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The efficacy of artemisinin-based and quinine-based treatments for uncomplicated falciparum malaria in pregnancy: a protocol for systematic review and individual patient data (IPD) meta-analysis

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1 The efficacy of artemisinin-based and quinine-based treatments for uncomplicated
2 falciparum malaria in pregnancy: a protocol for systematic review and individual patient data
3 (IPD) meta-analysis

4
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21
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23 Key words: malaria, pregnancy, treatment efficacy, individual patient data meta-analysis,
24 artemisinin, quinine

25 Abstract

26 *Introduction*

27 Pregnant women are more vulnerable to malaria leading to adverse impact on both mothers
28 and fetuses. However, knowledge on the efficacy and safety of antimalarials in pregnancy is
29 limited by the paucity of randomised control trials and the lack of standardised protocols in this
30 sub-population. Pooling individual patient data (IPD) for meta-analysis could address in part these
31 limitations to summarise accurately the currently available evidence on treatment efficacy and risk
32 factors of treatment failure.

33 *Methods and analysis*

34 To assess the treatment efficacy of artemisinin-based and quinine-based treatments for
35 uncomplicated falciparum malaria in pregnancy, seven databases (MEDLINE, Embase, Global
36 Health, Cochrane Library, Scopus, Web of Science and LILACS) and two clinical trial registries
37 (ICTRP and ClinicalTrial.gov) were searched. Both interventional and observational cohort
38 studies following up for at least 28 days will be included. IPD of the identified eligible published
39 or unpublished studies will be sought by inviting principal investigators. Raw IPD will be shared
40 through the web-based secure platform developed by WorldWide Antimalarial Resistance
41 Network (WWARN) using the established methodology. The primary objective is to compare the
42 risk of polymerase chain reaction (PCR)-corrected treatment failure among different treatments
43 and to find the risk factors. One-stage IPD meta-analysis by Cox model with shared frailty will be
44 conducted. Sensitivity analyses will assess the effect of studies with different study designs and
45 also those whose IPD are not obtained.

46 *Ethics and Dissemination*

47 This IPD meta-analysis consists of secondary analysis of existing anonymous data and
48 meets the criteria for waiver of ethical review by the Oxford Tropical Research Ethics Committee.
49 The results of this IPD meta-analysis will be disseminated through open-access publications at
50 peer-reviewed journals. The study results will lead to better understanding of malaria treatment in
51 pregnancy, which can be used for clinical decision-making and conducting further studies.

52 *PROSPERO registration number: CRD42018104013.*

53 Article Summary

54 *Strengths and limitations of this study*

- 55 • The research on the efficacy of antimalarials in pregnancy has been restricted by the paucity
56 of randomised control trials and the lack of a standard study design for pregnancy.
- 57 • This will be the first individual patient data (IPD) meta-analysis on the efficacy of currently
58 recommended antimalarials in pregnancy incorporating IPD from both interventional and
59 observational cohort studies.
- 60 • IPD that are standardised in the same format and analysed in a uniform way with
61 adjustment of covariates, will allow us to compare the efficacy of different treatment as
62 well as to find risk factors of treatment failure in this vulnerable but neglected population.
- 63 • The collection of IPD globally will ensure the generalisability of the results.

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3 64 • Limitations of this IPD meta-analysis include the potential difficulty in acquiring the IPD
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5 65 and the heterogeneity of the study designs, study population and parasite population. A risk
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7 66 of bias analysis will be conducted to address the impact of potential unshared data.
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- Limitations of this IPD meta-analysis include the potential difficulty in acquiring the IPD and the heterogeneity of the study designs, study population and parasite population. A risk of bias analysis will be conducted to address the impact of potential unshared data.

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67 Introduction

68 About 60% of all pregnancies are estimated to take place in malaria endemic areas.¹ In
69 addition, pregnant women are amongst the most vulnerable groups for malaria infection leading
70 to higher morbidity and mortality of both mothers and fetuses.² Although around 1500 studies on
71 the efficacy of antimalarials in malaria treatment have been conducted, pregnant women have been
72 excluded from the majority of clinical trials in the past, mainly because of safety concerns for the
73 fetus.

74 Due to the lack of evidence for both efficacy and safety, quinine, rather than artemisinin-
75 based combination therapy (ACT), has been recommended as the first-line treatment of
76 uncomplicated *Plasmodium falciparum* malaria for pregnant women in the first trimester by the
77 World Health Organization (WHO).³ However, recent studies measuring the safety of artemisinin
78 derivatives during pregnancy, including in the first trimester, have shown reassuring results⁴⁻⁷ and
79 it is likely that ACT will be recommended as the first-line treatment option for pregnant women
80 regardless of the trimester in the next WHO guideline.⁸ Nevertheless, the bulk of evidence is
81 limited.

82 The efficacy and safety of antimalarials in pregnancy can be different from the results from
83 the non-pregnant populations because of altered immunity, physiological change in
84 pharmacokinetics and sequestration of parasites to placenta. Besides, the risk factors of treatment
85 failure in pregnancy need to be assessed to improve the clinical care in pregnancy. However, there
86 are no agreed guidelines on how to assess the efficacy in pregnancy while it is standardised in the
87 non-pregnant patients by WHO.⁹ This lack of standard methodology makes it challenging to
88 conduct efficacy studies in pregnancy and leads to the variability of assessing and reporting the

1
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3 89 outcomes.^{10,11} Taken together, the current situation limits conducting aggregated data meta-
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5 90 analyses.¹¹
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8 91 The WorldWide Antimalarial Resistance Network (WWARN) has established a unique
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10 92 individual participant data (IPD)-sharing platform facilitating large-scale pooled meta-analyses.
11
12 93 We plan to include both published and unpublished studies exploring the efficacy and safety of
13
14 94 the treatment of malaria during pregnancy. We will conduct a one-stage IPD meta-analysis on the
15
16 95 currently recommended antimalarial drugs, i.e. artemisinin-based and quinine-based treatments,
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18 96 used for the treatment of uncomplicated falciparum malaria in pregnancy.
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24 97 Objectives

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26
27 98 The aim of this study is to evaluate and compare treatment outcomes of artemisinin-based
28
29 99 and quinine-based treatment for uncomplicated falciparum malaria in pregnancy.
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33 100 Primary objectives are:

- 34
35 101 • To compare antimalarial efficacies among artemisinin-based and quinine-based
36
37 102 treatments
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40 103 • To identify risk factors associated with treatment failure
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42
43 104 • To assess the relationship between the dosing (dose per body weight) of
44
45 105 artemisinin-based treatments and treatment efficacy
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49 106 Secondary objectives are:

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52 107 • To evaluate the risk of gametocyte carriage following antimalarial treatment
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55 108 • To evaluate the risk of adverse events following antimalarial treatment
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3 109 • To evaluate the risk of *Plasmodium vivax* infection following antimalarial treatment
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8 110 **Methods and analyses**
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12 111 *Criteria for study eligibility*
13

14
15 112 **Types of studies**
16

- 17 113 • Prospective clinical efficacy studies with a minimum 28-day active follow-up
18
19
20 114 • Both interventional and observational cohort studies regardless of the number of
21
22 115 treatment arms (i.e. comparative or single-arm)
23
24
25 116 • Genotyping conducted for distinguishing recrudescence and reinfection
26
27

28 117 The following studies will be excluded.
29

- 30
31 118 • ≤ 10 eligible pregnant women
32
33
34 119 • conducted in non-endemic countries (i.e. returned travellers)
35
36

37 120 **Types of participants**
38

- 39
40 121 • Pregnant women in any trimester
41
42
43 122 • Parasitologically confirmed *P. falciparum* parasitaemia
44
45
46 123 • either asymptomatic or symptomatic
47
48

49 124 **Types of intervention/exposure and controls**
50

- 51 125 • Treated with artemisinin-based or quinine-based treatments
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126 **Types of outcomes**

- 127 • Parasitological and clinical efficacy
- 128 • Adverse events

129 *Information sources and search strategy*

130 A systematic literature review was conducted to identify the potential studies to be included
131 in this IPD meta-analysis. Seven databases (MEDLINE, Embase, Global Health, Cochrane Library,
132 Scopus, Web of Science and LILACS) and two clinical trial registries (ICTRP and
133 ClinicalTrial.gov) were used. Both published and unpublished grey literatures such as conference
134 abstracts and registered trials were included. This systematic review and IPD meta-analysis is
135 registered to PROSPERO (CRD42018104013), and the search terms and conditions are available
136 there.

137 Briefly, the search combined five components: malaria; pregnancy; treatment or names of
138 anti-malarial drugs; study design (interventional or observational cohort studies); and outcome
139 types (efficacy) without limitation on publication year or language. The result of the literature
140 search was published elsewhere.¹¹ The initial search was conducted on 9 July 2016, and had been
141 updated until 5 July 2018 using PubMed and ICTRP. The IPD meta-analysis will be based on the
142 studies identified by the final updated search.

143 *Data acquisition and data management*

144 **Collecting IPD**

145 Principal investigators of the published and unpublished studies identified by the
146 systematic literature review will be invited to share their IPD with WWARN. Emails will be sent

1
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3 147 to the corresponding authors on at least three occasions asking whether they are willing to join the
4
5 148 study group. A secure web-based platform has been developed by WWARN, and IPD will be
6
7
8 149 uploaded after agreeing to the terms and conditions of the submission.¹² Data are fully anonymised
9
10 150 and handled in compliance with the UK Data Protection Act to protect personal information and
11
12 151 patient privacy. Original data are stored on a secure server hosted by the University of Oxford.

152 **Data management**

153 Raw data will be curated in a standardised format using the WWARN Clinical Module data
154 management plan to facilitate pooled IPD meta-analyses.¹³ After checking the raw data, any
155 queries on the availability of data, ambiguity of the variables or potential errors will be solved by
156 asking the data contributors. The protocol of the original studies will be sought from the data
157 contributors or from the publication when available. The standardised dataset is made traceable to
158 the raw data by use of a unique person (or episode) ID and study ID. This standardised dataset will
159 be used for the analyses.

160 *Statistical analysis plan*

161 **Study populations**

162 Pregnant women will be eligible for the purpose of this analysis if they meet the following
163 criteria:

- 164 • Confirmed pregnancy status on day 0 of the treatment
- 165 • Information on the type, date and dose of antimalarial drugs: artemisinin-based and
166 quinine-based treatments will be included
- 167 • Baseline data on patient age and estimated gestational age (or trimester of pregnancy)

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2
3 168 • Date of the last day of follow-up or length of follow-up
4
5

6 169 The following patients will be excluded:
7
8

- 9 170 • No or missing data on parasitological confirmation of *P. falciparum* infection at
10
11 171 enrolment
12
13
14 172 • Presenting with severe malaria symptoms at enrolment as defined by WHO³, except
15
16 173 uncomplicated hyperparasitaemia
17
18
19
20 174 • Incomplete dose
21
22

23 175 **Outcomes** 24

25 176 The primary outcome will be the polymerase chain reaction (PCR)-corrected *P. falciparum*
26
27 177 recrudescence. Secondary outcomes will include PCR-corrected *P. falciparum* reinfection; PCR-
28
29 178 uncorrected *P. falciparum* recurrence; parasite clearance; gametocyte carriage during follow up;
30
31 179 *P. vivax* infection during follow-up; and adverse events that developed after drug administration
32
33
34

