cIMPROVE2

Chemoprevention with monthly IPTp with dihydroartemisinin-piperaquine for malaria in HIV-infected pregnant participants on daily cotrimoxazole in Kenya and Malawi: a multi-centre placebo-controlled trial

STATISTICAL ANALYSIS PLAN

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SAP version history		
Version Date	SAP Version #	Details of Changes
17 February 2022	1.0	Original version
03 October 2022	2.0	• New outcomes added to be consistent with Improve 1 • mITT defined • Analysis of adherence to study regimen added • Baseline table added comparing participants with and without missing primary outcome data • Markers of SP resistance added as baseline covariate • Viral load removed a co-variate • Details of timing of start/switch to DTG-based antiretroviral therapy added

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2 ABBREVIATIONS

Abbreviation	**Explanation**
AE	Adverse Event
AIC	Akaike Information Criteria
ANC	Antenatal Clinic
AR	Adverse reaction
cARTs	combination Antiretroviral Therapy
CI	Chief Investigator
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRL	Crown-Rump Length
CTX	Cotrimoxazole
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DP	Dihydroartemisinin-Piperaquine
DTG	Dolutegravir
EFV	Efavirenz
FL	Femur Length
GLM	Generalised Linear Model
HC	Head Circumference
HIV	Human Immunodeficiency Virus
IPTp	Intermittent Preventive Treatment in pregnancy
IRR	Incidence Rate Ratio
ITT	Intention-to-treat
LBW	Low Birth Weight
LLIN	Long Lasting Insecticidal Net
LSTM	Liverpool School of Tropical Medicine
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MUAC	Mid Upper Arm Circumference
PCR	Polymerase Chain Reaction
PP	Per-protocol
PT	Pre-term
PTB	Pre-term Birth
RDT	Rapid Diagnostic Test
RR	Risk ratio
RTI	Reproductive Tract Infection
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SES	Socio-Economic Status
SGA	Small for Gestational Age

Abbreviation	**Explanation**
SOP	Standard Operating Procedure
STIs	Sexually Transmitted Infections
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
WHO	World Health Organization

3 INTRODUCTION

3.1 PURPOSE OF THE STATISTICAL ANALYSIS PLAN

The purpose of this Statistical Analysis Plan (SAP) is to define the outcome variables, statistical methods, and analysis strategies to address the study objectives of the IMPROVE2 trial: "Chemoprevention with monthly IPTp with dihydroartemisinin-piperaquine for malaria in HIV-infected pregnant participants on daily cotrimoxazole in Kenya and Malawi: a multi-centre placebo-controlled trial" (Protocol Version 2 – 11 July 2019) (IMPROVE-2)

3.2 BACKGROUND AND RATIONALE

In malaria-endemic Africa, Human Immunodeficiency Virus (HIV) and malaria conspire to increase the risks of adverse pregnancy outcomes. The World Health Organisation (WHO) recommends daily cotrimoxazole (CTX) for chemoprevention for malaria and prophylaxis against opportunistic infection for HIV-infected pregnant women. However, there is cross-resistance with SP, and high levels of antifolate resistance threaten the antimalarial effect of CTX. Recent trials in HIV-infected pregnant women who received daily CTX plus Intermittent Preventive Treatment in pregnancy (IPTp) with mefloquine suggested that chemoprevention with an effective antimalarial markedly reduces the risk of malaria compared to daily CTX alone. However, mefloquine was not well tolerated. The long-acting combination of dihydroartemisinin-piperaquine (DP) is well tolerated and has shown great promise as IPTp in HIV-negative women in East Africa. Chemoprevention with monthly DP has also been explored in HIV-infected women on daily CTX in Uganda. Unfortunately, the study was inconclusive as malaria transmission was too low. Furthermore, a clinically relevant drug-drug interaction between DP and efavirenz (EFV) was found to reduce DP drug levels. Following the recommendation from WHO, many countries in Africa are transitioning from EFV-based to dolutegravir (DTG) based combination antiretroviral therapy (cARTs). WHO now recommends DTG-based cARTS as the preferred first-line cART regimen in the 2nd and 3rd trimester of pregnancy. No such drug-drug interaction is expected between DTG and DP. Therefore, we will assess the safety and efficacy of malaria chemoprevention with monthly DP in HIV-infected women on daily CTX and DTG-based cARTs.

4 STUDY OBJECTIVES

This is a 2-arm multi-centre trial involving 898 (449 per arm) women in 8 hospitals in Kenya and Malawi, comparing daily CTX alone versus daily CTX plus monthly DP. The primary outcome is the incidence of malaria infection. This study is conducted alongside a sister trial among HIV-negative women (IMPROVE trial), also evaluating monthly DP.

4.1 PRIMARY OBJECTIVE

To determine if monthly IPTp-DP in HIV-infected women receiving daily CTX is safe and superior to daily CTX-alone for controlling malaria infection in areas with high antifolates resistance to SP and CTX in Malawi and Kenya.

4.2 SECONDARY OBJECTIVES

1. To determine if monthly IPTp-DP in HIV-infected pregnant women receiving daily CTX is safe and superior to daily CTX-alone for preventing adverse pregnancy outcomes due to malaria.
2. To determine the effect of co-administration of DP and current first-line cARTs on the pharmacokinetic properties of piperaquine, first-line cARTs and CTX
3. To determine if the level of SP drug resistance, assessed by molecular markers, affects the potential impact of CTX.
4. To determine the safety of monthly-DP in pregnant women receiving daily CTX and cARTs by conducting nested cardio monitoring studies.

5. To determine if monthly IPTp-DP in HIV-infected pregnant women receiving daily CTX affects the risk of mother-to-child transmission of HIV infection.
6. To determine if monthly IPTp-DP in HIV-infected pregnant women receiving daily CTX reduces the risk of viral infections.
7. To determine the impact of the interventions and prenatal exposure to HIV and/or malaria on adaptive and innate-like immune responses

5 STUDY DESIGN

5.1 DESIGN

This will be a multi-centre, 2-arm, parallel, placebo-controlled, individually randomised, phase-3, superiority trial in 898 (449 per arm) HIV-infected pregnant women receiving daily CTX and cARTs to compare the efficacy of monthly IPTp-DP ('CTX-DP') against monthly placebo-DP ('CTX-alone') (allocation ratio 1:1). The study will be conducted in about eight sites in high malaria endemic and high HIV endemic areas in southern Malawi and western Kenya. These are the same sites in Malawi and Kenya where the trial in HIV-negative women (IMPROVE) will be conducted.

HIV-infected pregnant women (all gravidae) attending for antenatal care (ANC) between 16-28 weeks' gestation irrespective of CTX or cART use, assessed by ultrasound dating, will be eligible. Participants will be seen monthly until delivery. Mothers and infants will be followed-up for 6 to 8 weeks post-partum. Sub-studies of cardiac safety and pharmacokinetics will be conducted.

At enrolment, all participants will be randomly allocated to receive one of two regimens:

- *CTX-alone: Daily,* one double-strength tablet of 160mg of sulfamethoxazole and 800mg of trimethoprim plus monthly placebo-DP, given as a fixed dose of 3 placebo-DP tablets daily for three days until delivery.
- *CTX-DP:* Daily, one double-strength tablet of 160mg of sulfamethoxazole and 800mg of trimethoprim plus monthly DP, given as a fixed dose of 3 tablets (40 mg of dihydroartemisinin and 320 mg of piperaquine) daily for three days until delivery.

Subsequent clinic visits will be scheduled monthly after the first visit. The range of monthly visits will be 3 to 7 visits, depending on the gestational age of the woman at enrolment and delivery. Since recruitment is restricted to 16-28 weeks gestation, a median of 4 to 5 monthly visits is expected.

5.2 ELIGIBILITY

Please see the current version of the study protocol for participant eligibility.

5.3 RANDOMISATION

Balanced randomisation will be used using permuted block randomisation methods stratified by site (i.e. hospital) and two HIV-status groups (known-positive and newly-diagnosed). A statistician at the Liverpool School of Tropical Medicine (LSTM) in the UK will generate the randomisation lists using dummy coding (e.g. A, B), and another independent statistician who is not involved in the study will assign the dummy codes to each of the two study arms. The list with the allocation sequence will then be forwarded to the trial pharmacists based in Kenya and Malawi, who will then prepare sequentially numbered, sealed, opaque boxes or envelopes for each participant with the randomisation assignments. Contained within each of these envelopes or boxes will be the pre-packed investigational product for the entire duration of the study for that participant. These opaque boxes/envelopes will be opened sequentially upon enrolment of a study participant at each site. Stratification by HIV status (known-positive vs newly-diagnosed) is essential to ensure balanced distribution among study arms as women newly diagnosed with HIV will not yet be on daily cotrimoxazole and may thus have a higher

risk of malaria at enrolment. The latter is an important determinant of the primary outcome of malaria infection. Minimisation or distance randomisation using central randomisation services by the internet is not feasible because of the unreliable internet connections and telephone services in some of the proposed sites.

