kala azar OR black fever – Trials at ALL stages  
2016 – date

NOTE: THIS PLATFORM IS UNAVAILABLE ON 14/05/2020

PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item
<b>Administrative information</b>		
Title:		
Identification	1a	A protocol for individual participant data meta-analysis; page 1; line 2-3.
Update	1b	Not applicable
Registration	2	PROSPERO registration: CRD42021284622; page 3; lines 47-48.
Authors:		
Contact	3a	Name with institutional affiliations of all authors and e-mail address corresponding authors; page 1; line 5-20. E-mail address of all authors; page 3; line 50-66
Contributions	3b	Authors' contribution; page 23; line 453-456.
Amendments	4	Not applicable
Support:		
Sources	5a	Funding; page 23; line 458-461.
Sponsor	5b	Funding; page 23; line 458-461.
Role of sponsor or funder	5c	Funding agency's role; page 23; line 461.
<b>Introduction</b>		
Rationale	6	Rationale; page 5-6; line 94-118.
Objectives	7	Study objectives; page 6; line 120-131.
<b>Methods</b>		
Eligibility criteria	8	PICOT statement, study eligibility and patient eligibility; page 7-8
Information sources	9	Identification of relevant studies; page 10; line 202-214.
Search strategy	10	Identification of relevant studies; page 10; line 202-214.
Study records:		
Data management	11a	Data management; page 11; line 222-230.

Section and topic	Item No	Checklist item
Selection process	11b	Identification of relevant studies; page 10; line 202-214.
Data collection process	11c	Collation of IPD; page 11; line 216-221.
Data items	12	Statistical methods for primary and secondary outcomes; page 13-14
Outcomes and prioritization	13	Outcomes; page 8-10; line 159-200.
Risk of bias in individual studies	14	Risk of bias assessment in included studies and in the IPD-MA; page 17-18; line 357-375.
Data synthesis	15a	Missing data; page 15; line 316-325.
	15b	Assessment of risk of potential bias in missing studies; page 18; line 369-375.
	15c	Subgroup analyses, Sensitivity analyses; page 17; line 320-339.
	15d	Assessment of risk of potential bias in missing studies; page 16; line 326-340.
Meta-bias(es)	16	Risk of bias assessment in included studies and in the IPD-MA; page 17-18; line 357-375.
Confidence in cumulative evidence	17	Risk of bias assessment in included studies and in the IPD-MA; page 17-18; line 357-375.