35 180 Recurrences of *P. falciparum* will be distinguished by PCR into recrudescence (treatment
36
37 181 failure) and reinfection.¹⁴ Indeterminate PCR will be regarded as being censored on the day of
38
39 182 recurrence in survival analyses for PCR-corrected outcomes. In studies where peripheral malaria
40
41 183 smears were examined regularly (e.g. every week), the time of parasite recurrence will be defined
42
43 184 as the time of the first positive parasite smear after the parasite clearance following the treatment.
44
45 185 For pregnant women with no recurrent parasitaemia recorded, the day of their last negative smear
46
47 186 will be regarded as their last visit and censoring time. In case of intermittent follow-up (e.g. missed
48
49 187 follow-ups), the following rules will be applied:
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51
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- 53
54 188 (i) Blood smears will be assumed negative between the two negative observations
55
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3 189 (ii) If patient came back to be followed up with a positive smear, the date of positive
4
5 190 parasitaemia will be assumed to be the date of observation if this date is within 31 days from the
6
7
8 191 last observation
9

10
11 192 (iii) If parasite clearance is not recorded after treatment but the positive parasite count
12
13 193 is recorded at least 7 days after starting the treatment, day of the first positive count will be treated
14
15 194 as day of recurrence
16
17

18 195 Definitions of status and other censorship are detailed in the Clinical Module DMSAP¹³
19
20 196 except the above modification. Early late treatment failure is not applied for quinine-based
21
22 197 treatment because quinine is given for 7 days.
23
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25

26 198 Adverse symptoms will include: abdominal pain, dizziness, headache, body pain/myalgia,
27
28 199 weakness/fatigue, vomiting, nausea, anorexia and tinnitus if data permit.
29
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31 200 **Variables and their definitions**

32

33 201 The following baseline characteristics of patients will be included as appropriate if enough
34
35 202 data will be shared: age; estimated gestational age (or trimester); parity or gravidity; weight
36
37 203 (weight before pregnancy and weight at treatment); body mass index (BMI); baseline parasitaemia;
38
39 204 presence of fever (body temperature > 37.5 degrees Celsius); haemoglobin (or haematocrit);
40
41 205 anaemia (Hb < 11 g/dL or Hct < 30% for anaemia and Hb < 7 g/dL or Hct < 20% for severe
42
43 206 anaemia);¹⁵ gametocytes on presentation; past history of malaria (time from the last treatment or
44
45 207 the number of past infection in the same pregnancy); description of infection (mixed species
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47 208 infections); total mg/kg dose for each drug component; and supervision of drug administration.
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49
50 209 The doses of drugs received will be calculated from the number of tablets administered to each
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3 210 patient. If the actual number of tablets received was not recorded, doses according to the protocol
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5 211 will be used.
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8 212 For each study, study locations and local transmission intensity will be considered. The
9
10 213 study sites will be classified into three categories: low, medium and high malaria transmission
11
12 214 based on the parasite prevalence estimates obtained from the Malaria Atlas Project for specific
13
14 215 location and year of study.^{16,17}
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18 216 *P. vivax* intercalated infection will be regarded as censored if the original study did not test
19
20 217 PCR for falciparum recurrences after intercalated vivax infection. If the original study tested PCR
21
22 218 for falciparum recurrences regardless of intercalated vivax infection, vivax infection will be
23
24 219 regarded as a time-dependent covariate.
25
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28 220 **Descriptive summaries**

29
30 221 A summary of the studies and baseline characteristics of the patients included in the
31
32 222 analysis will be presented. The number of available patients will be summarised for all variables
33
34 223 listed above, proportion will be used for categorical or binary variables, and mean and standard
35
36 224 deviation (or median and range) will be used for continuous variables.
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40 225 PCR-corrected and uncorrected outcomes will be used to compute the Kaplan-Meier (K-
41
42 226 M) estimates. The K-M estimates will be presented graphically together with the number of
43
44 227 pregnant women in the risk set. Log rank test will be used for assessing the overall K-M profiles
45
46 228 between treatment groups. The efficacy between treatments will be compared at fixed time points
47
48 229 (i.e. on day 28, 42, and 63) by constructing a chi-squared test statistics using the stratified (by
49
50 230 study sites) approach.¹⁸
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231 **Analysis of primary outcome**

232 A one-stage IPD meta-analysis using Cox model with shared frailty will be conducted to
233 identify the risk factors of treatment failure as well as comparing different treatments. Study sites
234 will be fitted as random effects. For repeated episodes, multi-level mixed effects model (if there
235 are enough data) or the previous history of malaria will be used. If data permit, non-linear
236 relationship will be examined for continuous variables.¹⁹ Cox-Snell and Schoenfeld residuals will
237 be examined to determine the appropriateness of model fit and proportional hazard assumption,
238 respectively. Alternative statistical approaches such as flexible parametric models or introducing
239 an interaction with time will be considered if the proportionality assumption is not satisfied.

240 **Analyses of secondary outcomes**

241 Analysis of secondary outcomes will be carried out provided enough data is present; else,
242 only summary statistics will be reported. Analyses similar to the primary outcome will be
243 conducted for *P. falciparum* reinfection, *P. falciparum* recurrence and *P. vivax* infection.

244 Parasite clearance will be assessed as the proportions of patients cleared asexual falciparum
245 parasitaemia on day 1, 2 and 3. Univariable and multivariable mixed effect logistic regression
246 models (or Cox models for the time to parasite clearance) will be used to identify the risk factors
247 associated with parasite positivity status.

248 Gametocyte carriage will be assessed as the proportion of patients with *P. falciparum*
249 gametocytes on day 0, 3, 7, 14 or 21. Proportions after day 0 will be stratified by the presence of
250 gametocytes at baseline. If enough data is available, mixed effects logistic regression models will
251 be used to assess the risk factors for gametocytes carriage on day 0 and after treatment stratified
252 by the presence of gametocytes at baseline.

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3 253 Adverse symptoms will be assessed as the proportion of patients who developed adverse
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5 254 symptoms after the treatment initiation. Proportions of patients who developed symptoms after
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8 255 day 0 will be stratified by whether or not that symptom was present before the treatment initiation.
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10 256 If enough data are available, mixed effects logistic regression models will be used to assess the
11
12 257 risk factors of adverse symptoms developed after the treatment initiation. Symptoms on day 0
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14 258 (before treatment) will be added as a covariate. Primarily the symptoms developed in the first week
15
16 259 will be included. Symptoms developed at any time during the study period may be added.
17
18
19 260 Pregnancy outcomes may be assessed if enough data will be gathered.
20
21

22 261 **Variable selection**

23
24 262 For any regression models, the following strategy recommended by Collet²⁰ will be used
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26
27 263 to determine independent risk factors. Initially all possible risk factors will be examined in the
28
29 264 univariable model to assess if any of the variables are related to the treatment outcome. All
30
31 265 significant variables with a p-value ≤ 0.05 will then be added to the baseline model. The variables
32
33 266 with p-value of > 0.05 will be excluded from the baseline model one by one starting from the
34
35
36 267 variable with the largest p-value. Once only significant covariates remained in the model, all
37
38 268 excluded variables will be added to this model one by one to check whether there are any variables
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40
41 269 that become significant in the presence of other risk factors. Likelihood Ratio Test (LRT) and
42
43 270 Akaike's Information Criterion (AIC) will be used to compare nested and non-nested models,
44
45 271 respectively. Treatment and baseline parasitaemia will be included in the multivariable models as
46
47 272 *a priori* forced variables regardless of the statistical significance. Variables that are missing more
48
49 273 than 50% will not be included in multivariable analyses.²¹ Interaction between gravidity (parity)
50
51 274 and endemicity will be assessed, as the impact of gravidity (i.e. pregnancy-specific immunity) can
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53
54 275 be different depending on the endemicity.
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276 **Assessment of statistical heterogeneity across studies**

277 The multilevel logistic or Cox models would be used for explaining the study-site
278 heterogeneity. Heterogeneity across study sites will be statistically assessed as the variance of the
279 shared frailty term estimated in the random effect Cox model or variance of the random intercepts
280 in logistic regression. Additionally, intra-class correlation in logistic regression model will be
281 reported.

282 **Subgroup analyses**

283 Analyses will be conducted by geographical regions and by treatment (for assessing dose
284 impact of each drug) if data permit.

285 **Sensitivity analyses**

286 Three types of sensitivity analyses will be performed. Firstly, a model will be refitted
287 excluding non-RCTs to assess whether the baseline imbalance due to observational cohort studies
288 or single-arm interventional studies will influence the results. Secondly, a model will be refitted
289 with excluding one study at a time to identify any influential studies. Thirdly, to assess the impact
290 of covariates with missing values, multiple imputation may be used.²¹

291 **Strength of the body of evidence / risk of bias across studies**

292 The risk of bias within and across the included studies will be assessed following the
293 GRADE guideline.²² Publication bias will be evaluated by a funnel plot of the log-transformed
294 hazards ratio (odds ratio or proportion),²³ if more than 10 studies will be included.²⁴ Despite the
295 effort, all the studies identified in the systematic review may not be shared and included in this
296 IPD meta-analysis. The bias by the studies that are unable to be included in the analyses will be
297 evaluated as a sensitivity analysis.²⁵ The reported aggregated efficacy will be extracted from the
298 publication and a two-stage meta-analysis combining shared and unshared data will be attempted.²⁶

299 **Further development of statistical analysis plan**

300 The main analysis is planned as described above. Modification or additional analyses may
301 be required as the data collection progresses. Updated statistical analysis plans will be available at
302 the WWARN website.²⁷

303 **Software**

304 Statistical analysis will be conducted using R (The R Foundation for Statistical Computing)
305 or STATA (College Station, Texas, USA).

306 **Ethics and dissemination**

307 This IPD meta-analysis met the criteria for waiver of ethical review as defined by the
308 Oxford Tropical Research Ethics Committee (OxTREC) as the research consists of secondary
309 analysis of existing anonymous data.²⁸ All studies included in this analysis will have received local
310 ethical approvals and our pooled IPD meta-analysis will be addressing scientific questions that are
311 very similar to the original research questions.

312 Findings will be reported following the PRISMA-IPD guideline²⁹ at peer-reviewed
313 journals with open access. The progress will be updated on our study group website.²⁷ This
314 protocol is reported following PRISMA-P guideline^{30,31} and the systematic literature review and
315 IPD meta-analysis is registered to PROSPERO (CRD42018104013). Any publications based on
316 the findings of this IPD meta-analysis will be in accordance with the guidelines of the International
317 Committee of Medical Journal Editors.

318 Discussion

319 This IPD meta-analysis will update the previous aggregated data meta-analyses that
320 included only four or five RCTs,^{11,32} by incorporating the IPD from single-arm interventional or
321 observational cohort studies. As the data can be standardised and analysed in a uniform way, IPD
322 meta-analyses are particularly useful when there is no standard study design such as in this case.
323 Risk factors associated with treatment failures particularly the dosing of the currently used
324 treatments can be assessed in IPD meta-analyses, but rarely in aggregated data meta-analyses.
325 Although meta-analyses of secondary data cannot include variables that were not assessed in the
326 original studies, the results of this IPD meta-analysis can identify the pregnant women in need of
327 close clinical monitoring based on what is commonly assessed. Despite the increased time and
328 effort of gathering and standardising the IPD, the advantages of IPD meta-analysis outweigh
329 particularly for answering research questions on these neglected minority populations.

330 WWARN has developed the secure and equitable data platform and the international
331 collaborative network of malaria researchers worldwide over the last decade. With this unique
332 collaborative effort, we hope that these findings will lead to the improvement of clinical
333 management of this vulnerable but neglected population.

334 Author Contributions

335 MS, RoM and PG conceived the idea. MS and RM drafted the manuscript. KK, FN, RoM,
336 PG and KS critically revised the manuscript. All authors have read and approved the final
337 manuscript.

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343 decision to publish, or preparation of the manuscript.

344 Competing interests

345 None declared.

346 Ethics approval

347 This individual patient data meta-analysis met the criteria for waiver of ethical review as
348 defined by the Oxford Tropical Research Ethics Committee (OxTREC) since the research consists
349 of secondary analysis of existing anonymous data. Each study included in the analysis will have
350 received local ethics approvals.