5.4 SAMPLE SIZE

The primary outcome will be the cumulative incidence of malaria infection detected from 2 weeks after the first day of the first dose of the first course to delivery inclusive, defined as the presence of peripheral (maternal) or placental (maternal) Plasmodium infection detected by either molecular diagnostics (henceforth referred to as Polymerase Chain Reaction (PCR)), microscopy, Rapid Diagnostic Test (RDT) or placental histology (active infection). A sample size of 898 (449 per arm) (359 contributors and 90 non-contributors) is required to detect a 50% reduction (RR=0.50) from 12% in the CTX-alone arm (control arm) to 6% in the intervention arm with 80% power (alpha=0.05) allowing for 20% non-contributors (N=90). The effect size of 50% is more conservative than the 68% pooled effect size observed in a fixed-effects meta-analysis from the three completed trials to date that compared IPTp-DP vs IPTp-SP in HIV-negative women (95% Confidence Interval (CI) 61% to 73%, I-squared=0%, P<0.0001).[1-3]

A key secondary outcome is 'adverse pregnancy outcome' defined as the composite of fetal loss (spontaneous abortion or stillbirth), or singleton live births born small-for-gestational-age (SGA), or with low birthweight (LBW), or preterm (PT) (SGA-LBW-PT), or subsequent neonatal death by day 28. The sample size of 718 contributors (359 per arm) provides 80% power to detect a 27.6% reduction (RR=0.724) in adverse pregnancy outcomes from 34.5% with CTX-alone (control) to 25.0% in the DP arm (alpha=0.05). The 34.5% proportion for this outcome in the control arm (CTX-alone) is based on data from our recently completed pregnancy trials in Malawi[4] and Kenya.[1] The frequency of this outcome was 23.0% in HIV-negative women receiving IPTp-SP. It was assumed that this outcome is at least 1.5 times more common in HIV-infected women on cART (i.e. 1.5x23.0=34.5%), based on a recent meta-analysis comparing the risk of low birthweight and preterm delivery in HIV-infected vs HIV-negative women.[5]

5.5 OUTCOMES

5.5.1 Primary outcome

The primary outcome will be the cumulative incidence of malaria infection detected from 2 weeks after the first day of the first dose of the first course to delivery inclusive, defined as the presence of peripheral (maternal) or placental (maternal) Plasmodium infection detected by either molecular diagnostics (henceforth referred to as PCR), microscopy, RDT or placental histology (active infection) (Binary Yes/No). The numerator will include any event occurring in any of the individual components of the composite primary outcome. The denominator will include all women at risk with at least one valid (non-missing) outcome (Yes/No) for at least one of the individual components of the primary outcome (i.e., including women that do not have data on all individual components of the composite). For women to contribute to the primary outcome, they need to have been followed for at least 2 weeks following randomisation.

5.5.2 Secondary outcomes

Note that all Incidence Rates for the secondary outcomes exclude immediate follow-up visits related to the primary episode, defined as 14 days exclusion period for that endpoint following from 2 weeks after the first day of the first dose of the first course, defined below as "from 2 weeks after enrolment" with the words "excluding delivery" for outcomes that reflect "during pregnancy".

5.5.2.1 Efficacy

5.5.2.1.1 Maternal outcomes

1. Incidence of clinical malaria during pregnancy. (Binary (yes/no), Incidence Rate (Rate/100 person-years))

   Definition: During pregnancy and excluding delivery, both:

   - Documented fever (≥37.5°C), or recent history of fever in the past 24 hours, or other symptoms of acute illness that resulted in a woman seeking care or alerting the study team to request a home visit.
   - Maternal malaria infection detectable by microscopy or RDT

2. The individual components of the composite of the primary outcome (excluding histology which is described as outcome outcome #7, below) (Binary- Yes/No, Incidence Rate (Rate/100 person years).
   a. Any malaria during pregnancy or at delivery detected by RDT
   b. Any malaria during pregnancy or at delivery detected by microscopy
   c. Any malaria during pregnancy or at delivery detected by PCR

   Definition: Defined as any malaria infection detected by each diagnostic method from 2 weeks after enrolment and including delivery.

3. Incidence of any malaria infection in the peripheral blood during pregnancy (Binary-Yes/No, Incidence Rate (Rate/100 person-years))

   Definition: Defined as the composite of malaria detected in the peripheral blood by RDT (for point of care), or microscopy (not for point of care), or by PCR (not for point of care), from 2 weeks after enrolment and excluding delivery.

4. The individual components of the composite malaria infection endpoints during pregnancy, excluding delivery (Binary-Yes/No, Incidence Rate (Rate/100 person-years))
   a. Any malaria during pregnancy detected by RDT
   b. Any malaria during pregnancy detected by microscopy
   c. Any malaria during pregnancy detected by PCR

   Definition: Defined as the any malaria infection detected by each diagnostic method from 2 weeks after enrolment and excluding delivery.

5. Any malaria infection at delivery (Binary-Yes/No)

   Definition: Malaria infection detected in maternal peripheral or placental blood by either molecular diagnostics, microscopy, RDT, or placental histology (active infection).

6. Maternal peripheral malaria infection at delivery by any measure (Binary – Yes/No)

   Definition: Malaria infection detected in maternal peripheral blood by either molecular diagnostics, microscopy or RDT

7. Placental malaria by histology (active or past) (Binary-Yes/No)

   Definition: Maternal malaria infection detectable by placental histology (active and past infections pooled).

8. Placental histology: (Binary – Yes/No)

a. Placental histology (any)
b. Placental histology (active)
c. Placental histology (past)
d. Placental histology (active-acute)
e. Placental histology (active-chronic)

Definition:

- Past Infection: Pigment in fibrin detected in the absence of asexual parasites.
- Active Infection: Asexual parasites present (i.e. acute or chronic)
- Chronic: Pigment present and asexual parasites present
- Acute: Pigment absent and asexual parasites present

9. Placental malaria by any measure (Binary-Yes/No)

Definition: Malaria infection detected in placental blood by either molecular diagnostics, microscopy or RDT; or by placental histology (active and past infections pooled).

10. Placental inflammation or chorioamnionitis (Binary – Yes/No)

Definition: Placental Inflammation or chorioamnionitis detected by placental histology.

11. Prevalence of maternal anaemia in the third trimester (Binary-Yes/No)

Definition: Low haemoglobin (see below) in the third trimester of pregnancy, excluding delivery using Hb measured in either venous or capillary blood.

a.) Any anaemia - Hb<11.0g/dL
b.) Moderate-severe anaemia - Hb<9.0g/dL
c.) Severe anaemia – Hb<7.0g/dL

12. Mean haemoglobin in the third trimester (Continuous (g/dL))

Definition: Haemoglobin in g/dL in the third trimester of pregnancy, excluding delivery using Hb measured in either venous or capillary blood.

13. Prevalence of maternal anaemia at delivery (Binary – Yes/No)

Definition: Low haemoglobin measured just prior to delivery (e.g. the day of delivery, but before the actual time of delivery of the baby) using Hb concentrations measured in either venous or capillary blood. If the time of delivery or blood sample is unavailable, the Hb value would not be used in the analysis.

a.) Any anaemia - Hb<11.0g/dL
b.) Moderate-severe anaemia - Hb<9.0g/dL
c.) Severe anaemia – Hb<7.0g/dL

14. Mean haemoglobin at delivery (Continuous(g/dL))

Definition: Haemoglobin at delivery using Hb measured in either venous or capillary blood at the same times points as for secondary outcome 12.

15. Prevalence of maternal anaemia at third trimester or delivery (Binary- Yes/No)

Definition: Low haemoglobin (see below) in the third trimester of pregnancy or delivery using Hb measured in either venous or capillary blood. If both third trimester Hb and a valid delivery

Hb (i.e. taken before delivery of the baby) are available, the delivery Hb will be used. The rational is that the delivery Hb may be missing for many women, which can then be replaced with a third trimester Hb. The valid delivery Hb is considered of primary importance as this is taken after all IPTp courses have been taken during pregnancy. In contrast, third-trimester Hb may be taken just before a subsequent IPTp course is taken.

a.) Any anaemia - Hb<11.0g/dL
b.) Moderate-severe anaemia - Hb<9.0g/dL
c.) Severe anaemia – Hb<7.0g/dL

16. Gestational weight gain per week (Continuous(kg/week))

Definition: Maternal weight at the last measured time point before delivery (e.g. in the third trimester) minus the maternal weight at enrolment, divided by the number of weeks between these dates

17. Serial gestational weight gain per week (Continuous(kg/week))
Definition: Pooled serial maternal weight measurements using the maternal weights taken at any timepoint during pregnancy post-enrolment and before delivery (i.e. excluding delivery as weights were taken just after the delivery of the baby) analysed by mixed models for repeated measures, adjusting for the baseline value.

18. Maternal Mid-upper arm circumference (MUAC) at delivery (Continuous(cm))

Definition: Mid-upper arm circumference (MUAC) measured at delivery

19. Low Mid-upper arm circumference (MUAC) measured at delivery (Binary – Yes/No),

Definition: MUAC less than 23 cm measured at delivery or at the last time point in the third trimester (28 weeks gestation or later) if MUAC at delivery is not available

20. Mid-upper arm circumference gain per week (Continuous(cm/week))

Definition: Maternal MUAC at the last measured time point at or before delivery (e.g. in the third trimester or at delivery) minus the MUAC enrolment, divided by the number of weeks between these dates

21. Serial mid-upper arm circumference gain per week (Continuous(cm/week))

Definition: Pooled serial maternal MUAC taken at any time point at or before delivery (e.g. in the third trimester or at delivery) analysed by mixed models for repeated measures, adjusting for the baseline value.

5.5.2.1.2 Pregnancy and newborn outcomes

22. Adverse pregnancy outcome (Binary-Yes/No):

Definition: The composite of fetal loss (spontaneous abortion or stillbirth), or singleton live births born small-for-gestational age (SGA), or with low birthweight (LBW), or preterm (PT) (SGA-LBW-PT), or subsequent neonatal death by day 28.

Small for gestational age will be defined as <10th percentile of the INTERGROWTH reference population.[6]

Birthweight (grams) - Weight taken within 7 days of birth using digital scales (precision +/- 10grams) in live singleton babies and corrected to reflect weight at birth. We will use a corrected birthweight that takes time since birth into account. This will be based on a model developed from newborn weights measured daily since birth for seven days as part of a nested study among the newborns in the IMPROVE study designed to assess the physiological fall in birthweight in breastfed newborns during the first week of life.

A table of correction factors based on the sex of the infant, its measured weight (increasing from 2kg – 4kg in increments of 10g), and time from birth to weighing (in hourly increments from 1hr to 168hrs) computed from the model will be used to impute adjusted birthweight.

For infants with a measured weight of <2kg or >4kg, the adjusted weight will be imputed using a different table of correction factors, based on its sex and time from birth to weighing (increasing in 6-hourly increments from 0-168 hrs).

For infants where sex is not available, the midpoint between girls and boys for that time point will be used. For infants for which the exact hour of birth and /or measurement of (birth)weight is not known, the weighing timepoint is assumed to be 0 hours (if birth and measurement on the same day), then 24, 48, 72… hours if weighing is 1, 2, 3… days after delivery.