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354 References

- 355 1. Dellicour S, Tatem AJ, Guerra CA, et al. Quantifying the number of pregnancies at risk of
356 malaria in 2007: a demographic study. *PLoS Med* 2010;7(1):e1000221.

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3 357 2. Rogerson SJ, Desai M, Mayor A, et al. Burden, pathology, and costs of malaria in pregnancy:
4 358 new developments for an old problem. *Lancet Infect Dis* 2018;18(4):e107-e18.
- 5 359 3. WHO. Guidelines for the treatment of malaria. Third edition. Geneva: World Health
6 360 Organization 2015.
- 7 361 4. Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine
8 362 treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis
9 363 of observational studies. *PLoS Med* 2017;14(5):e1002290.
- 10 364 5. Kovacs SD, van Eijk AM, Sevene E, et al. The Safety of Artemisinin Derivatives for the
11 365 Treatment of Malaria in the 2nd or 3rd Trimester of Pregnancy: A Systematic Review and
12 366 Meta-Analysis. *PLoS One* 2016;11(11):e0164963.
- 13 367 6. McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax malaria
14 368 and the safety of antimalarial treatment in early pregnancy: a population-based study.
15 369 *Lancet Infect Dis* 2012;12(5):388-96.
- 16 370 7. Moore KA, Simpson JA, Paw MK, et al. Safety of artemisinins in first trimester of prospectively
17 371 followed pregnancies: an observational study. *Lancet Infect Dis* 2016;16(5):576-83.
- 18 372 8. WHO Malaria Policy Advisory Committee Secretariat. Malaria Policy Advisory Committee to
19 373 the WHO: conclusions and recommendations of eighth biannual meeting (September 2015).
20 374 *Malar J* 2016;15:117.
- 21 375 9. World Health Organization. Methods for surveillance of antimalarial drug efficacy. Geneva:
22 376 World Health Organization 2009.
- 23 377 10. Saito M, Gilder ME, Nosten F, et al. Methodology of assessment and reporting of safety in
24 378 anti-malarial treatment efficacy studies of uncomplicated falciparum malaria in pregnancy:
25 379 a systematic literature review. *Malar J* 2017;16:491.
- 26 380 11. Saito M, Gilder ME, Nosten F, et al. Systematic literature review and meta-analysis of the
27 381 efficacy of artemisinin-based and quinine-based treatments for uncomplicated falciparum
28 382 malaria in pregnancy: methodological challenges. *Malar J* 2017;16:488.
- 29 383 12. WorldWide Antimalarial Resistance Network (WWARN). Terms of Submission 2017 [cited
30 384 5 July 2018]. Available from: <http://www.wwarn.org/tools-resources/terms-submission>.
- 31 385 13. WorldWide Antimalarial Resistance Network (WWARN). Clinical Module: Data
32 386 Management and Statistical Analysis Plan Version 1.2. 2012 [cited 5 July 2018]. Available
33 387 from: <http://www.wwarn.org/sites/default/files/ClinicalDMSAP.pdf>.
- 34 388 14. World Health Organization. Methods and techniques for clinical trials on antimalarial drug
35 389 efficacy: Genotyping to identify parasite populations. Geneva: World Health Organization
36 390 2008.
- 37 391 15. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and
38 392 assessment of severity. Geneva: World Health Organization 2011.
- 39 393 16. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on Plasmodium falciparum
40 394 in Africa between 2000 and 2015. *Nature* 2015;526(7572):207-11.
- 41 395 17. Gething PW, Patil AP, Smith DL, et al. A new world malaria map: Plasmodium falciparum
42 396 endemicity in 2010. *Malar J* 2011;10:378.
- 43 397 18. Klein JP, Logan B, Harhoff M, et al. Analyzing survival curves at a fixed point in time. *Stat*
44 398 *Med* 2007;26(24):4505-19.
- 45 399 19. Royston P, Sauerbrei W. Fractional Polynomials for One Variable. Multivariable Model-
46 400 building: A pragmatic approach to regression analysis based on fractional polynomials for
47 401 modelling continuous variables. Chuchester: John Wiley & Sons 2008:71-98.

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2
3 402 20. Collett D. 3.6 Strategy for model selection. *Modelling survival data in medical research* Third
4 403 edition. New York: CRC Press 2015:83-90.
- 5 404 21. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and
6 405 guidance for practice. *Stat Med* 2011;30(4):377-99.
- 7 406 22. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence
8 407 profiles and summary of findings tables. *J Clin Epidemiol* 2011;64(4):383-94.
- 9 408 23. Silcocks P. Hazard ratio funnel plots for survival comparisons. *J Epidemiol Community Health*
10 409 2009;63(10):856-61.
- 11 410 24. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting
12 411 funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*
13 412 2011;343:d4002.
- 14 413 25. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable
15 414 data in meta-analyses using individual participant data: a database survey. *BMJ* 2012;344
- 16 415 26. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale,
17 416 conduct, and reporting. *BMJ* 2010;340:c221.
- 18 417 27. WorldWide Antimalarial Resistance Network (WWARN). Malaria in pregnancy treatment
19 418 efficacy study group 2016 [cited 5 July 2018]. Available from:
20 419 <http://www.wwarn.org/working-together/study-groups/malaria-pregnancy-treatment->
21 420 [efficacy-study-group](http://www.wwarn.org/working-together/study-groups/malaria-pregnancy-treatment-).
- 22 421 28. Oxford Tropical Research Ethics Committee. 2018 [cited 23 October 2018]. Available from:
23 422 <https://researchsupport.admin.ox.ac.uk/governance/ethics/committees/ox trec>.
- 24 423 29. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and
25 424 Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA*
26 425 2015;313(16):1657-65.
- 27 426 30. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and
28 427 meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349
- 29 428 31. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and
30 429 meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015;4(1):1.
- 31 430 32. Burger RJ, van Eijk AM, Bussink M, et al. Artemisinin-based combination therapy versus
32 431 quinine or other combinations for treatment of uncomplicated *Plasmodium falciparum*
33 432 malaria in the second and third trimester of pregnancy: a systematic review and meta-
34 433 analysis. *Open Forum Infect Dis* 2016;3(1):ofv170.
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-20
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	346-349
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	78-94
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	95-114

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	✓	<input type="checkbox"/>	116-133
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	✓	<input type="checkbox"/>	135-141
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	<input type="checkbox"/>	135-147
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	<input type="checkbox"/>	158-165
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	✓	<input type="checkbox"/>	134-157
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	<input type="checkbox"/>	149-165
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	✓	<input type="checkbox"/>	209-228
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	<input type="checkbox"/>	182-208
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓	<input type="checkbox"/>	295-309
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	✓	<input type="checkbox"/>	182-228
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	✓	<input type="checkbox"/>	229-291
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓	<input type="checkbox"/>	292-300
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓	<input type="checkbox"/>	307-309

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	301-309
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	302-303

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BMJ Open

The efficacy of artemisinin-based and quinine-based treatments for uncomplicated falciparum malaria in pregnancy: a protocol for systematic review and individual patient data (IPD) meta-analysis

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Pharmacology and therapeutics
Keywords:	malaria, pregnancy, treatment efficacy, individual patient data meta-analysis, artemisinin, quinine

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1 The efficacy of artemisinin-based and quinine-based treatments for uncomplicated
2 falciparum malaria in pregnancy: a protocol for systematic review and individual patient data
3 (IPD) meta-analysis

4
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21
22 Word count: 2998

23 Key words: malaria, pregnancy, treatment efficacy, individual patient data meta-analysis,
24 artemisinin, quinine

25 Abstract

26 *Introduction*

27 Pregnant women are more vulnerable to malaria leading to adverse impact on both
28 mothers and fetuses. However, knowledge on the efficacy and safety of antimalarials in
29 pregnancy is limited by the paucity of randomised control trials and the lack of standardised
30 protocols in this special sub-population. Pooling individual patient data (IPD) for meta-analysis
31 could address in part these limitations to summarise accurately the currently available evidence
32 on treatment efficacy and risk factors of treatment failure.

33 *Methods and analysis*

34 To assess the treatment efficacy of artemisinin-based and quinine-based treatments for
35 uncomplicated falciparum malaria in pregnancy, seven databases (MEDLINE, Embase, Global
36 Health, Cochrane Library, Scopus, Web of Science and Literatura Latino Americana em
37 Ciências da Saúde) and two clinical trial registries (International Clinical Trials Registry
38 Platform and ClinicalTrial.gov) were searched. Both interventional and observational cohort
39 studies following up for at least 28 days will be included. IPD of the identified eligible
40 published or unpublished studies will be sought by inviting principal investigators. Raw IPD
41 will be shared through the web-based secure platform developed by WorldWide Antimalarial
42 Resistance Network using the established methodology. The primary objective is to compare
43 the risk of polymerase chain reaction (PCR)-corrected treatment failure among different
44 treatments and to find the risk factors. One-stage IPD meta-analysis by Cox model with shared
45 frailty will be conducted. A risk of bias assessment will be conducted to address the impact of
46 potential unshared data and of the quality of individual studies. Potential limitations include
47 difficulty in acquiring the IPD and heterogeneity of the study designs due to the lack of standard.

48 *Ethics and Dissemination*

49 This IPD meta-analysis consists of secondary analyses of existing anonymous data and
50 meets the criteria for waiver of ethical review by the Oxford Tropical Research Ethics
51 Committee. The results of this IPD meta-analysis will be disseminated through open-access
52 publications at peer-reviewed journals. The study results will lead to a better understanding of
53 malaria treatment in pregnancy, which can be used for clinical decision-making and conducting
54 further studies.

55 *PROSPERO registration number*: CRD42018104013.

56 Article Summary

57 *Strengths and limitations of this study*

- 58 • The research on the efficacy of antimalarials in pregnancy has been restricted by the
59 paucity of randomised control trials and the lack of a standard study design for
60 pregnancy.
- 61 • This study will be the first individual patient data (IPD) meta-analysis on the efficacy
62 of currently recommended antimalarials in pregnancy incorporating IPD from both
63 randomised control trials and single-arm cohort studies.
- 64 • IPD that are standardised in the same format and analysed in a uniform way with
65 adjustment of covariates will allow us to compare the efficacy of different treatment as
66 well as to find risk factors of treatment failure in this vulnerable but understudied
67 population.
- 68 • The collection of IPD globally will ensure the generalisability of the results.

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3 69 • Limitations of this IPD meta-analysis include the potential difficulty in acquiring the
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5 70 IPD and the heterogeneity of the study designs, study population and parasite
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8 71 population. A risk of bias assessment will be conducted to address the impact of
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10 72 potential unshared data and of the quality of individual studies.
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73 Introduction

74 About 60% of all pregnancies are estimated to take place in malaria-endemic areas.¹ In
75 addition, pregnant women are amongst the most vulnerable groups for malaria infection leading
76 to higher morbidity and mortality of both mothers and fetuses.² Although around 1500 studies
77 on the efficacy of antimalarials in malaria treatment have been conducted,³ pregnant women
78 have been excluded from the majority of clinical trials in the past, mainly because of safety
79 concerns for the fetus.

80 Due to the lack of evidence for both efficacy and safety of antimalarials in pregnancy,
81 quinine, rather than artemisinin-based combination therapy (ACT), has been recommended as
82 the first-line treatment of uncomplicated *Plasmodium falciparum* malaria for pregnant women
83 in the first trimester by the World Health Organization (WHO).⁴ However, recent studies
84 measuring the safety of artemisinin derivatives during pregnancy, including in the first
85 trimester, have shown reassuring results⁵⁻⁸ and it is likely that ACT will be recommended as
86 the first-line treatment option for pregnant women regardless of the trimester in the next WHO
87 guidelines.⁹ Evidence on the treatment efficacy during pregnancy needs to be assembled.

88 The efficacy and safety of antimalarials in pregnancy can be different from the results
89 from the non-pregnant populations because of altered immunity, physiological change in
90 pharmacokinetics and sequestration of parasites to the placenta. The risk factors of treatment
91 failure in pregnancy need to be assessed to improve clinical care in pregnancy. However, there
92 are no agreed guidelines on how to assess the efficacy in pregnancy while it is standardised in
93 the non-pregnant patients by WHO.¹⁰ This lack of standard methodology makes it challenging
94 to conduct efficacy studies in pregnancy and leads to the variability of assessing and reporting
95 the outcomes.^{11,12} Taken together, the current situation limits conducting aggregated data meta-
96 analyses.¹²

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3 97 The WorldWide Antimalarial Resistance Network (WWARN) has established a unique
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5 98 individual participant data (IPD)-sharing platform facilitating large-scale pooled meta-analyses.
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8 99 We plan to include both published and unpublished studies exploring the efficacy and safety
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10 100 of the treatment of malaria during pregnancy. We will conduct a one-stage IPD meta-analysis
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12 101 on the currently recommended antimalarial drugs, i.e. artemisinin-based and quinine-based
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14 102 treatments, used for the treatment of uncomplicated falciparum malaria in pregnancy.
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19 103 Objectives

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22 104 The aim of this study is to evaluate and compare treatment outcomes of artemisinin-
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24 105 based and quinine-based treatment for uncomplicated falciparum malaria in pregnancy.
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27 106 Primary objectives are:

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30 107 • To compare antimalarial efficacies among artemisinin-based and quinine-based
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35 109 • To identify risk factors associated with treatment failure
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38 110 Secondary objectives are:

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41 111 • To assess the relationship between the dosing (dose per body weight) of
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43 112 artemisinin-based treatments and treatment efficacy
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46 113 • To evaluate the risk of gametocyte carriage following artemisinin-based and
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52 115 • To evaluate the safety and tolerability of artemisinin-based and quinine-based
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117 Methods and analyses

118 *Criteria for study eligibility*

119 **Types of studies**

- 120 • Prospective clinical efficacy studies with a minimum 28-day active follow-up
- 121 • Both interventional and observational cohort studies regardless of the number of
- 122 treatment arms (i.e. comparative or single-arm)
- 123 • Genotyping conducted for distinguishing recrudescence and reinfection

124 The following studies will be excluded.

- 125 • ≤ 10 eligible pregnant women
- 126 • Conducted in non-endemic countries (i.e. returned travellers)

127 **Types of participants**

- 128 • Pregnant women in any trimester
- 129 • Parasitologically confirmed *P. falciparum* parasitaemia
- 130 • Either asymptomatic or symptomatic

131 **Types of intervention/exposure and controls**

- 132 • Treated with artemisinin-based or quinine-based treatments

133 **Types of outcomes**

- 134 • Parasitological and clinical efficacy
- 135 • Adverse events

136 *Information sources and search strategy*

137 A systematic literature review was conducted to identify the potential studies to be
138 included in this IPD meta-analysis. Seven databases (MEDLINE, Embase, Global Health,
139 Cochrane Library, Scopus, Web of Science and Literatura Latino Americana em Ciências da
140 Saúde) and two clinical trial registries (International Clinical Trials Registry Platform and
141 ClinicalTrial.gov) were used. Both published and unpublished grey literature such as
142 conference abstracts and registered trials were included. This systematic review and IPD meta-
143 analysis is registered to PROSPERO (CRD42018104013), and the search terms and conditions
144 are available there.

145 Briefly, the search combined five components: malaria; pregnancy; treatment or names
146 of anti-malarial drugs; study design (interventional or observational cohort studies); and
147 outcome types (efficacy) without limitation on publication year or language. The result of the
148 literature search was published elsewhere.¹² The initial search was conducted on 9 July 2016.
149 The final search will be updated in April 2019.

150 *Data acquisition and data management*

151 **Collecting IPD**

152 Principal investigators of the published and unpublished studies identified by the
153 systematic literature review will be invited to share their IPD with WWARN. Emails will be
154 sent to the corresponding authors on at least three occasions asking whether they are willing to
155 join the study group. A secure web-based platform has been developed by WWARN, and IPD
156 will be uploaded after agreeing to the terms and conditions of the submission, retaining the
157 ownership and full control of their shared data.¹³ Data are fully anonymised and handled in
158 compliance with the UK Data Protection Act to protect personal information and patient
159 privacy. Original data are stored on a secure server hosted by the University of Oxford.

160 **Data management**

161 Raw data will be curated in a standardised format using the WWARN Clinical Module
162 data management plan to facilitate pooled IPD meta-analyses.¹⁴ After checking the raw data,
163 any queries on the availability of data, ambiguity of the variables or potential errors will be
164 resolved by asking the data contributors. The protocol of the original studies will be sought
165 from the data contributors or the publication when available. The standardised dataset will be
166 used for the analyses.

167 *Statistical analysis plan*

168 **Study populations**

169 Pregnant women will be eligible for the purpose of this analysis if they meet the
170 following criteria:

- 171 • Confirmed pregnancy status on day 0 of the treatment
- 172 • Information on the type, date and dose of antimalarial drugs: artemisinin-based and
173 quinine-based treatments will be included
- 174 • Baseline data on patient age and estimated gestational age (or trimester of
175 pregnancy)
- 176 • Date of the last day of follow-up or length of follow-up

177 The following patients will be excluded:

- 178 • No or missing data on parasitological confirmation of *P. falciparum* infection at
179 enrolment
- 180 • Presenting with severe malaria symptoms at enrolment as defined by WHO⁴,
181 except uncomplicated hyperparasitaemia

182 **Outcomes**

183 The primary outcome will be the polymerase chain reaction (PCR)-corrected *P.*
184 *falciparum* treatment failure. Secondary outcomes will include any recurrence of malaria
185 (PCR-uncorrected treatment failure); parasite clearance; gametocyte carriage during follow up;
186 and adverse events that developed after drug administration.

187 Recurrences of *P. falciparum* will be distinguished by PCR into recrudescence
188 (treatment failure) and reinfection.¹⁵ Indeterminate PCR will be excluded, and reinfection will
189 be regarded as being censored on the day of recurrence in survival analyses for PCR-corrected
190 outcomes following the WHO guidelines.¹⁰ In studies where peripheral malaria smears were
191 examined regularly (e.g. every week), the time of parasite recurrence will be defined as the
192 time of the first positive parasite smear after the parasite clearance following the treatment. For
193 pregnant women with no recurrent parasitaemia recorded, the day of their last negative smear
194 will be regarded as their last visit and censoring time. In the case of intermittent follow-up (e.g.
195 missed follow-ups), the following rules will be applied:

- 196 (i) Blood smears will be assumed negative between the two negative observations
- 197 (ii) If a patient came back to be followed up with a positive smear, the date of
198 positive parasitaemia will be assumed to be the date of observation if this date is within 28 (± 3)
199 days from the last observation
- 200 (iii) If parasite clearance is not recorded after treatment but the positive parasite
201 count is recorded at least 7 days after starting the treatment, the day of the first positive count
202 will be treated as the day of recurrence

203 Definitions of status and other censorship are detailed in the Clinical Module DMSAP¹⁴
204 except for the above modification. The presence of parasitaemia within the first seven days will

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3 205 not be regarded as treatment failure for quinine-based treatment because quinine is given for
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5 206 seven days.

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8 207 Adverse symptoms will include: abdominal pain, dizziness, headache, body
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10 208 pain/myalgia, weakness/fatigue, vomiting, nausea, anorexia and tinnitus if data permit.

13 209 **Variables and their definitions**

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16 210 The following baseline characteristics of patients will be included as appropriate if
17
18 211 enough data are shared: age; estimated gestational age (or trimester); parity or gravidity; weight
19
20 212 (weight before pregnancy and weight at treatment); body mass index (BMI); baseline
21
22 213 parasitaemia; presence of fever (body temperature > 37.5 degrees Celsius); haemoglobin (or
23
24 214 haematocrit); anaemia (Hb < 11 g/dL or Hct < 30% for anaemia and Hb < 7 g/dL or Hct < 20%
25
26 215 for severe anaemia);¹⁶ gametocytes on presentation; past history of malaria or antimalaria use
27
28 216 description of infection (mixed species infections); total mg/kg dose for each drug component;
29
30 217 and supervision of drug administration. The doses of drugs received will be calculated from
31
32 218 the number of tablets administered to each patient. If the actual number of tablets received was
33
34 219 not recorded, doses according to the protocol will be used. Only those who completed the
35
36 220 standard dose will be included in the primary analysis. The proportion of partial treatment will
37
38 221 be presented.

39
40
41 222 For each study, study locations and local transmission intensity will be considered. The
42
43 223 study sites will be classified into three categories: low, medium and high malaria transmission
44
45 224 based on the parasite prevalence estimates obtained from the Malaria Atlas Project for specific
46
47 225 location and year of study.^{17,18}

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49 226 *Plasmodium vivax* intercalated infection (i.e. *P. vivax* mono-infection before the
50
51 227 recurrence of *P. falciparum* parasitaemia) will be regarded as censored if the original study did
52
53 228 not test PCR for falciparum recurrences after intercalated vivax infection, following the WHO
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3 229 guidelines.¹⁰ If the original study tested PCR for falciparum recurrences regardless of
4
5 230 intercalated vivax infection, vivax infection will be regarded as a time-dependent covariate.
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8 231 **Descriptive summaries**

9
10 232 A summary of the studies and baseline characteristics of the patients included in the
11
12 233 analysis will be presented. The number of available patients will be summarised for all
13
14 234 variables listed above, proportion will be used for categorical or binary variables, and mean
15
16 235 and standard deviation (or median and interquartile range) will be used for continuous variables.
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19
20 236 PCR-corrected and uncorrected outcomes will be used to compute the Kaplan-Meier
21
22 237 (K-M) estimates. The efficacy of each treatment will be summarised at fixed time points (i.e.
23
24 238 on day 28, 42, and 63) by constructing a chi-squared test statistics using the stratified (by study
25
26 239 sites) approach.¹⁹
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28

29 240 **Analysis of primary outcome**

30
31 241 A one-stage IPD meta-analysis using the Cox model with shared frailty will be
32
33 242 conducted to identify the risk factors of treatment failure as well as comparing different
34
35 243 treatments. Study sites will be fitted as random effects. For repeated episodes, if any, multi-
36
37 244 level mixed effects model (if there are enough data) or the previous history of malaria will be
38
39 245 used. If data permit, a non-linear relationship will be examined for continuous variables.²⁰ Cox-
40
41 246 Snell and Schoenfeld residuals will be examined to determine the appropriateness of model fit
42
43 247 and proportional hazard assumption, respectively. Alternative statistical approaches such as
44
45 248 flexible parametric models or introducing an interaction term with time will be considered if
46
47 249 the proportionality assumption is not satisfied.
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250 **Analyses of secondary outcomes**

251 Analysis of secondary outcomes will be carried out provided enough data are present;
252 else, only summary statistics will be reported. Analyses similar to the primary outcome will be
253 conducted for PCR-uncorrected treatment failure (i.e. any recurrence of malaria).

254 Parasite clearance will be assessed as the proportions of patients cleared asexual
255 falciparum parasitaemia on day 1, 2 and 3. Univariable and multivariable mixed-effects logistic
256 regression models (or Cox models for the time to parasite clearance) will be used to identify
257 the risk factors associated with parasite positivity status.

258 Gametocyte carriage will be assessed as the proportion of patients with *P. falciparum*
259 gametocytes on day 0, 3, 7, 14 or 21. Proportions after day 0 will be stratified by the presence
260 of gametocytes at baseline. If enough data are available, mixed effects logistic regression
261 models will be used to assess the risk factors for gametocytes carriage after treatment stratified
262 by the presence of gametocytes at baseline.