See supplemental tables 1-3 for birthweight correction factors.

Examples using the above methods:

- A male infant with a measured weight of 3.00kg taken 30 hours after delivery would have an adjusted birthweight of 3.14kg (supplemental Table 1).
- A female infant with a measured weight of 1.90kg taken 48 hours after delivery would have an adjusted birthweight of 1.90 x (100/95.726) = 1.98kg (supplemental Table 3).

Gestational age at delivery – number of days between delivery and enrolment/registration, plus gestation age (days) at registration defined by:

- By ultrasound scan, if the booking visit occurred at gestational age up to 196 days (28 weeks)
  - On head circumference (HC) and femur length (FL)
  - By only FL if HC is missing
  - By only HC if FL is missing
  - By Crown Rump Length (CRL) if gestational age <14weeks (i.e. CRL≤79mm)
- By Last Menstrual Period if the exact date is known and the preceding measure is not available
- By fundal height measurement if no other measure of gestational age is available.

Low birth weight (LBW) – birthweight <2500g

Preterm birth (PTB) - spontaneous birth before 259 days (37 weeks) gestation

23. The individual components of the above composites

Definition: See also secondary outcome 22, Adverse pregnancy outcome (Binary-Yes/No):
As Categorical Variables:

a.) Fetal loss (spontaneous abortion or stillbirth) (Binary-Yes/No)
b.) Neonatal mortality (Binary-Yes/No)
c.) Small for Gestational Age (Binary-Yes/No)

d.) Low Birthweight (Binary-Yes/No)
e.) Preterm (Binary-Yes/No)

As Continuous Variables:

f.) Birthweight (kg)
g.) Gestational age (days)
h.) Z-score for birthweight from INTERGROWTH population reference

24. Spontaneous abortion (Binary – Yes/No)

Definition: Spontaneous fetal loss (miscarriage) that has not yet reached a birth weight of 1000 g, or if birth weight is unavailable, a gestational age of less than 28 weeks or crown-to-heel length of less than 35 cm

25. Stillbirth (Binary – Yes/No)

Definition: A baby born with no signs of life that has reached a birth weight of 1000 g, or if birth weight is unavailable, a gestational age of 28 weeks or more or crown-to-heel length of 35 cm or more (International WHO/ICD definition)

26. Early neonatal death (Binary – Yes/No)

Definition: Death of a live-born baby within the first 7 days of birth

27. Perinatal death (Binary – Yes/No)

Definition: Composite of stillbirth or early neonatal death

28. Composite of fetal loss and neonatal mortality (Binary-Yes/No)

Definition: Neonatal mortality or fetal loss

29. SGA-LBW-PT composite. (Binary – Yes/No)

Definition: See also secondary outcome 22, for definitions and timepoints

30. Neonatal length (Continuous (cm))

Definition: Neonatal length recorded within 24 hours of birth and Z-score for birth length (cm) using the INTERGROWTH reference https://intergrowth21.tghn.org/newborn-size-birth/#ns1 (continuous).

31. Stunting (newborn): (Binary – Yes/No),

Definition: <3rd centile of birth length for gestational age using the INTERGROWTH reference

32. Wasting: (Binary – Yes/No),

Definition: <3rd centile of adjusted birthweight for gestational age

33. Stunting and Wasting (newborn): (Binary – Yes/No),

Definition: Both <3rd centile of birth length for and <3rd centile of adjusted birthweight for gestational age

34. Congenital malaria infection (newborn) (Binary-Yes/No)

Definition: Malaria infection, detected in fetal cord blood or peripheral blood of the newborn at birth or within 7 days (168 hours) after birth, by either:

- RDT (parasite Lactate Dehydrogenase (pLDH) only)

- Standard microscopy

35. Congenital anaemia (newborn) (Binary-Yes/No), Continuous(g/dL)

    Definition: Hb<12.5 g/dL in umbilical cord blood at birth

36. Cord blood haemoglobin (Continuous (g/dL)
    Definition: Haemoglobin concentration measured in umbilical cord blood at birth

5.5.2.2 Safety

1. QTc-prolongation (Binary-Yes/No), Continuous (ms)

   Definition: Mean QTc (QTcF and QTcB), mean delta QTc, and binary QTc > 480ms, QTc>500ms, delta QTc 60ms alone and any of these combined with cardiac symptoms (e.g. syncope).

2. Congenital malformations (Binary-Yes/No)

   Definition: Physical abnormality of live-born baby detected at delivery or newly noted abnormality during the infant visits (7 days or 6-8 weeks post-natal).

3. Maternal mortality (Binary-Yes/No)

   Definition: Maternal mortality from registration until 42 days after delivery or termination of pregnancy.

4. Other Serious Adverse Events (SAEs) and Adverse Events (AEs) (listings) - (Incidence Rate (Rate/100 person-years), Cumulative Prevalence (Binary – Yes/No)

   Definition: AEs and SAEs will be defined according to the Medical Dictionary for Regulatory Activities (MedDRA) and reported by study arm

   a) Overall
   b) by system organ class and preferred term

5. Mother-to-child transmission of HIV (Binary – Yes/No) (exploratory)

   Definition: Infant diagnosed as HIV positive by PCR DNA analysis of peripheral blood sample.

6. Any neonatal jaundice (newborn) (Binary-Yes/No)
   Definition: Yellow discolouration of the skin in neonates from birth to 28 days of life.

   Any jaundice- yellow discolouration of the skin at any point (Binary- Yes/No)

5.5.2.3 Tolerance

7. Vomiting study drug- (% with at least one event and Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

   Definition: Vomited within 30 minutes of taking study drug at any scheduled administration.

8. Later vomiting- (% with at least one event and Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

   Definition: Vomiting at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

9. Nausea - (Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

Definition: Nausea at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

10. Dizziness - (Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

    Definition: Dizziness at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

11. Gastrointestinal complaints - (Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

    Definition: Nausea or vomiting at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

12. Abdominal pain - (Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

    Definition: Abdominal pain at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

13. Diarrhoea - (Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

    Definition: Diarrhoea at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

14. Headache - (Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

    Definition: headache at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

15. Rash - (Incidence Rate (Rate/100 person-years), prevalence at each cycle of treatment (Binary – Yes/No), Cumulative Prevalence (Binary – Yes/No)

    Definition: Rash at any point within 96hrs (4 days) of the first drug administered during a treatment cycle

5.5.2.4 Exploratory outcomes

16. Incidence of antibodies against SARS-Cov-2 and other viral infections during pregnancy or at delivery (Binary (yes/no)

    Definition: At any point after enrolment to delivery inclusive, antibodies against SARS-Cov-2 or other viral infections in women who were antibody negative at enrolment.

17. Evidence of arboviral infections during pregnancy or at delivery (Binary (yes/no), Incidence Rate (Rate/100 person-years))

    Definition: At any point after enrolment to delivery inclusive arboviral infections detected by qRT-PCR assays.

6 BASELINE COVARIATE

Molecular markers of sulfadoxine-pyrimethamine resistance in Plasmodium falciparum infections during pregnancy and delivery per study site or region derived from IMPROVE trial.

Definition: Presence of the following haplotypes reported from samples of IMPROVE trial participants recruited from sites and/or regions that also recruited IMPROVE-2 trial participants.

- Quadruple (Either CIRNI-SGKAA or CIRNI-AGKAA)
- Quintuple (Either CIRNI-SGEAA or CIRNI-AGEAA)
- Sextuple (Either CIRNI-SGEGA or CIRNI-AGEGA)

7 ANALYSIS POPULATIONS

The membership of each analysis set will be determined and documented, and the reasons for exclusion will be given prior to database lock. A summary table will list the individual subjects sorted by treatment group and describe their protocol deviation/violation.

The analysis populations will be listed as follows:

7.1 INTENTION-TO-TREAT (ITT) POPULATION

All randomised participants with valid informed consent will be included in the ITT population according to the treatment to which they are randomised, regardless of whether they prematurely discontinue treatment or are otherwise protocol violators/deviators. Analyses for tabulations of demographic and baseline characteristics, population disposition and important protocol deviation will utilise this analysis set.

7.2 MODIFIED INTENTION-TO-TREAT (MITT) POPULATION (PRIMARY ANALYSIS)

The modified ITT population (mITT) will be defined as the ITT population with valid outcome data for that outcome, and after exclusion of screening failures (pregnant women randomised but subsequently found to be ineligible).

7.3 PER-PROTOCOL (PP) POPULATION

The per-protocol population will be defined as the mITT population minus the participants with the following major protocol deviations:

1. Mother did not adhere to study treatment (e.g. missed any study dose at any occasion when measured).
2. Mother switched treatment (e.g. a participant is randomised to CTX-DP but received CTX-alone, and *vice versa*).
3. Mother did not attend all scheduled study visits
4. Mother used prohibited medication

This population will be used for the supportive analyses. There is no single Case Report Form (CRF) question that determines the per-protocol population, and the PP population will be determined and documented by the Chief Investigator (CI), data manager and the trial statistician prior to data lock and summarised in the final report.

7.4 SAFETY POPULATION

This population is a subset of the ITT population, consisting of all randomised subjects who receive at least one dose or a partial dose of the study drug. Subjects will be analysed according to the randomised treatment unless a subject has received the incorrect treatment during the entire study period. Analysis for safety endpoints will utilise this analysis set.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1 REPORTING GUIDELINES

We will follow the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement: updated guidelines for reporting parallel group randomised trials (http://www.consort-statement.org/).

8.2 PARTICIPANT DISPOSITION AND FLOW CHART

A flow chart will be drawn up showing the number of subjects screened, enrolled, and followed-up in each study arm and the number contributing to the ITT, per-protocol and safety analysis.

The number screened and not enrolled, and the reasons for non-enrollment will be reported, along with the number of screening failures (enrolled but subsequently found to be ineligible), subjects who were lost for follow up (with reasons), and the number withdrew for safety reasons, and who crossed-over between study arms.

A list of major protocol deviations will be presented before the data have been unblinded.

8.3 DATA SUMMARIES

Continuous variables will be summarised according to the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum.

Categorical variables will be summarised according to the absolute frequency and percentage of subjects (%) in each category level. The denominator for the percentages is the number of subjects in the treatment arm with data available unless noted otherwise.