263 Adverse effects will be assessed as the proportion of patients who developed symptoms
264 after the treatment initiation. Proportions of patients who developed symptoms after day 0 will
265 be stratified by whether or not that symptom was present before the treatment initiation. If
266 enough data are available, mixed effects logistic regression models will be used to assess the
267 risk factors of adverse symptoms developed after the treatment initiation. Symptoms on day 0
268 (before treatment) will be added as a covariate. Primarily the symptoms developed in the first
269 week will be included. Pregnancy outcomes and placental malaria may be assessed if enough
270 data are gathered.

271 **Variable selection**

272 For any regression models, the following strategy recommended by Collet ²¹ will be
273 used to determine independent risk factors. Initially, all possible risk factors will be examined

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3 274 in the univariable model to assess if any of the variables are related to the treatment outcome.
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5 275 All significant variables with a p-value ≤ 0.05 will then be added to the baseline model. The
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8 276 variables with a p-value of > 0.05 will be excluded from the baseline model one by one starting
9
10 277 from the variable with the largest p-value. Once only significant covariates will remain in the
11
12 278 model, all excluded variables will be added to this model one by one to check whether there
13
14 279 will be any variables that become significant in the presence of other risk factors. Likelihood
15
16
17 280 Ratio Test (LRT) and Akaike's Information Criterion (AIC) will be used to compare nested
18
19 281 and non-nested models, respectively. Treatment and baseline parasitaemia will be included in
20
21 282 the multivariable models on treatment efficacy as *a priori* forced variables regardless of the
22
23 283 statistical significance. Variables that are missing more than 50% will not be included in
24
25
26 284 multivariable analyses.²² Interaction between gravidity (parity) and endemicity, or age and
27
28 285 endemicity will be assessed if age or gravidity is included in the multivariable model, as the
29
30 286 impact of age and gravidity (i.e. pregnancy-specific immunity) can be different depending on
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32
33 287 the endemicity.²³
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288 **Assessment of statistical heterogeneity across studies**

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38 289 The multilevel logistic or Cox models would be used for explaining the study-site
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40 290 heterogeneity. Heterogeneity across study sites will be statistically assessed as the variance of
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43 291 the shared frailty term estimated in the random effect Cox model or variance of the random
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45 292 intercepts in logistic regression. Additionally, the intra-class correlation in logistic regression
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47 293 model will be reported.
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294 **Subgroup analyses**

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52 295 Analyses will be conducted by malaria transmission intensity and by treatment (for
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55 296 assessing dose impact of each drug) if data permit.
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297 **Sensitivity analyses**

298 Two types of sensitivity analyses will be performed. Firstly, a model will be refitted
299 with excluding one study at a time to identify any influential studies. Secondly, to assess the
300 impact of covariates with missing values, multiple imputation may be used.²²

301 **Strength of the body of evidence / risk of bias across studies**

302 The risk of bias within and across the included studies will be assessed following the
303 GRADE guidelines.²⁴ Publication bias will be evaluated by a funnel plot of the log-transformed
304 hazards ratio (odds ratio or proportion),²⁵ if more than ten studies are included.²⁶ Despite the
305 effort, all the studies identified in the systematic review may not be shared and included in this
306 IPD meta-analysis. The bias by the studies that are unable to be included in the analyses will
307 be evaluated.²⁷ The reported aggregated efficacy will be extracted from the publication and
308 compared to the studies included. A two-stage meta-analysis combining shared and unshared
309 data will be attempted if data permit.²⁸ The impact of artemisinin resistance in the study year
310 at the study site will be evaluated by using the reported prevalence on molecular resistance
311 marker (K-13).

312 **Further development of statistical analysis plan**

313 The main analysis is planned as described above. Modification or additional analyses
314 may be required as the data collection progresses. Updated statistical analysis plans will be
315 available at the WWARN website if an amendment is required.²⁹

316 **Software**

317 Statistical analysis will be conducted using R (The R Foundation for Statistical
318 Computing) or Stata MP 14.2 (College Station, Texas, USA).

319 *Patient and Public Involvement*

320 This IPD meta-analysis will use existing secondary data. Patients and public were not
321 involved in the design, recruitment or conduct of this IPD meta-analysis. The results of this
322 study will be shared with the primary investigators of the shared studies and disseminated as
323 publications in open access journals.

324 **Ethics and dissemination**

325 This IPD meta-analysis met the criteria for waiver of ethical review as defined by the
326 Oxford Tropical Research Ethics Committee (OxTREC) as the research consists of secondary
327 analyses of existing anonymous data.³⁰ All studies included in this analysis will have received
328 local ethical approvals.

329 Findings will be reported following the PRISMA-IPD guideline³¹ at peer-reviewed
330 journals with open access. The progress will be updated on our study group website.²⁹ This
331 protocol is reported following PRISMA-P guideline^{32,33} and the systematic literature review
332 and IPD meta-analysis is registered to PROSPERO (CRD42018104013). Any publications
333 based on the findings of this IPD meta-analysis will be in accordance with the guidelines of the
334 International Committee of Medical Journal Editors.

335 **Discussion**

336 This IPD meta-analysis will update the previous aggregated data meta-analyses that
337 included only four or five RCTs.^{12,34} In IPD meta-analyses, data from single-arm interventional
338 or observational cohort studies can be included. As the data can be standardised and analysed
339 in a uniform way, IPD meta-analyses are particularly useful when there is no standard study
340 design such as in this case. Risk factors associated with treatment failures particularly the
341 dosing of the currently used treatments can be assessed in IPD meta-analyses, but rarely in

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3 342 aggregated data meta-analyses. Although meta-analyses of secondary data cannot include
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5 343 variables that were not assessed in the original studies, the results of this IPD meta-analysis
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8 344 can identify the pregnant women in need of close clinical monitoring based on what is
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10 345 commonly assessed. Despite the increased time and effort of gathering and standardising the
11
12 346 IPD, the advantages of IPD meta-analysis outweigh particularly for answering research
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15 347 questions on these neglected or understudied populations.
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17
18 348 WWARN has developed the secure and equitable data platform and the international
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20 349 collaborative network of malaria researchers worldwide over the last decade. With this unique
21
22 350 collaborative effort, we hope that these findings will lead to the improvement of clinical
23
24
25 351 management of this vulnerable but understudied population.
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29 352 Author Contributions

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32 353 MS, RoM and PG conceived the idea. MS and RM drafted the manuscript. KK, FN,
33
34 354 RoM, PG and KS critically revised the manuscript. All authors have read and approved the
35
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37 355 final manuscript.
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52
53 361 paper, decision to publish, or preparation of the manuscript.
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362 Competing interests

363 None declared.

364 Ethics approval

365 This individual patient data meta-analysis met the criteria for waiver of ethical review
366 as defined by the Oxford Tropical Research Ethics Committee (OxTREC) since the research
367 consists of secondary analyses of existing anonymous data. Each study included in the analysis
368 will have received local ethics approvals.

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372 References

- 373 1. Dellicour S, Tatem AJ, Guerra CA, et al. Quantifying the number of pregnancies at risk of
374 malaria in 2007: a demographic study. *PLoS Med* 2010;7(1):e1000221.
- 375 2. Rogerson SJ, Desai M, Mayor A, et al. Burden, pathology, and costs of malaria in pregnancy:
376 new developments for an old problem. *Lancet Infect Dis* 2018;18(4):e107-e18.
- 377 3. WorldWide Antimalarial Resistance Network. WWARN clinical trials publication library
378 2017 [cited 20 March 2019] Available from: [https://www.wwarn.org/tools-](https://www.wwarn.org/tools-resources/literature-reviews/wwarn-clinical-trials-publication-library)
379 [resources/literature-reviews/wwarn-clinical-trials-publication-library](https://www.wwarn.org/tools-resources/literature-reviews/wwarn-clinical-trials-publication-library).
- 380 4. World Health Organization. Guidelines for the treatment of malaria. Third edition. Geneva:
381 World Health Organization 2015.
- 382 5. Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine
383 treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-
384 analysis of observational studies. *PLoS Med* 2017;14(5):e1002290.
- 385 6. Kovacs SD, van Eijk AM, Sevene E, et al. The Safety of Artemisinin Derivatives for the
386 Treatment of Malaria in the 2nd or 3rd Trimester of Pregnancy: A Systematic Review
387 and Meta-Analysis. *PLoS One* 2016;11(11):e0164963.
- 388 7. McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax
389 malaria and the safety of antimalarial treatment in early pregnancy: a population-based
390 study. *Lancet Infect Dis* 2012;12(5):388-96.

- 391 8. Moore KA, Simpson JA, Paw MK, et al. Safety of artemisinins in first trimester of
392 prospectively followed pregnancies: an observational study. *Lancet Infect Dis*
393 2016;16(5):576-83.
- 394 9. WHO Malaria Policy Advisory Committee Secretariat. Malaria Policy Advisory Committee
395 to the WHO: conclusions and recommendations of eighth biannual meeting (September
396 2015). *Malar J* 2016;15:117.
- 397 10. World Health Organization. Methods for surveillance of antimalarial drug efficacy.
398 Geneva: World Health Organization 2009.
- 399 11. Saito M, Gilder ME, Nosten F, et al. Methodology of assessment and reporting of safety in
400 anti-malarial treatment efficacy studies of uncomplicated falciparum malaria in
401 pregnancy: a systematic literature review. *Malar J* 2017;16:491.
- 402 12. Saito M, Gilder ME, Nosten F, et al. Systematic literature review and meta-analysis of the
403 efficacy of artemisinin-based and quinine-based treatments for uncomplicated
404 falciparum malaria in pregnancy: methodological challenges. *Malar J* 2017;16:488.
- 405 13. WorldWide Antimalarial Resistance Network (WWARN). Terms of Submission 2017
406 [cited 5 July 2018]. Available from: [http://www.wwarn.org/tools-resources/terms-](http://www.wwarn.org/tools-resources/terms-submission)
407 [submission](http://www.wwarn.org/tools-resources/terms-submission).
- 408 14. WorldWide Antimalarial Resistance Network (WWARN). Clinical Module: Data
409 Management and Statistical Analysis Plan Version 1.2. 2012 [cited 5 July 2018].
410 Available from: <http://www.wwarn.org/sites/default/files/ClinicalDMSAP.pdf>.
- 411 15. World Health Organization. Methods and techniques for clinical trials on antimalarial drug
412 efficacy: Genotyping to identify parasite populations. Geneva: World Health
413 Organization 2008.
- 414 16. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and
415 assessment of severity. Geneva: World Health Organization 2011.
- 416 17. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on *Plasmodium*
417 *falciparum* in Africa between 2000 and 2015. *Nature* 2015;526(7572):207-11.
- 418 18. Gething PW, Patil AP, Smith DL, et al. A new world malaria map: *Plasmodium falciparum*
419 endemicity in 2010. *Malar J* 2011;10:378.
- 420 19. Klein JP, Logan B, Harhoff M, et al. Analyzing survival curves at a fixed point in time.
421 *Stat Med* 2007;26(24):4505-19.
- 422 20. Royston P, Sauerbrei W. Fractional Polynomials for One Variable. Multivariable Model-
423 building: A pragmatic approach to regression analysis based on fractional polynomials
424 for modelling continuous variables. Chichester, UK: John Wiley & Sons 2008:71-98.
- 425 21. Collett D. 3.6 Strategy for model selection. In: Collett D, ed. Modelling survival data in
426 medical research Third edition. New York: CRC Press 2015:83-90.
- 427 22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and
428 guidance for practice. *Stat Med* 2011;30(4):377-99.
- 429 23. Rogerson SJ, Hviid L, Duffy PE, et al. Malaria in pregnancy: pathogenesis and immunity.
430 *Lancet Infect Dis* 2007;7(2):105-17.
- 431 24. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE
432 evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64(4):383-
433 94.
- 434 25. Silcocks P. Hazard ratio funnel plots for survival comparisons. *J Epidemiol Community*
435 *Health* 2009;63(10):856-61.
- 436 26. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting
437 funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*
438 2011;343:d4002.

- 1
2
3 439 27. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and
4 440 unavailable data in meta-analyses using individual participant data: a database survey.
5 441 *BMJ* 2012;344
6 442 28. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale,
7 443 conduct, and reporting. *BMJ* 2010;340:c221.
8 444 29. WorldWide Antimalarial Resistance Network (WWARN). Malaria in pregnancy treatment
9 445 efficacy study group 2016 [cited 5 July 2018]. Available from:
10 446 <http://www.wwarn.org/working-together/study-groups/malaria-pregnancy-treatment->
11 447 [efficacy-study-group.](http://www.wwarn.org/working-together/study-groups/malaria-pregnancy-treatment-)
12 448 30. Oxford Tropical Research Ethics Committee. 2018 [cited 23 October 2018]. Available
13 449 from: <https://researchsupport.admin.ox.ac.uk/governance/ethics/committees/oxtrece>.
14 450 31. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review
15 451 and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA*
16 452 2015;313(16):1657-65.
17 453 32. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and
18 454 meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*
19 455 2015;349
20 456 33. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and
21 457 meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015;4(1):1.
22 458 34. Burger RJ, van Eijk AM, Bussink M, et al. Artemisinin-based combination therapy versus
23 459 quinine or other combinations for treatment of uncomplicated *Plasmodium falciparum*
24 460 malaria in the second and third trimester of pregnancy: a systematic review and meta-
25 461 analysis. *Open Forum Infect Dis* 2016;3(1):ofv170.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-20
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	346-349
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	78-94
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	95-114

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	✓	<input type="checkbox"/>	116-133
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	✓	<input type="checkbox"/>	135-141
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	<input type="checkbox"/>	135-147
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	<input type="checkbox"/>	158-165
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	✓	<input type="checkbox"/>	134-157
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	<input type="checkbox"/>	149-165
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	✓	<input type="checkbox"/>	209-228
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	<input type="checkbox"/>	182-208
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓	<input type="checkbox"/>	295-309
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	✓	<input type="checkbox"/>	182-228
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	✓	<input type="checkbox"/>	229-291
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓	<input type="checkbox"/>	292-300
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓	<input type="checkbox"/>	307-309

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	301-309
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	302-303

For peer review only

BMJ Open

The efficacy of artemisinin-based and quinine-based treatments for uncomplicated falciparum malaria in pregnancy: a protocol for systematic review and individual patient data (IPD) meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027503.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Jun-2019
Complete List of Authors:	Saito, Makoto; WorldWide Antimalarial Resistance Network (WWARN), ; University of Oxford, Centre for Tropical Disease and Global Health, Nuffield Department of Medicine Mansoor, Rashid; WorldWide Antimalarial Resistance Network (WWARN); University of Oxford, Centre for Tropical Disease and Global Health, Nuffield Department of Medicine Kennon, Kalynn; WorldWide Antimalarial Resistance Network (WWARN); University of Oxford, Centre for Tropical Disease and Global Health, Nuffield Department of Medicine McGready, Rose; Shoklo Malaria Research Unit, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University; Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford Nosten, François; Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford; Shoklo Malaria Research Unit, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University Guerin, Philippe; WorldWide Antimalarial Resistance Network (WWARN); University of Oxford, Centre for Tropical Disease and Global Health, Nuffield Department of Medicine Stepniewska, Kasia; WorldWide Antimalarial Resistance Network (WWARN); University of Oxford, Centre for Tropical Disease and Global Health, Nuffield Department of Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Pharmacology and therapeutics, Obstetrics and gynaecology
Keywords:	malaria, pregnancy, treatment efficacy, individual patient data meta-analysis, artemisinin, quinine

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1 The efficacy of artemisinin-based and quinine-based treatments for uncomplicated
2 falciparum malaria in pregnancy: a protocol for systematic review and individual patient data
3 (IPD) meta-analysis

4
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21
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23 Key words: malaria, pregnancy, treatment efficacy, individual patient data meta-analysis,
24 artemisinin, quinine

25 Abstract

26 *Introduction*

27 Pregnant women are more vulnerable to malaria leading to adverse impact on both
28 mothers and fetuses. However, knowledge on the efficacy and safety of antimalarials in
29 pregnancy is limited by the paucity of randomised control trials and the lack of standardised
30 protocols in this special sub-population. Pooling individual patient data (IPD) for meta-analysis
31 could address in part these limitations to summarise accurately the currently available evidence
32 on treatment efficacy and risk factors for treatment failure.

33 *Methods and analysis*

34 To assess the treatment efficacy of artemisinin-based and quinine-based treatments for
35 uncomplicated falciparum malaria in pregnancy, seven databases (MEDLINE, Embase, Global
36 Health, Cochrane Library, Scopus, Web of Science and Literatura Latino Americana em
37 Ciências da Saúde) and two clinical trial registries (International Clinical Trials Registry
38 Platform and ClinicalTrial.gov) were searched. Both interventional and observational cohort
39 studies following up for at least 28 days will be included. IPD of the identified eligible
40 published or unpublished studies will be sought by inviting principal investigators. Raw IPD
41 will be shared through the web-based secure platform developed by WorldWide Antimalarial
42 Resistance Network using the established methodology. The primary objective is to compare
43 the risk of polymerase chain reaction (PCR)-corrected treatment failure among different
44 treatments and to find the risk factors. One-stage IPD meta-analysis by Cox model with shared
45 frailty will be conducted. A risk of bias assessment will be conducted to address the impact of
46 potential unshared data and of the quality of individual studies. Potential limitations include
47 difficulty in acquiring the IPD and heterogeneity of the study designs due to the lack of standard.

48 *Ethics and Dissemination*

49 This IPD meta-analysis consists of secondary analyses of existing anonymous data and
50 meets the criteria for waiver of ethics review by the Oxford Tropical Research Ethics
51 Committee. The results of this IPD meta-analysis will be disseminated through open-access
52 publications at peer-reviewed journals. The study results will lead to a better understanding of
53 malaria treatment in pregnancy, which can be used for clinical decision-making and conducting
54 further studies.

55 *PROSPERO registration number: CRD42018104013.*

56 Article Summary

57 *Strengths and limitations of this study*

- 58 • This study will be the first individual patient data (IPD) meta-analysis on the efficacy
59 of currently recommended antimalarials in pregnancy incorporating IPD from both
60 randomised control trials and single-arm cohort studies, overcoming the limitation of
61 aggregated data meta-analysis that can only include randomised control trials.
- 62 • IPD that are standardised in the same format and analysed in a uniform way with
63 adjustment of covariates will, in contrast to aggregated data, allow us to compare the
64 efficacy of different treatments as well as to find risk factors for treatment failure in this
65 vulnerable but understudied population.
- 66 • Limitations of this IPD meta-analysis include the potential difficulty in acquiring the
67 IPD and the heterogeneity of the study designs, study population and parasite
68 population. A risk of bias assessment will be conducted to address the impact of
69 potential unshared data and of the quality of individual studies.

70 Introduction

71 About 60% of all pregnancies are estimated to take place in malaria-endemic areas.¹ In
72 addition, pregnant women are amongst the most vulnerable groups for malaria infection leading
73 to higher morbidity and mortality of both mothers and fetuses.² Although around 1500 studies
74 on the efficacy of antimalarials in malaria treatment have been conducted,³ pregnant women
75 have been excluded from the majority of clinical trials in the past, mainly because of safety
76 concerns for the fetus.

77 Due to the lack of evidence for both efficacy and safety of antimalarials in pregnancy,
78 quinine, rather than artemisinin-based combination therapy (ACT), has been recommended as
79 the first-line treatment of uncomplicated *Plasmodium falciparum* malaria for pregnant women
80 in the first trimester by the World Health Organization (WHO).⁴ However, recent studies
81 measuring the safety of artemisinin derivatives during pregnancy, including in the first
82 trimester, have shown reassuring results⁵⁻⁸ and it is likely that ACT will be recommended as
83 the first-line treatment option for pregnant women regardless of the trimester in the next WHO
84 treatment guidelines.⁹ Evidence on the treatment efficacy during pregnancy needs to be
85 assembled.

86 The efficacy and safety of antimalarials in pregnancy can be different from the results
87 from the non-pregnant populations because of altered immunity, physiological change in
88 pharmacokinetics and sequestration of parasites to the placenta. The risk factors for treatment
89 failure in pregnancy need to be assessed to improve clinical care in pregnancy. However, there
90 are no agreed guidelines on how to assess the efficacy in pregnancy while it is standardised in
91 the non-pregnant patients by WHO.¹⁰ This lack of standard methodology makes it challenging
92 to conduct efficacy studies in pregnancy and leads to the variability of assessing and reporting

1
2
3 93 the outcomes.^{11 12} Taken together, the current situation limits conducting aggregated data meta-
4
5 94 analyses.¹²
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8 95 The WorldWide Antimalarial Resistance Network (WWARN) has established a unique
9
10 96 individual participant data (IPD)-sharing platform facilitating large-scale pooled meta-analyses.
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13 97 We plan to include both published and unpublished studies exploring the efficacy and safety
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15 98 of the treatment of malaria during pregnancy. We will conduct a one-stage IPD meta-analysis
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17 99 on the currently recommended antimalarial drugs, i.e. artemisinin-based and quinine-based
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19
20 100 treatments, used for the treatment of uncomplicated falciparum malaria in pregnancy.
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24 101 Objectives

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26
27 102 The aim of this study is to evaluate and compare treatment outcomes of artemisinin-
28
29 103 based and quinine-based treatment for uncomplicated falciparum malaria in pregnancy.
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32 104 Primary objectives are:

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35 105 • To compare antimalarial efficacies among artemisinin-based and quinine-based
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37 106 treatments
- 38
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40 107 • To identify risk factors associated with treatment failure

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43 108 Secondary objectives are:

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46 109 • To assess the relationship between the dosing (dose per body weight) of
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48 110 artemisinin-based treatments and treatment efficacy
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51 111 • To evaluate the risk of gametocyte carriage following artemisinin-based and
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53 112 quinine-based treatments
- 54
55
56 113 • To evaluate the safety and tolerability of artemisinin-based and quinine-based
57
58 114 treatments

115 Methods and analyses

116 *Criteria for study eligibility*

117 **Types of studies**

- 118 • Prospective clinical efficacy studies with a minimum 28-day active follow-up
- 119 • Both interventional and observational cohort studies regardless of the number of
120 treatment arms (i.e. comparative or single arm)
- 121 • Genotyping conducted for distinguishing recrudescence and reinfection

122 The following studies will be excluded.

- 123 • ≤ 10 eligible pregnant women
- 124 • Conducted in non-endemic countries (i.e. returned travellers)

125 **Types of participants**

- 126 • Pregnant women in any trimester
- 127 • Parasitologically confirmed *P. falciparum* parasitaemia
- 128 • Either asymptomatic or symptomatic

129 **Types of intervention/exposure and controls**

- 130 • Treated with artemisinin-based or quinine-based treatments

131 **Types of outcomes**

- 132 • Parasitological and clinical efficacy
- 133 • Adverse events

134 *Information sources and search strategy*

135 A systematic literature review was conducted to identify the potential studies to be
136 included in this IPD meta-analysis. Seven databases (MEDLINE, Embase, Global Health,
137 Cochrane Library, Scopus, Web of Science and Literatura Latino Americana em Ciências da
138 Saúde) and two clinical trial registries (International Clinical Trials Registry Platform and
139 ClinicalTrial.gov) were used. Both published and unpublished grey literature such as
140 conference abstracts and registered trials were included. This systematic review and IPD meta-
141 analysis is registered to PROSPERO (CRD42018104013), and the search terms and conditions
142 are available there.