Event rates per 100 person-years will also be reported for time-to-event outcomes, count outcomes and adverse events of special interest. All Incidence rates of malaria infection outcomes exclude immediate follow-up visits related to the primary episode, defined as 14 days exclusion period for that endpoint from the time of the first dose of the first course of IPTp. Event rates during pregnancy for any of the malaria infection outcomes will exclude data collected (events and person-time) in the 14 days after each treatment provided for clinical malaria (usually with artemether-lumefantrine) because this treatment is anticipated to provide at least two weeks of post-treatment prophylaxis and any recurring event within 14 days is considered a treatment failure of the treated event.

8.4 PLANNED COVARIATES

Covariate analyses will be performed on the primary outcome on the mITT population. The prespecified covariates in this study will be:

8.4.1 Stratification factors

- study site (Chikwawa, Madziabango, Mpemba, Zomba, Mangochi (all Malawi); Homa Bay, Ahero, Rabour, Akala, Bondo, Chulaimbo (all Kenya))
- HIV status (known-positive vs newly diagnosed)

8.4.2 Baseline values

- gravidity (paucigravidae [1st and 2nd] vs multigravidae [3rd+])
- malaria status (positive-negative, based on microscopy where available and otherwise RDT (pLDH band), and otherwise PCR)
- socio-economic status (SES)
- season (average rainfall last 6 months before delivery),
- malaria transmission intensity by site (based on the prevalence of malaria at enrolment, continuous)

** Baseline prevalence of malaria is computed by taking the rolling average 6-month parasite prevalence on admission in all women recruited during three months before and after a participant was recruited. Doing this gives a 365-day prevalence for each date of the year.*

Stratification factors will use the value used for randomisation unless otherwise stated. Other covariate analyses will be performed if deemed necessary. These may include the presence of SARS-CoV-2 antibodies if these are found to be associated with the primary outcome.

Viral load (copies/ml) was initially included in the protocol and v1 of the SAP but will not be considered as a covariate or for subgroup analysis (section 8.5, below) because it will not be collected as a research sample but copied from existing health records. Therefore, viral load is expected to be unavailable for many participants.

8.5 Subgroup Analysis

Prespecified subgroup analyses will be performed for the primary outcome on the mITT population. Sub-group analysis will be conducted on variables defined in section 8.4, Planned covariates, plus country and the number of IPTp courses received.

- gravidity (paucigravidae [1st and 2nd] vs multigravidae [3rd+])
- malaria status at enrolment (positive, negative)
- socio-economic status (SES) (terciles)
- season (terciles of average rainfall last 6 months before delivery),
- malaria transmission intensity by site (defined by less than or greater than the median)
- gestational age at enrolment (defined by less than or greater than the median)
- Country (Kenya, Malawi)
- number of IPTp courses received (per dose)
- number of IPTp courses received (1-2, 3-4, 5+)
- degree of SP resistance by site (defined by less than or greater than the median)

The sub-group analysis by gravidity is considered of special interest because the risk of malaria during pregnancy is modified by gravidity.

The treatment effect within each category of these variables will be estimated, and the interaction effect between treatment and each variable will be assessed to explore effect modification. The result will be expressed as the P-value of the interaction test and as the ratio of the effect size between subgroups (e.g. ratio of the relative risk) and corresponding 95% confidence intervals.

8.6 Missing data

8.6.1 Baseline covariates

Missing baseline covariates will be imputed using simple imputation methods in the covariate-adjusted analysis based on the covariate distributions, should the missing values for a particular covariate be less than 5%. For a continuous variable, missing values will be imputed from random values from a normal distribution with mean and SD calculated from the available sample. For a categorical variable, missing values will be imputed from random values from a uniform distribution with probabilities P_1, P_2, …, and P_k from the sample. The seed for the imputation is set as 128.

If the missing values for a covariate are ≥5%, then they will be imputed using Markov chain Monte Carlo (MCMC) methods.

Note for imputing baseline malaria status, six distributions will be taken into consideration, depending on which tercile of rainfall for the study site the enrolment date fell in and the gravidity of the woman.

8.6.2 Efficacy outcomes

For the primary analysis, a complete case analysis will be performed in the mITT population, and no imputation for missing efficacy outcome values will be performed. For the primary composite

endpoint (Cumulative incidence of malaria infection), data will be considered non-missing if any of the individual components of the primary outcome is available.

In addition, analyses will be performed to compare the baseline characteristics among women with missing versus non-missing outcomes in the ITT population and determine how missingness is distributed between treatment arms. Missing outcomes will be imputed using MCMC methods. Finally, sensitivity analyses will be performed on the effect of missing outcome data on the treatment effect of the primary outcome (see section 9.2.3).

8.6.3 Safety outcomes

Missing safety data will not be imputed.

8.7 MULTIPLICITY

8.7.1 Multiple secondary outcomes:

For secondary outcomes, confidence intervals and p-values will not be adjusted for multiple testing. However, care will be taken when interpreting the findings from these analyses. Because there is a total of about 59 secondary outcomes, some may be significant by chance alone. For example, for a total of twenty analyses, up to one would be expected to be statistically significant at the $p<0.05$ level by chance alone. This would be 2.95 for 59 comparisons (59 x 0.05). Subject to journal requirements, the following statement will be added to the figure or table notes comparing multiple secondary outcomes: *"The P-values and widths of the confidence intervals have not been adjusted for multiplicity, so should not be used to infer definitive treatment effects for secondary outcomes."*[7]

8.7.2 Multiple subgroup analyses:

Confidence intervals and p-values for the effect size of secondary outcomes by subgroup, and the p-values for the interaction tests, will not be adjusted for multiple testing. However, subject to journal requirements, the following statement will be added to the figure or table notes comparing effect size by sub-groups: *"The P-values and widths of the confidence intervals have not been adjusted for multiplicity, so should not be used to infer definitive treatment effects by subgroups or differences between subgroups."* [7]

8.8 FURTHER EXPLORATORY ANALYSES

Further exploratory analyses may be carried out should they be deemed necessary; this will be at the discretion of the Trial Management Group (TMG). These will be added to the analysis plan as an amendment along with justification, where appropriate.

8.9 SOFTWARE

8.9.1 Data management:

A combination of paper-based and electronic record forms will be used. For the questionnaires that are administered in paper format, the study will utilise QED ScanForm software to design the paper-based CRFs for semi-automated transcribing into an electronic database using scanning and Optical Character Recognition, intelligent document recognition and data validation using checksum algorithms, cross-field validation, and human verification of information against source documents. Once validated, the data will be transferred to the target database along with a PDF of the original image of the CRFs, such that there is an electronic copy of all paper-based documents. For the electronic-only data capture, such as home visits to administer drug adherence and bednet questionnaires, the study will use tablets with integrated sim cards to transfer encrypted data to the ODK or similar servers where the participants' electronic clinical data will be stored hosted.

Once the central data manager completes the data validation phase, the database will be locked and transferred to a statistical programmer who will do further syntax driven consistency checks and syntax driven data cleaning. The statistical programmer will have access to the PDF copies of the source data. He/she will check the data quality (e.g. searching for outliers), and a query will be sent back to the central data manager if found. He/she will then prepare the database for data analysis by the trial statistician by creating the final variables for data analysis, such as creating the composite endpoints. The final cleaned database will be available in SAS, STATA, and SPSS format, with an embedded data dictionary.

Further details of data management are described in the trial-specific Standard Operating Procedures (SOPs) for databases, scanning procedures and data entry.

8.9.2 Statistical analysis:

SAS® (version 9.4) or Stata (v15 or higher) or other appropriate statistical software will be used to perform all data analyses and generate most data displays.

8.10 STUDY FILES ARCHIVING

All study files, including the protocol, SAP, CRFs and study SOP etc., will be stored in the trial master file.

9 STATISTICAL ANALYSES

The trial statistician will conduct the analyses, and a second statistician will validate the primary analysis. The crude analysis using the mITT population, unadjusted for covariates other than the stratification factors site and HIV status (known-positive and newly diagnosed), will be considered the primary analysis. This will be supported by covariate analysis that includes additional covariates. In addition, per protocol and sensitivity analyses for primary and secondary efficacy endpoints will be performed to test the robustness of the treatment effects observed. The safety analysis set will be used to analyse safety endpoints.

9.1 COMPLIANCE WITH TREATMENT / EXTENT OF EXPOSURE

Compliance with study treatment is measured by participant as a % of prescribed doses courses of IPTp with DP or DP-placebo. Th extent of exposure is provided as a cumulative number of courses per arm and as median (IQR, and range) and mean (SD) exposure per participant.

For the purpose of inclusion in the PP set, compliance with study treatment is defined as:

- With each course: took all tablets on each of the 3 daily doses of treatment
- With the overall regimen: Attended all scheduled visits until delivery (exclude visits that could not have occurred because delivery was before the scheduled visit date)

9.2 PRIMARY OUTCOME ANALYSIS

9.2.1 mITT analysis of the primary outcome - the primary analysis

The primary outcome in this trial is the cumulative incidence of malaria infection, which is a binary endpoint. The primary analysis will be based on the mITT population as defined above and summarised by the number (%) of participants by treatment group.

The generalised linear model (GLM) with the log-link function and binomial distribution (log-binomial regression) will be used to analyse the primary endpoint. The crude GLM model will have the treatment arm as the only predictor and stratification factors site and HIV status (known positive and newly diagnosed) as covariates. The risk ratio (RR) of IPTp DP plus CTX versus CTX alone with

associated 95% confidence intervals (CI) will be derived from the GLM model. If the above log-link binomial regression model does not converge, the following alternative Stata commands will be used in the following order:[8]

- A model fitted using the "binreg" Stata command. Because binreg constrains risk estimates to be greater than 0 and less than 1, it may converge when maximum likelihood will not.
- The GLM model with the log-link function and binomial distribution with "difficult" option specified, which will change Stata's convergence algorithm.
- The GLM model with the log-link function and Poisson distribution with a robust variance estimator[8]
- The GLM model with the log-link function and Gaussian (normal) distribution with a robust variance estimator[8]
- If models above do not converge, the adjusted GLM model will be established by dropping a covariate one by one (with covariates being dropped in the order the weakest to strongest (largest p-value to smallest in single-variable analysis from the covariates listed in section 8.4 (page 17) until the adjusted GLM model becomes converged.
- If all models fail to converge, the Mantel-Haenszel method will be used.

9.2.2 Per-protocol analysis of the primary outcome

A supportive analysis of the primary outcome will also be performed on the per-protocol populations. Statistical methods will be the same as used in Section 9.2.1.

9.2.3 Sensitivity analysis of the primary outcome

Missing results for the primary outcome will be imputed as part of a sensitivity analysis (see section 8.6.2, Efficacy outcomes, page 18) to assess the effect of missingness in the primary outcome.

Estimates of the treatment effect will be derived and then compared with the primary analysis to assess whether the estimate of the treatment effect would substantially change in this alternative scenario.

9.2.4 Covariate adjusted analysis of the primary outcome

Adjusted analyses will be carried out for the primary endpoint to determine whether the estimate of treatment-effect is affected by the inclusion of additional covariables. The prespecified covariables included in the adjusted analyses are described in Sections 8.4, Planned covariates, page 17.

9.2.5 Subgroup analysis of the primary outcome

We will perform a series of subgroup analyses according to the list of subgroups in section 8.4, Planned covariates, page 17. Imputation for these baseline missing covariates (see section 8.6, Missing data, page 18) will be carried out before categorising. Assessment of the homogeneity of treatment effect by a subgroup variable will be conducted by a GLM-based analysis with the treatment, subgroup variable, and their interaction term as predictors and the *P*-value presented for the interaction term.

9.3 SECONDARY OUTCOME ANALYSIS

All secondary outcomes will be analysed as a superiority design, and two-sided 95% CIs for the treatment differences in these outcomes between two treatment groups will be calculated and presented. Unless specified, secondary efficacy outcome analyses will be based on both the mITT and Per protocol population.

9.3.1 Analysis of binary outcomes

The same generalised linear model (GLM) will be used for the primary analysis.

9.3.2 Analysis of continuous outcomes

9.3.2.1 Continuous outcomes, single time point measures (e.g. delivery)

Continuous outcomes with normal distribution such as birthweight will be summarised using the number of subjects (n), mean, standard deviation (SD), median, minimum, 25% and 75% percentile, and maximum by treatment group, and will be analysed by a GLM model with treatment as the predictor and with normal distribution and identity link function, and the stratification factors 'site' and 'HIV status' (known-positive and newly diagnosed) as covariates. Results will be expressed as mean differences with their two-sided 95% confidence intervals and will be derived from the GLM model.

Continuous outcomes that do not follow a normal distribution, such as parasite density, will be log-transformed and summarised as geometric mean, 95% CI of the geometric mean, median, minimum, maximum by treatment group, and will also be analysed by a GLM model with treatment as the predictor and with normal distribution and identity link function, and the stratification factors 'site' and 'HIV status' (known-positive and newly diagnosed) as covariates. Results will be expressed as the ratio of geometric mean differences with their two-sided 95% confidence intervals and will be derived from the GLM model.

If variables do not attain a normal distribution after transformation, results will be expressed as the median and 25% and 75% percentile by arm and compared using the Wilcoxon rank-sum test.

9.3.2.2 Continuous outcome, repeated measures

The pooled effect on repeated measures of continuous outcomes such as maternal gestational weight gain, maternal mid-upper arm circumference, haemoglobin etc, will be analyses using linear or non-linear mixed-effects models. The effect will be expressed as the mean difference (95% CI) and p-value at the last measurement during pregnancy (e.g. third trimester) and overall by pooling all measures taken after enrolment. The analysis will start from the first follow-up visit at least two weeks after enrolment, coded as zero. The model will include the variables treatment, time, and interaction between treatment and time as well as baseline confounder(s), including the baseline measurement of the outcome (e.g. maternal weight, maternal MUAC, etc).

9.3.3 Analysis of count outcomes

The count outcome will be summarised using the number of events and incidence rate by treatment group. They will be analysed by a GLM model with treatment as the predictors and with Poisson distribution and log link function, and the stratification factors 'site' and 'HIV status' (known-positive and newly diagnosed) as) as covariates. The incidence rate ratio with their two-sided 95% confidence intervals will be derived from the GLM model.

9.3.4 Analysis of other secondary outcomes

Other statistical methods may be used if deemed necessary.

10 SAFETY ANALYSES

Safety analysis of the AEs and SAE and other 'tolerance' data will be performed on the safety population. First, adverse events (AEs) will be summarised as per treatment arm as 'any AE' (all AEs per treatment arm), and per specific AE as the number (%) of participants with at least one event (cumulative risk), the total number of events per arm, the person time, and the incidence rate per 100 person-years (95% CI). They will then be compared between the two study arms as RR and IRR.

The same process will be performed for serious adverse events (SAEs), serious adverse reactions (SARs); suspected unexpected serious adverse reactions (SUSARs), and deaths occurring after randomisation.

11 REFERENCES

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12 APPENDIX

12.1 TABLE SHELLS

12.1.1 Table shells overall (both countries pooled)

Table-1: Baseline characteristics ITT population (not mITT)

Overall

	CTX (n=)	CTX+DP (n=)	p-value
Maternal characteristics			
Newly-diagnosed HIV infection			
On EFV-based retroviral therapy			
On DTG-based retroviral therapy			
Switched to DTG-based retroviral therapy during this pregnancy before enrolment			
Switched to DTG-based retroviral therapy during this pregnancy at enrolment			
Newly diagnosed HIV infection, started DTG-based retroviral therapy at enrolment			
On Cotrimoxazol prophylaxis			
Maternal age (years)			
Residence Rural vs Semi-urban/Urban			
Marital status Single† vs Married/Cohabiting			
Used a bednet previous night			
Attended school			
Schooling level			
None			
Primary school			
Secondary school			
Higher			
SES index score (terciles)			
Low			
Medium			
High			
Pregnancy number (gravidity)			
First			
Second			
Third or higher			
Gestational age (weeks)			
Weight (kg)			
Height (cm)			
MUAC (cm)			
Body-mass index (BMI) (kg/m^2)			
Laboratory findings			
HIV viral load >= 400 (copies/mL)*			
Detectable SARS-CoV-2 antibodies			
Haemoglobin (g/dL)			

Overall

	CTX (n=)	**CTX+DP (n=)**	**p-value**
Malaria infection			
mRDT			
Microscopy			
PCR			
Any			

Viral load was copied from existing health records only available for xxx participants (CTX=xxx, CTX+DP=xxx)

Table-2: Serious Adverse Events

	CTX (n= women, n= infants)*			CTX+DP (n= women, n= infants)**						
	No with event (%)	Total Events	Incidence per 100 person-years (95% CI)	No with event (%)	Total Events	Incidence per 100 person-years (95% CI)	RR (95% CI)	p-value	IRR (95% CI)	p-value
Women										
Any serious adverse event										
By System Organ Class										
Infants										
Any serious adverse event										
By System Organ Class										

Table-3: Secondary outcomes (continuous) in the mITT population score by treatment group and site

	Number of women, mean (SD)				Mean difference*(95% CI), p-value	
	DP		CTX			
	N	Mean (SD)	N	Mean (SD)	Unadjusted	Adjusted
Birthweight (grams)						
Birthweight for gestational age (Z-score)						
Gestational age at birth (weeks)						
Neonatal length (cm)						
Maternal MUAC (cm)						
Gestational weight gain per week (kg)						
Maternal Hb third trimester (g/dL)						
Maternal Hb delivery (g/dL)						
Cord blood Hb (g/dL)						

ITT population; [a] adjusted for site and HIV status as per stratification factors

ITT population; [a] adjusted for site and HIV status as per stratification factors

Table 4: ECG safety outcomes in the safety population

					Bazett				Fridericia			
Dose	**Day and Time**	**N**		**Measure**	**CTX**	**CTX+DP**	**MD (95% CI) or RR (95% CI)**	**p-value**	**CTX**	**CTX+DP**	**MD (95% CI) or RR (95% CI)**	**p-value**
First	0 (b/line)		QTc	Mean (SD)								
				Range								
				>480ms, n								
				>500ms, n								
	2 + 4hr			Mean (SD)								
				Range								
				>480ms, n								
				>500ms, n								
	from Day-0		dQTc	Mean (SD)								
				>60ms, n (%)								
Middle	0 (b/line)		QTc	Mean (SD)								
				Range								
				>480ms, n								
				>500ms, n								
	2 + 4hr			Mean (SD)								
				Range								
				>480ms, n								
				>500ms, n								
	from Day-0 middle		dQTc	Mean (SD)								
				>60ms, n (%)								
	from Day-0 first course		dQTc	Mean (SD)								
				>60ms, n (%)								
Last	0 (b/line)		QTc	Mean (SD)								
				Range								
				>480ms, n								
				>500ms, n								
	2 + 4hr			Mean (SD)								

					Bazett				Fridericia			
Dose	**Day and Time**	**N**		**Measure**	**CTX**	**CTX+DP**	**MD (95% CI) or RR (95% CI)**	**p-value**	**CTX**	**CTX+DP**	**MD (95% CI) or RR (95% CI)**	**p-value**
				Range								
				>480ms, n								
				>500ms, n								
	from Day-0 last course		dQTc	Mean (SD)								
				>60ms, n (%)								
	from Day-0 first course		dQTc	Mean (SD)								
				>60ms, n (%)								

P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Table-5: ECG safety outcomes in the safety population (study specific correction factor – QTcD)

					Derived			
Dose	**Day and Time**	**N**		**Measure**	**CTX**	**CTX+DP**	**MD (95% CI) or RR (95% CI)**	**p-value**
First	0 (b/line)		QTc	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
	2 + 4hr			Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
	from Day-0		dQTc	Mean (SD)				
				>60ms, n (%)				
Middle	0 (b/line)		QTc	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
	2 + 4hr			Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
	from Day-0 middle		dQTc	Mean (SD)				
				>60ms, n (%)				
	from Day-0 first course		dQTc	Mean (SD)				
				>60ms, n (%)				
Last	0 (b/line)		QTc	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
	2 + 4hr			Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
	from Day-0 last course		dQTc	Mean (SD)				
				>60ms, n (%)				
	from Day-0 first course		dQTc	Mean (SD)				
				>60ms, n (%)				