143 Briefly, the search combined five components: malaria; pregnancy; treatment or names
144 of anti-malarial drugs; study design (interventional or observational cohort studies); and
145 outcome types (efficacy) without limitation on publication year or language. The result of the
146 literature search was published elsewhere.¹² The initial search was conducted on 9 July 2016.
147 The final search will be updated in April 2019.

148 *Data acquisition and data management*

149 **Collecting IPD**

150 Principal investigators of the published and unpublished studies identified by the
151 systematic literature review will be invited to share their IPD with WWARN. Emails will be
152 sent to the corresponding authors on at least three occasions asking whether they are willing to
153 join the study group. A secure web-based platform has been developed by WWARN, and IPD
154 will be uploaded after agreeing to the terms and conditions of the submission, retaining the
155 ownership and full control of their shared data.¹³ Data are fully anonymised and handled in
156 compliance with the UK Data Protection Act to protect personal information and patient
157 privacy. Original data are stored on a secure server hosted by the University of Oxford.

158 **Data management**

159 Raw data will be curated in a standardised format using the WWARN Clinical Module
160 data management plan to facilitate pooled IPD meta-analyses.¹⁴ After checking the raw data,
161 any queries on the availability of data, ambiguity of the variables or potential errors will be
162 resolved by asking the data contributors. The protocol of the original studies will be sought
163 from the data contributors or the publication when available. The standardised dataset will be
164 used for the analyses.

165 *Statistical analysis plan*

166 **Study populations**

167 Pregnant women will be eligible for the purpose of this analysis if they meet the
168 following criteria:

- 169 • Confirmed pregnancy status on day 0 of the treatment
- 170 • Information on the type, date and dose of antimalarial drugs: artemisinin-based and
171 quinine-based treatments will be included
- 172 • Baseline data on patient age and estimated gestational age (or trimester of
173 pregnancy)
- 174 • Date of the last day of follow-up or length of follow-up

175 The following patients will be excluded:

- 176 • No or missing data on parasitological confirmation of *P. falciparum* infection at
177 enrolment
- 178 • Presenting with severe malaria symptoms at enrolment as defined by WHO⁴,
179 except hyperparasitaemia and severe anaemia, which will be included

180 **Outcomes**

181 The primary outcome will be the polymerase chain reaction (PCR)-corrected *P.*
182 *falciparum* treatment failure. Secondary outcomes will include any recurrence of malaria
183 (PCR-uncorrected treatment failure); parasite clearance; gametocyte carriage during follow up;
184 and adverse events that developed after drug administration.

185 Recurrences of *P. falciparum* will be distinguished by PCR into recrudescence
186 (treatment failure) and reinfection.¹⁵ Indeterminate PCR will be excluded, and reinfection will
187 be regarded as being censored on the day of recurrence in survival analyses for PCR-corrected
188 outcomes following the WHO guidelines.¹⁰ In studies where peripheral malaria smears were
189 examined regularly (e.g. every week), the time of parasite recurrence will be defined as the
190 time of the first positive parasite smear after the parasite clearance following the treatment. For
191 pregnant women with no recurrent parasitaemia recorded, the day of their last negative smear
192 will be regarded as their last visit and censoring time. In the case of intermittent follow-up (e.g.
193 missed follow-ups), the following rules will be applied:

- 194 (i) Blood smears will be assumed negative between the two negative observations
- 195 (ii) If a patient came back to be followed up with a positive smear, the date of
196 positive parasitaemia will be assumed to be the date of observation if this date is within 28 (± 3)
197 days from the last observation
- 198 (iii) If parasite clearance is not recorded after treatment but the positive parasite
199 count is recorded at least 7 days after starting the treatment, the day of the first positive count
200 will be treated as the day of recurrence

201 Definitions of status and other censorship are detailed in the Clinical Module data
202 management plan¹⁴ except for the above modification. The presence of parasitaemia within

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3 203 the first seven days will not be regarded as treatment failure for quinine-based treatment
4
5 204 because quinine is given for seven days.

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8 205 Adverse symptoms will include abdominal pain, dizziness, headache, body
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10 206 pain/myalgia, weakness/fatigue, vomiting, nausea, anorexia and tinnitus if data permit.

11 12 13 207 **Variables and their definitions**

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15
16 208 The following baseline characteristics of patients will be included as appropriate if
17
18 209 enough data are shared: age; estimated gestational age (or trimester); parity or gravidity; weight
19
20 210 (weight before pregnancy and weight at treatment); body mass index (BMI); baseline
21
22 211 parasitaemia; presence of fever (body temperature > 37.5 degrees Celsius); haemoglobin (or
23
24 212 haematocrit); anaemia (haemoglobin < 11 g/dL or haematocrit < 30% for anaemia and
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26 213 haemoglobin < 7 g/dL or haematocrit < 20% for severe anaemia);¹⁶ gametocytes on
27
28 214 presentation; past history of malaria or antimalaria use; description of infection (mixed species
29
30 215 infections); total mg/kg dose for each drug component; and supervision of drug administration.
31
32 216 The doses of drugs received will be calculated from the number of tablets administered to each
33
34 217 patient. If the actual number of tablets received was not recorded, doses according to the
35
36 218 protocol will be used. Only those who completed the standard dose will be included in the
37
38 219 primary analysis. The proportion of partial treatment will be presented.

39
40
41 220 For each study, study locations and local transmission intensity will be considered. The
42
43 221 study sites will be classified into three categories: low, medium and high malaria transmission
44
45 222 based on the parasite prevalence estimates obtained from the Malaria Atlas Project for specific
46
47 223 location and year of study.^{17 18}

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49 224 *Plasmodium vivax* intercalated infection (i.e. *P. vivax* mono-infection before the
50
51 225 recurrence of *P. falciparum* parasitaemia) will be regarded as censored if the original study did
52
53 226 not test PCR for falciparum recurrences after intercalated vivax infection, following the WHO
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3 227 guidelines.¹⁰ If the original study tested PCR for falciparum recurrences regardless of
4
5 228 intercalated vivax infection, vivax infection will be regarded as a time-dependent covariate.
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8 229 **Descriptive summaries**

9
10 230 A summary of the studies and baseline characteristics of the patients included in the
11
12 231 analysis will be presented. The number of available patients will be summarised for all
13
14 232 variables listed above, proportion will be used for categorical or binary variables, and mean
15
16 233 and standard deviation (or median and interquartile range) will be used for continuous variables.
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19
20 234 PCR-corrected and uncorrected outcomes will be used to compute the Kaplan-Meier
21
22 235 (K-M) estimates for each study site. The efficacy of each treatment will then be summarised at
23
24 236 fixed time points (i.e. on day 28, 42, and 63) by the aggregated meta-analysis approach.
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28 237 **Analysis of primary outcome**

29
30 238 A one-stage IPD meta-analysis using the Cox model with shared frailty for study sites
31
32 239 will be conducted to identify the risk factors for treatment failure as well as comparing different
33
34 240 treatments. For repeated episodes, if any, multi-level mixed-effects model (if there are enough
35
36 241 data) or the previous history of malaria will be used. If data permit, a non-linear relationship
37
38 242 will be examined for continuous variables.¹⁹ Cox-Snell and Schoenfeld residuals will be
39
40 243 examined to determine the appropriateness of model fit and proportional hazard assumption,
41
42 244 respectively. Alternative statistical approaches such as flexible parametric models or
43
44 245 introducing an interaction term with time will be considered if the proportionality assumption
45
46 246 is not satisfied.
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51 247 **Analyses of secondary outcomes**

52
53 248 Analysis of secondary outcomes will be carried out provided enough data are present;
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55 249 else, only summary statistics will be reported. Analyses similar to the primary outcome will be
56
57 250 conducted for PCR-uncorrected treatment failure (i.e. any recurrence of malaria).
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3 251 Parasite clearance will be assessed as the proportions of patients cleared asexual
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5 252 falciparum parasitaemia on day 1, 2 and 3. Univariable and multivariable mixed-effects logistic
6
7 253 regression models (or Cox models for the time to parasite clearance) will be used to identify
8
9 254 the risk factors associated with parasite positivity status.
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13 255 Gametocyte carriage will be assessed as the proportion of patients with *P. falciparum*
14
15 256 gametocytes on day 0, 3, 7, 14 or 21. Proportions after day 0 will be stratified by the presence
16
17 257 of gametocytes at baseline. If enough data are available, mixed-effects logistic regression
18
19 258 models will be used to assess the risk factors for gametocytes carriage after treatment stratified
20
21 259 by the presence of gametocytes at baseline.
22
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24

25 260 Adverse effects will be assessed as the proportion of patients who developed symptoms
26
27 261 after the treatment initiation. Proportions of patients who developed symptoms after day 0 will
28
29 262 be stratified by whether or not that symptom was present before the treatment initiation. If
30
31 263 enough data are available, mixed-effects logistic regression models will be used to assess the
32
33 264 risk factors for adverse symptoms developed after the treatment initiation. Symptoms on day 0
34
35 265 (before treatment) will be added as a covariate. Primarily the symptoms developed in the first
36
37 266 week will be included. Pregnancy outcomes and placental malaria may be assessed if enough
38
39 267 data are gathered.
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44 268 **Variable selection**

45
46 269 For any regression models, the following strategy recommended by Collet²⁰ will be
47
48 270 used to determine independent risk factors. Initially, all possible risk factors will be examined
49
50 271 in the univariable model to assess if any of the variables are related to the treatment outcome.
51
52 272 All significant variables with a p-value ≤ 0.05 will then be added to the baseline model. The
53
54 273 variables with a p-value of > 0.05 will be excluded from the baseline model one by one starting
55
56 274 from the variable with the largest p-value. Once only significant covariates will remain in the
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1
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3 275 model, all excluded variables will be added to this model one by one to check whether there
4
5 276 will be any variables that become significant in the presence of other risk factors. Likelihood
6
7 277 Ratio Test (LRT) and Akaike's Information Criterion (AIC) will be used to compare nested
8
9 278 and non-nested models, respectively. Treatment and baseline parasitaemia will be included in
10
11 279 the multivariable models on treatment efficacy as *a priori* forced variables regardless of the
12
13 280 statistical significance. Variables that are missing more than 50% will not be included in
14
15 281 multivariable analyses.²¹ Interaction between gravidity (parity) and endemicity, or age and
16
17 282 endemicity will be assessed if age or gravidity is included in the multivariable model, as the
18
19 283 impact of age and gravidity (i.e. pregnancy-specific immunity) can be different depending on
20
21 284 the endemicity.²²

27 285 **Assessment of statistical heterogeneity across studies**

28
29 286 The multilevel logistic or Cox models would be used for explaining the study-site
30
31 287 heterogeneity. Heterogeneity across study sites will be statistically assessed as the variance of
32
33 288 the shared frailty term estimated in the Cox model or variance of the random intercepts in
34
35 289 logistic regression. Additionally, the intra-class correlation in logistic regression model will be
36
37 290 reported.

41 291 **Subgroup analyses**

42
43 292 Analyses will be conducted by malaria transmission intensity and by treatment (for
44
45 293 assessing dose impact of each drug) if data permit.

49 294 **Sensitivity analyses**

50
51 295 Two types of sensitivity analyses will be performed. Firstly, a model will be refitted
52
53 296 with excluding one study at a time to identify any influential studies. Secondly, to assess the
54
55 297 impact of covariates with missing values, multiple imputation may be used.²¹

298 **Strength of the body of evidence / risk of bias across studies**

299 The risk of bias within and across the included studies will be assessed following the
300 GRADE guidelines.²³ Publication bias will be evaluated by a funnel plot of the log-transformed
301 hazards ratio (odds ratio or proportion),²⁴ if more than ten studies are included.²⁵ Despite the
302 effort, all the studies identified in the systematic review may not be shared and included in this
303 IPD meta-analysis. The bias by the studies that are unable to be included in the analyses will
304 be evaluated.²⁶ The reported aggregated efficacy will be extracted from the publication and
305 compared with the studies included. A two-stage meta-analysis combining shared and unshared
306 data will be attempted if data permit.²⁷ The impact of artemisinin resistance in the study year
307 at the study site will be evaluated by using the reported prevalence on molecular resistance
308 marker (K-13).