Table 6: ECG safety outcomes in the safety population – subjects exceeding safety criteria

Dose	Day and Time	N	Criterion	CTX (n=)	CTX+DP (n=)	RR (95% CI)	p-value
First	**0 (b/line)**		**1, n(%)**	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
	2+4h		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
Middle	0 (b/line)		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
	2+4h		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
Last	0 (b/line)		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
	2+4h		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		

Criterion 1 – QT>460ms & HR<70bpm & (QTcb>500ms or QTcF>500ms) & (DeltaQTcb>60ms or DeltaQTcf>60ms)
Criterion 2 – QT>460ms & HR<70bpm & report of "syncope" / "seizure" / "faint(ing)" / "ventricular (tachyarrhythmia)"
Criterion 3 – QT>460ms & HR<70bpm

Table 7:ECG safety outcomes in the safety population – subjects exceeding safety criteria – study specific correction factor (QTcD)

Dose	Day and Time	N	Criterion	CTX (n=)	CTX+DP (n=)	RR (95% CI)	p-value
First	**0 (b/line)**		**1, n(%)**	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
	2+4h		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
Middle	0 (b/line)		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
	2+4h		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
Last	0 (b/line)		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		
	2+4h		1, n(%)	**/ (%)**	**/ (%)**		
			2, n(%)	**/ (%)**	**/ (%)**		
			3, n(%)	**/ (%)**	**/ (%)**		

Criterion 1 – QT>460ms & HR<70bpm & QTcD>500ms & DeltaQTcD>60ms
Criterion 2 – QT>460ms & HR<70bpm & report of "syncope" / "seizure" / "faint(ing)" / "ventricular (tachyarrhythmia)"
Criterion 3 – QT>460ms & HR<70bpm

Table 8: ECG safety outcomes in the safety population – uncorrected QT

Dose	Day and Time	N		Measure	CTX	CTX+DP	MD (95% CI) or RR (95% CI)	p-value
First	0 (b/line)		QT	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
			HR	Mean (SD)				
				Range				
	2+4hr		QT	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
			HR	Mean (SD)				
				Range				
	From Day 0		dQT	Mean (SD)				
				>60ms, n (%)				
			dHR	Mean (SD)				
				Range				
Middle	0 (b/line)		QT	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
			HR	Mean (SD)				
				Range				
	2+4hr		QT	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
			HR	Mean (SD)				
				Range				
	From Day 0 – middle course		dQT	Mean (SD)				
				>60ms, n (%)				
			dHR	Mean (SD)				
				Range				
	From Day 0 – first course		dQT	Mean (SD)				
				>60ms, n (%)				
			dHR	Mean (SD)				
				Range				
Last	0 (b/line)		QT	Mean (SD)				
				Range				
				>480ms, n (%)				

Dose	Day and Time	N		Measure	CTX	CTX+DP	MD (95% CI) or RR (95% CI)	p-value
				>500ms, n (%)				
			HR	Mean (SD)				
				Range				
	2+4hr		QT	Mean (SD)				
				Range				
				>480ms, n (%)				
				>500ms, n (%)				
			HR	Mean (SD)				
				Range				
	From Day 0 – last course		dQT	Mean (SD)				
				>60ms, n (%)				
			dHR	Mean (SD)				
				Range				
	From Day 0 – first course		dQT	Mean (SD)				
				>60ms, n (%)				
			dHR	Mean (SD)				
				Range				

Table 9: ECG safety outcomes (continuous) in the safety population – Cardiac Safety Table

			Bazett					Fridericia				
Dose	**N**		**CTX**	**CTX+DP**	**Overall**	**MD (95% CI)****	**p-value****	**CTX**	**CTX+DP**	**Overall**	**MD (95% CI)****	**p-value****
First		Delta QTc (ms) (95% CI)*										
Middle		Delta QTc (ms) (95% CI)*										
Last		Delta QTc (ms) (95% CI)*										
Overall		Delta QTc (ms) (95% CI)*										

*Intercept and 95% CI of the delta QTc v delta RR regression slope; delta QTc and delta RR are calculated as change from baseline before drug administration on the first visit. ** mean difference and P-value for difference between CTX and CTX+DP

Note results in this table are normalised to no change in HR in each group.

Table 10: ECG safety outcomes (continuous) in the safety population – Cardiac Safety Table – study specific correction factor (QTcD)

			Derived				
Dose	**N**		**CTX**	**CTX+DP**	**Overall**	**MD (95% CI)****	**p-value****
First		Delta QTc (ms) (95% CI)*					
Middle		Delta QTc (ms) (95% CI)*					
Last		Delta QTc (ms) (95% CI)*					
Overall		Delta QTc (ms) (95% CI)*					

*Intercept and 95% CI of the delta QTc v delta RR regression slope; delta QTc and delta RR are calculated as change from baseline before drug administration on the first visit. ** mean difference and P-value for difference between CTX and CTX+DP

Note results in this table are normalised to no change in HR in each group.

Table 11: Adverse events (binary) in the safety population by treatment group

	Number of women affected, n/N (%)		crude RR (95% CI), p-value
	CTX	**CTX-DP**	**CTX v CTX-DP**
Vomiting (within 30 minutes of taking study drug)			
Any			
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
Rate (IRR)			
Dizziness (within 4 days of first drug administered during a treatment cycle)			
Any			
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
Rate (IRR)			
GI Complaints (within 4 days of first drug administered during a treatment cycle)			
Any			
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
Rate (IRR)			
Later vomiting (within 4 days of first drug administered during a treatment cycle)			
Any			
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
Rate (IRR)			
Nausea (within 4 days of first drug administered during a treatment cycle)			
Any			

	Number of women affected, n/N (%)		**crude RR (95% CI), p-value**
	CTX	**CTX-DP**	**CTX v CTX-DP**
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
Rate (IRR)			

ITT population
RR=Relative Risk; IRR=Incident Rate Ratio.
Crude RR/IRR is adjusted for site and HIV status as per stratification factors
P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Table 12: Follow-up visits schedule (ITT population)

	Overall	CTX	CTX+DP	p-value
	(n=)	(n=)	(n=)	CTX+DP v CTX
Duration of follow-up until delivery, pregnancy loss, or loss-to-follow-up (in months)				
Median (IQR) (range)				
`Possible No. of scheduled visits adjusted for early delivery, including enrolment, excluding delivery[a,b] No. (%)				
1				
2				
3				
4				
5				
6				
Total planned scheduled visits				
Total achieved scheduled visits				
% achieved of planned visits				
Achieved number of scheduled visits, including enrolment, excluding delivery, No. (%)				
1				
2				
3				
4				
5				
6				
Total				
Number of IPTp received, No. (%)				
0				
1				
2				

	Overall	CTX	CTX+DP	p-value
	(n=)	(n=)	(n=)	CTX+DP v CTX
3				
4				
5				
6				
Total number of IPTp courses				
Number of IPTp courses, median (IQR, range)				
% of DP or placebo-DP doses on day 2 and 3 correctly self-administered at home as prescribed (random home visits)				

[a] The number of monthly scheduled visits was dependent on the gestational age at enrolment.

[b] Adjusted for early delivery (i.e. excludes all planned antenatal visits that could not have occurred because the pregnancy ended before that scheduled date)

IQR=interquartile range

Table 12: Proportion of women with missing data for the primary outcome by treatment arm

	no/No (%) of patients with missing primary endpoint		Risk Ratio (95% CI), p-value
Outcome	CTX	CTX+DP	CTX v CTX+DP
Primary endpoint (adverse pregnancy outcome)			
Overall			
Kenya			
Malawi			

DP=dihydroartemisinin-piperaquine. CTX=cotrimoxazole

Table 13: treatment interaction P-values for primary outcome

Group	Subgroup variable	ITT – Interaction p-values	
		Crude	**Adjusted**
CTX+DP v CTX	Study Site		
	HIV status (known positive and newly diagnosed)		
	Gravidity (pauci and multigravidae)		
	Socio-Economic Stratus (terciles)		
	Season (terciles of average rainfall last 6m before delivery)		
	Malaria status (positive-negative, based on microscopy)		
	Malaria transmission intensity by site (less than or greater than median)		
	Country		
	Number of cycles received		

P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Table 14: Adverse events associated with drug tolerability

	CTX				CTX+DP							
Within 30 minutes following drug administration												
Vomiting initial dose												
Vomiting repeat dose												
Tolerability 1-7 days following drug administration												
Number of women (number of courses)												
	Women (%)	**Events**	**IR[a] (95% CI)**		**Women (%)**	**Events**	**IR[a] (95% CI)**		**RR (95% CI)**	**p-value**		**IRR (95% CI)**	**p-value**
Any reported drug tolerability event													
Pyrexia													
Asthenia													
Headache													
Abdominal pain[b]													
Myalgia													
Nausea													
Rash[c]													
Diarrhoea[d]													
Vomiting[e]													
Dizziness													

[a] incidence rate per 100 person-years

[b] includes MeDRA's preferred terms for 'abdominal pain', 'abdominal pain lower' and 'abdominal pain upper'

[c] includes MeDRA's preferred terms for 'rash pruritic' and 'rash macular'

[d] includes MeDRA's preferred terms for 'diarrhoea' and 'diarrhoea haemorrhagic'

[e] Late vomiting (>30 minutes following drug administration). All of these events occurred within the first 3 days after the start of drug intake, i.e. during or within the 24h after drug intake but excluding the first 30 minutes.