309 **Further development of statistical analysis plan**

310 The main analysis is planned as described above. Modification or additional analyses
311 may be required as the data collection progresses. Updated statistical analysis plans will be
312 available at the WWARN website if an amendment is required.²⁸

313 **Software**

314 Statistical analysis will be conducted using R (The R Foundation for Statistical
315 Computing, Vienna, Austria) or Stata MP 15.1 (StataCorp, College Station, Texas, USA).

316 *Patient and Public Involvement*

317 This IPD meta-analysis will use existing secondary data. Patients and public were not
318 involved in the design, recruitment or conduct of this IPD meta-analysis. The results of this
319 study will be shared with the primary investigators of the shared studies and disseminated as
320 publications in open access journals.

321 Ethics and dissemination

322 This IPD meta-analysis met the criteria for waiver of ethics review as defined by the
323 Oxford Tropical Research Ethics Committee (OxTREC) as the research consists of secondary
324 analyses of existing anonymous data.²⁹ All studies included in this analysis will have received
325 local ethical approvals.

326 Findings will be reported following the PRISMA-IPD guideline³⁰ at peer-reviewed
327 journals with open access. The progress will be updated on our study group website.²⁸ This
328 protocol is reported following PRISMA-P guideline^{31 32} and the systematic literature review
329 and IPD meta-analysis is registered to PROSPERO (CRD42018104013). Any publications
330 based on the findings of this IPD meta-analysis will be in accordance with the guidelines of the
331 International Committee of Medical Journal Editors.

332 Discussion

333 This IPD meta-analysis will update the previous aggregated data meta-analyses that
334 included only four or five RCTs.^{12 33} In IPD meta-analyses, data from single-arm interventional
335 or observational cohort studies can be included. As the data can be standardised and analysed
336 in a uniform way, IPD meta-analyses are particularly useful when there is no standard study
337 design such as in this case. Risk factors associated with treatment failures particularly the
338 dosing of the currently used treatments can be assessed in IPD meta-analyses, but rarely in
339 aggregated data meta-analyses. Although meta-analyses of secondary data cannot include
340 variables that were not assessed in the original studies, the results of this IPD meta-analysis
341 can identify the pregnant women in need of close clinical monitoring based on what is
342 commonly assessed. Despite the increased time and effort of gathering and standardising the

1
2
3 343 IPD, the advantages of IPD meta-analysis outweigh particularly for answering research
4
5 344 questions on these neglected or understudied populations.
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8 345 WWARN has developed the secure and equitable data platform and the international
9
10 346 collaborative network of malaria researchers worldwide over the last decade. With this unique
11
12 347 collaborative effort, we hope that these findings will lead to the improvement of clinical
13
14 348 management of this vulnerable but understudied population.
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19 349 Author Contributions

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21
22 350 MS, RoM and PG conceived the idea. MS and RM drafted the manuscript. KK, FN,
23
24 351 RoM, PG and KS critically revised the manuscript. All authors have read and approved the
25
26 352 final manuscript.
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44 359 manuscript.
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50 360 Competing interests

51
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53 361 None declared.
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362 Ethics approval

363 This individual patient data meta-analysis met the criteria for waiver of ethics review
364 as defined by the Oxford Tropical Research Ethics Committee (OxTREC) since the research
365 consists of secondary analyses of existing anonymous data. Each study included in the analysis
366 will have received local ethics approvals.

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369 literature review and Dr Prabin Dahal for his comments on the draft.

370 References

- 371 1. Dellicour S, Tatem AJ, Guerra CA, et al. Quantifying the number of pregnancies at risk of
372 malaria in 2007: a demographic study. *PLoS Med* 2010;7(1):e1000221. doi:
373 10.1371/journal.pmed.1000221
- 374 2. Rogerson SJ, Desai M, Mayor A, et al. Burden, pathology, and costs of malaria in pregnancy:
375 new developments for an old problem. *Lancet Infect Dis* 2018;18(4):e107-e18. doi:
376 10.1016/S1473-3099(18)30066-5
- 377 3. WorldWide Antimalarial Resistance Network. WWARN clinical trials publication library
378 2017 [cited 20 March 2019]. Available from: [https://www.wwarn.org/tools-](https://www.wwarn.org/tools-resources/literature-reviews/wwarn-clinical-trials-publication-library)
379 [resources/literature-reviews/wwarn-clinical-trials-publication-library](https://www.wwarn.org/tools-resources/literature-reviews/wwarn-clinical-trials-publication-library).
- 380 4. World Health Organization. Guidelines for the treatment of malaria. Third edition. Geneva:
381 WHO Press 2015.
- 382 5. Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine
383 treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-
384 analysis of observational studies. *PLoS Med* 2017;14(5):e1002290. doi:
385 10.1371/journal.pmed.1002290
- 386 6. Kovacs SD, van Eijk AM, Sevene E, et al. The Safety of Artemisinin Derivatives for the
387 Treatment of Malaria in the 2nd or 3rd Trimester of Pregnancy: A Systematic Review
388 and Meta-Analysis. *PLoS One* 2016;11(11):e0164963. doi:
389 10.1371/journal.pone.0164963
- 390 7. McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax
391 malaria and the safety of antimalarial treatment in early pregnancy: a population-based
392 study. *Lancet Infect Dis* 2012;12(5):388-96. doi: 10.1016/S1473-3099(11)70339-5
- 393 8. Moore KA, Simpson JA, Paw MK, et al. Safety of artemisinins in first trimester of
394 prospectively followed pregnancies: an observational study. *Lancet Infect Dis*
395 2016;16(5):576-83. doi: 10.1016/s1473-3099(15)00547-2

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41
42
43
44
45
46
47
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56
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58
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60

- 396 9. WHO Malaria Policy Advisory Committee Secretariat. Malaria Policy Advisory Committee
397 to the WHO: conclusions and recommendations of eighth biannual meeting (September
398 2015). *Malar J* 2016;15:117. doi: 10.1186/s12936-016-1169-x
- 399 10. World Health Organization. Methods for surveillance of antimalarial drug efficacy.
400 Geneva: WHO Press 2009.
- 401 11. Saito M, Gilder ME, Nosten F, et al. Methodology of assessment and reporting of safety in
402 anti-malarial treatment efficacy studies of uncomplicated falciparum malaria in
403 pregnancy: a systematic literature review. *Malar J* 2017;16:491. doi: 10.1186/s12936-
404 017-2136-x
- 405 12. Saito M, Gilder ME, Nosten F, et al. Systematic literature review and meta-analysis of the
406 efficacy of artemisinin-based and quinine-based treatments for uncomplicated
407 falciparum malaria in pregnancy: methodological challenges. *Malar J* 2017;16:488.
408 doi: 10.1186/s12936-017-2135-y
- 409 13. WorldWide Antimalarial Resistance Network (WWARN). Terms of Submission 2017
410 [cited 5 July 2018]. Available from: [http://www.wwarn.org/tools-resources/terms-
411 submission](http://www.wwarn.org/tools-resources/terms-submission).
- 412 14. WorldWide Antimalarial Resistance Network (WWARN). Clinical Module: Data
413 Management and Statistical Analysis Plan Version 1.2. 2012 [cited 5 July 2018].
414 Available from: <http://www.wwarn.org/sites/default/files/ClinicalDMSAP.pdf>.
- 415 15. World Health Organization. Methods and techniques for clinical trials on antimalarial drug
416 efficacy: Genotyping to identify parasite populations. Geneva: WHO Press 2008.
- 417 16. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and
418 assessment of severity. Geneva: WHO Press 2011.
- 419 17. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on Plasmodium
420 falciparum in Africa between 2000 and 2015. *Nature* 2015;526(7572):207-11. doi:
421 10.1038/nature15535
- 422 18. Gething PW, Patil AP, Smith DL, et al. A new world malaria map: Plasmodium falciparum
423 endemicity in 2010. *Malar J* 2011;10:378. doi: 10.1186/1475-2875-10-378
- 424 19. Royston P, Sauerbrei W. Fractional Polynomials for One Variable. Multivariable Model-
425 building: A pragmatic approach to regression analysis based on fractional polynomials
426 for modelling continuous variables. Chichester, UK: John Wiley & Sons 2008:71-98.
- 427 20. Collett D. 3.6 Strategy for model selection. Modelling survival data in medical research
428 Third edition. New York: CRC Press 2015:83-90.
- 429 21. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and
430 guidance for practice. *Stat Med* 2011;30(4):377-99. doi: 10.1002/sim.4067
- 431 22. Rogerson SJ, Hviid L, Duffy PE, et al. Malaria in pregnancy: pathogenesis and immunity.
432 *Lancet Infect Dis* 2007;7(2):105-17. doi: 10.1016/s1473-3099(07)70022-1
- 433 23. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE
434 evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64(4):383-
435 94. doi: 10.1016/j.jclinepi.2010.04.026
- 436 24. Silcocks P. Hazard ratio funnel plots for survival comparisons. *J Epidemiol Community
437 Health* 2009;63(10):856-61. doi: 10.1136/jech.2008.075069
- 438 25. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting
439 funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*
440 2011;343:d4002. doi: 10.1136/bmj.d4002
- 441 26. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and
442 unavailable data in meta-analyses using individual participant data: a database survey.
443 *BMJ* 2012;344 doi: 10.1136/bmj.d7762
- 444 27. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale,
445 conduct, and reporting. *BMJ* 2010;340:c221. doi: 10.1136/bmj.c221

- 1
2
3 446 28. WorldWide Antimalarial Resistance Network (WWARN). Malaria in pregnancy treatment
4 447 efficacy study group 2016 [cited 5 July 2018]. Available from:
5 448 [http://www.wwarn.org/working-together/study-groups/malaria-pregnancy-treatment-
7 449 efficacy-study-group](http://www.wwarn.org/working-together/study-groups/malaria-pregnancy-treatment-
6 449 efficacy-study-group).
8 450 29. Oxford Tropical Research Ethics Committee. 2018 [cited 23 October 2018]. Available
9 451 from:<https://researchsupport.admin.ox.ac.uk/governance/ethics/committees/oxtrac>.
10 452 30. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review
11 453 and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA*
12 454 2015;313(16):1657-65. doi: 10.1001/jama.2015.3656
13 455 31. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and
14 456 meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*
15 457 2015;349 doi: 10.1136/bmj.g7647
16 458 32. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and
17 459 meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015;4(1):1.
18 460 doi: 10.1186/2046-4053-4-1
19 461 33. Burger RJ, van Eijk AM, Bussink M, et al. Artemisinin-based combination therapy versus
20 462 quinine or other combinations for treatment of uncomplicated Plasmodium falciparum
21 463 malaria in the second and third trimester of pregnancy: a systematic review and meta-
22 464 analysis. *Open Forum Infect Dis* 2016;3(1):ofv170. doi: 10.1093/ofid/ofv170
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-20
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	346-349
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	350-355
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	78-94
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	95-114

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	✓	<input type="checkbox"/>	116-133
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	✓	<input type="checkbox"/>	135-141
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	<input type="checkbox"/>	135-147
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	<input type="checkbox"/>	158-165
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	✓	<input type="checkbox"/>	134-157
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	<input type="checkbox"/>	149-165
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	✓	<input type="checkbox"/>	209-228
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	<input type="checkbox"/>	182-208
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓	<input type="checkbox"/>	295-309
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	✓	<input type="checkbox"/>	182-228
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	✓	<input type="checkbox"/>	229-291
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓	<input type="checkbox"/>	292-300
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓	<input type="checkbox"/>	307-309

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	301-309
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	302-303

For peer review only