Table 15: Drug tolerability in a sub-group of 10% women visited at home within the first three days after the start of an IPTp course

	Number of women, n/N(%)		Crude RR (95% CI)	p-value
	CTX+DP	CTX-alone	CTX+DP vs CTX-alone	
Vomiting				
Any				
Month 1				
Month 2				
Month 3				
Month 4				
Month 5				
Month 6				
Month 7				
Nausea				
Any				
Month 1				
Month 2				
Month 3				
Month 4				
Month 5				
Month 6				
Month 7				
Abdominal pain				
Any				
Month 1				
Month 2				
Month 3				
Month 4				
Month 5				
Month 6				
Month 7				
Diarrhoea				
Any				
Month 1				
Month 2				
Month 3				
Month 4				
Month 5				
Month 6				
Month 7				
Other gastrointestinal complaints				
Any				

Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Month 7

Dizziness

Any
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Month 7

RR=Risk ratio. CI=confidence interval. NA=Not available because of zero values,

Tolerability was assessed by assessing adverse events during random home visits in a pre-selected random sample 10% of participants.

DP=dihydroartemisinin-piperaquine. AZ=azithromycin. SP=sulfadoxine-pyrimethamine.

Table-16: Baseline characteristics among women with vs without missing primary outcomes (ITT population)

Overall

	missing (n=)	Non-missing (n=)	p-value
Maternal characteristics			
Newly-diagnosed HIV infection			
On EFV-based retroviral therapy			
On DTG-based retroviral therapy			
Switched to DTG-based retroviral therapy during this pregnancy before enrolment			
Switched to DTG-based retroviral therapy during this pregnancy at enrolment			
Newly diagnosed HIV infection, started DTG-based retroviral therapy at enrolment			
On Cotrimoxazol prophylaxis			
Maternal age (years)			
Residence Rural vs Semi-urban/Urban			
Marital status Single† vs Married/Cohabiting			
Used a bednet previous night			
Attended school			
Schooling level			
None			
Primary school			
Secondary school			
Higher			
SES index score (terciles)			
Low			
Medium			
High			
Pregnancy number (gravidity)			
First			
Second			
Third or higher			
Gestational age (weeks)			
Weight (kg)			
Height (cm)			
MUAC (cm)			
Body-mass index (BMI) (kg/m2)			
Laboratory findings			
HIV viral load >= 400 (copies/mL)			

Overall

	missing (n=)	**Non-missing (n=)**	**p-value**
Detectable SARS-CoV-2 antibodies			
Haemoglobin (g/dL)			
Malaria infection			
mRDT			
Microscopy			
PCR			
Any			

12.1.2 Table shells by country

Table S1: Baseline characteristics ITT population (not mITT)

		Kenya					Malawi			
		CTX	CTX+DP		p		CTX	CTX+DP		p
		(n=)	(n=)				(n=)	(n=)		
Maternal characteristics										
Newly-diagnosed HIV infection										
On EFV-based retroviral therapy										
On DTG-based retroviral therapy										
Switched to DTG-based retroviral therapy during this pregnancy before enrolment										
Switched to DTG-based retroviral therapy during this pregnancy at enrolment										
Newly diagnosed HIV infection, started DTG-based retroviral therapy at enrolment										
On Cotrimoxazol prophylaxis										
Maternal age (years)										
Residence Rural vs Semi-urban/Urban										
Marital status Single† vs Married/Cohabiting										
Used a bednet previous night										
Attended school										
Schooling level										
	None									
	Primary school									
	Secondary school									
	Higher									
SES index score (terciles)										
	Low									
	Medium									
	High									

	Kenya				Malawi			
	CTX	**CTX+DP**		**p**	**CTX**	**CTX+DP**		**p**
	(n=)	**(n=)**			**(n=)**	**(n=)**		
Pregnancy number (gravidity)								
First								
Second								
Third or higher								
Gestational age (weeks)								
Weight (kg)								
Height (cm)								
MUAC (cm)								
Body-mass index (BMI) (kg/m2)								
Laboratory findings								
HIV viral load >= 400 (copies/mL)								
Detectable SARS-CoV-2 antibodies								
Haemoglobin (g/dL)								
Malaria infection								
mRDT								
Microscopy								
PCR								
Any								
Viral load was copied from existing health records only available for xxx participants: Kenya (CTX=xxx, CTX+DP=xxx), Malawi: (CTX=xxx, CTX+DP=xxx)								

Table-S2: Follow-up visits schedule (ITT population) (not mITT)

	Kenya		Malawi	
	CTX (n=)	CTX+DP (n=)	CTX (n=)	CTX+DP (n=)
Possible No. of scheduled visits adjusted for early delivery, including enrolment, excluding delivery[a,b] No. (%)				
1				
2				
3				
4				
5				
6				
Total				
Achieved number of scheduled visits, including enrolment, excluding delivery, No. (%)				
1				
2				
3				
4				
5				
6				
Total				
Number of IPTp received, No. (%)				
0				
1				
2				
3				
4				
5				
6				
Total				
Person days contributed till delivery or till lost to follow-up, median (IQR)				

[a] The number of monthly scheduled visits was dependent on the gestational age at enrolment.

[b] Adjusted for early delivery (i.e. excludes all planned antenatal visits that could not have occurred because the pregnancy ended before that scheduled date)

IQR=interquartile range

Table-S3: Secondary efficacy endpoints (continuous) by country (modified ITT population)

	Number of women, mean (SD)				Mean difference*(95% CI), p-value	
	DP		CTX			
	N	Mean (SD)	N	Mean (SD)	Unadjusted	Adjusted
Birthweight (grams)						
Overall						
Kenya						
Malawi						
Birthweight for gestational age (Z-score)						
Overall						
Kenya						
Malawi						
Gestational age at birth (weeks)						
Overall						
Kenya						
Malawi						
Neonatal length (cm)						
Overall						
Kenya						
Malawi						
Maternal MUAC (cm)						
Overall						
Kenya						
Malawi						
Gestational weight gain per week (kg) †						
Overall						
Kenya						
Malawi						
Maternal Hb third trimester (g/dL)						

Overall

Kenya

Malawi

Maternal Hb delivery (g/dL)

Overall

Kenya

Malawi

Cord blood Hb (g/dL)

Overall

Kenya

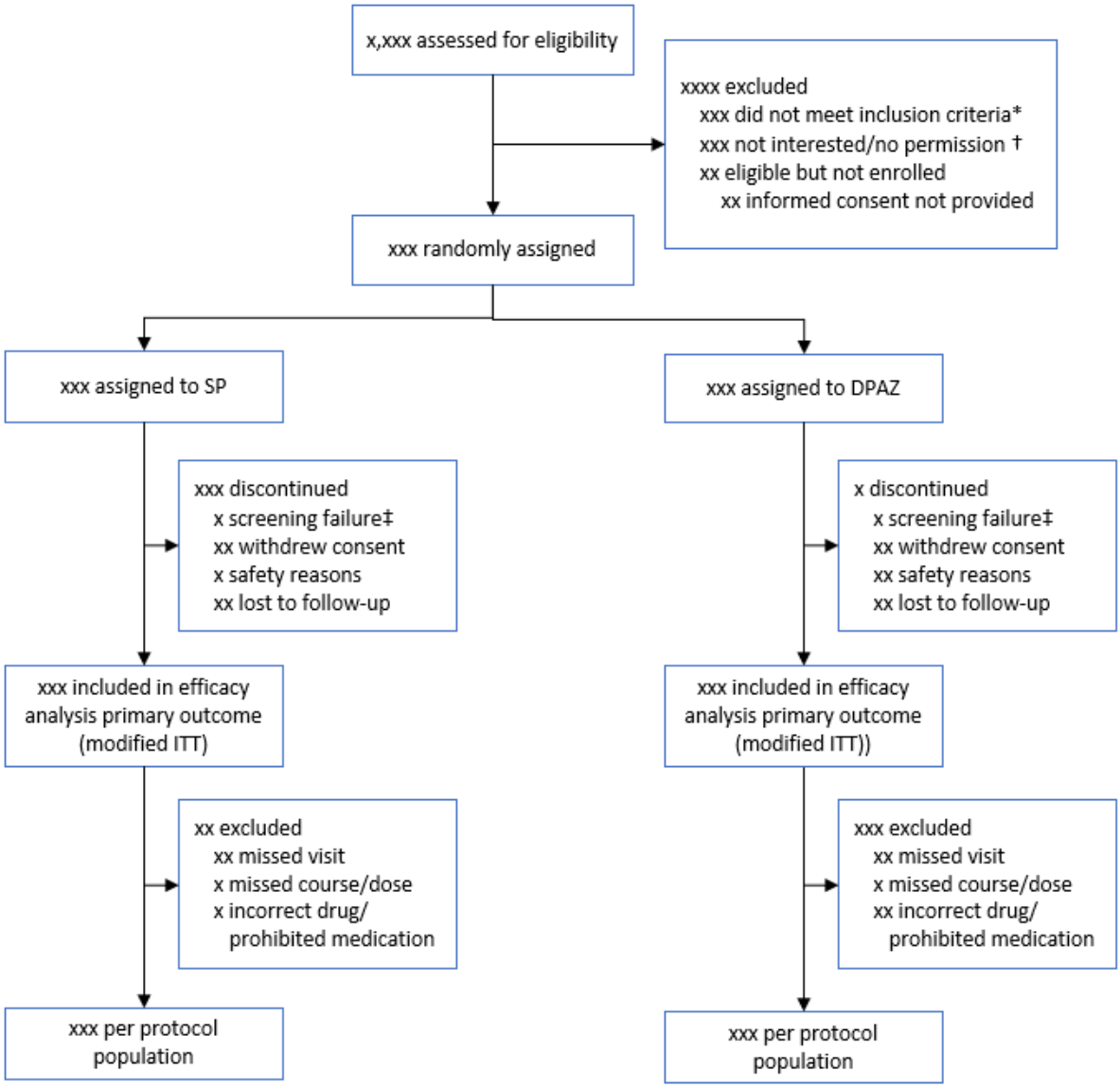
Malawi

The crude models include the stratification factors site and HIV status (newly diagnosed Yes/No) as covariates. *The adjusted models include six additional prespecified covariates: patent malaria status at enrolment (positive/negative), gestational age in days at enrolment (continuous), socioeconomic status (socioeconomic index calculated using principal component analysis) (continuous), season (based on average ranked rainfall during the last 6 months of pregnancy) (continuous), malaria transmission intensity by site (based on the prevalence of malaria at enrolment) (continuous)and the degree of SP resistance by site (very high vs high based on the prevalence of the dhps-A581G mutation >40% vs <= 40%). † Post-hoc. P-values and the widths of the confidence intervals for the secondary endpoints have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects. ITT=Intention to treat. SD=standard deviation. DP=dihydroartemisinin-piperaquine. AZ=azithromycin. SP=sulfadoxine-pyrimethamine. Cm=centimetre. US=ultrasound scan. Kg=kilogram. Hb=haemoglobin. g/dL=grams per decilitre. All other effect estimates were obtained by standard linear regression. The unadjusted linear mixed models contained visit, study arm, the interaction between visit and study arm, and the stratification factors site and gravidity (paucigravidae and multigravidae) as fixed effect and participant as random effects to account for the clustering within subject. The adjusted linear mixed models also included the six additional prespecified covariates listed above (under *) as fixed effect, and participant as random effects.

12.2 FIGURE SHELLS

12.2.1 Figure shells overall (both countries pooled) (ITT, not mITT)

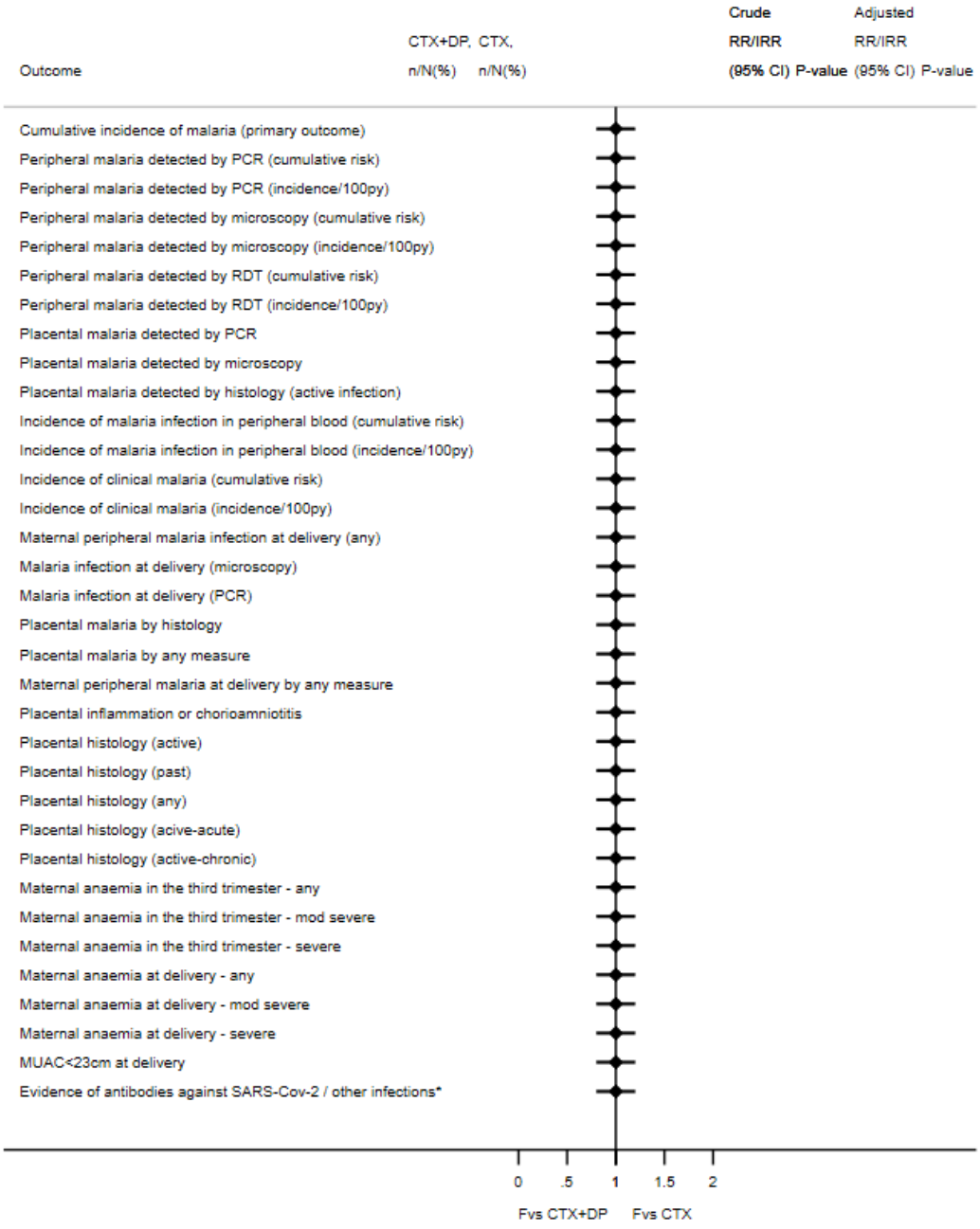
Figure 1:Trial Profile



CTX=cotrimoxazol. DP=dihydroartemisinin-piperaquine. ITT=intention to treat population.

* The reasons for not meeting the exclusion criteria included: <16 or >28 weeks pregnant (n=XXX); fetal abnormality or non-viable pregnancy (US) (n=XXX); plans to relocate outside study area/resides outside study area (n=XXX); history of allergy to study drugs (n=XX); HIV negative or not willing to be tested (n=XXX); history of heart disease (n=XX); multiple pregnancies (e.g. twins) (n=XX); committed/enrolled in another study (n=XX); negative pregnancy test or ultrasound (n=X); not switching to DTG-based antiretrovail therapy (n=XXX), other (n=XX). †The full eligibility criteria could not be assessed in a further X,XXX pregnant women who either expressed hesitation to join a study, or whose spouse/husband, or another family member discouraged them from joining research studies. ‡ Screening failures include participants who were found not to fulfil the eligibility criteria after enrolment (e.g. HIV-negative (n=X), twin pregnancy (n=X), already enrolled in another study (n=X), etc.

Figure 2 Cumulative incidence of malaria (primary outcome) and malaria infection related secondary outcomes in the mITT population



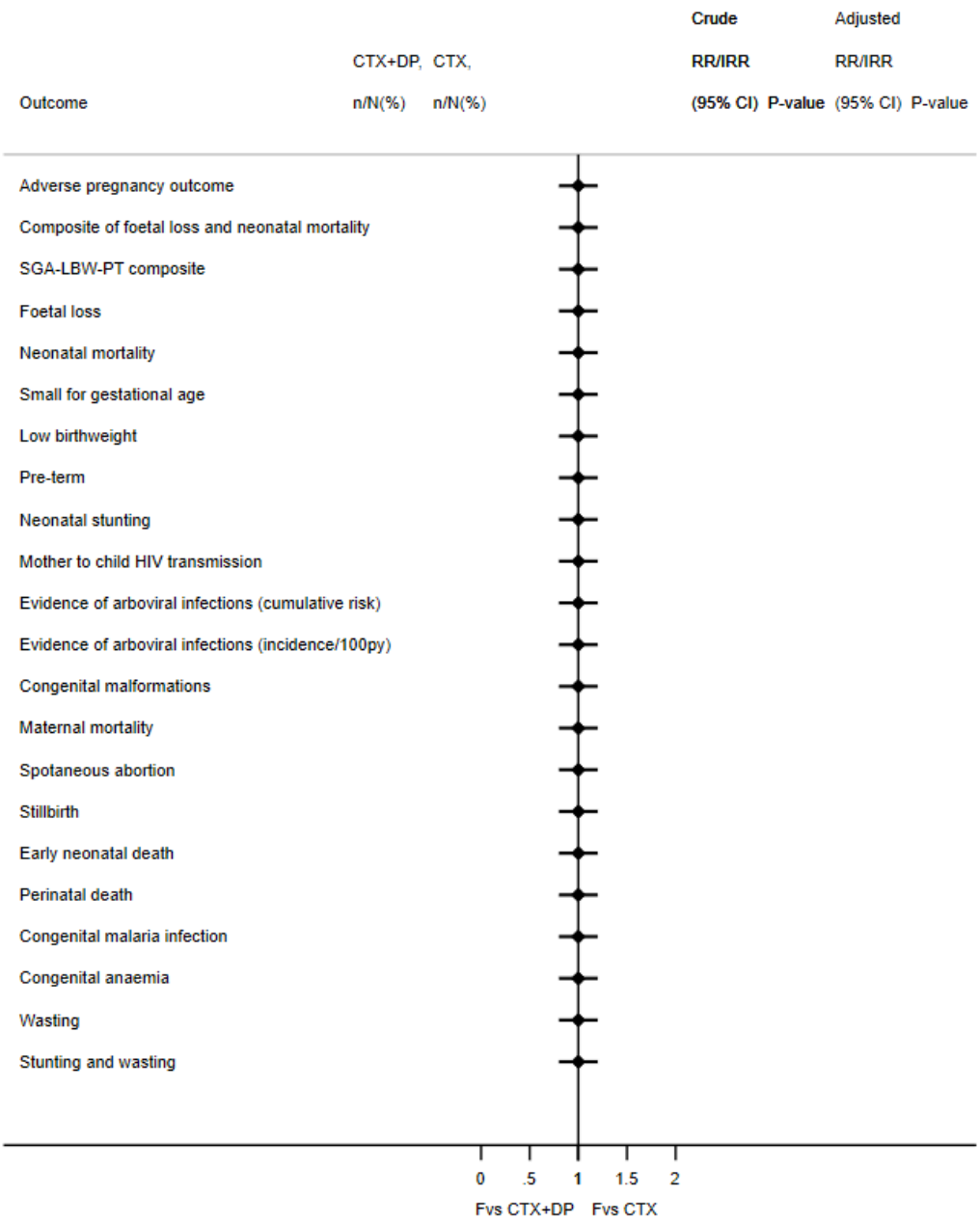
RR=Relative Risk; IRR=Incident Rate Ratio.

Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

† RR and p-value could not be computed because of zero events in at least one of the arms

Figure 3: Secondary pregnancy outcomes in the mITTpopulation



RR=Relative Risk; IRR=Incident Rate Ratio.

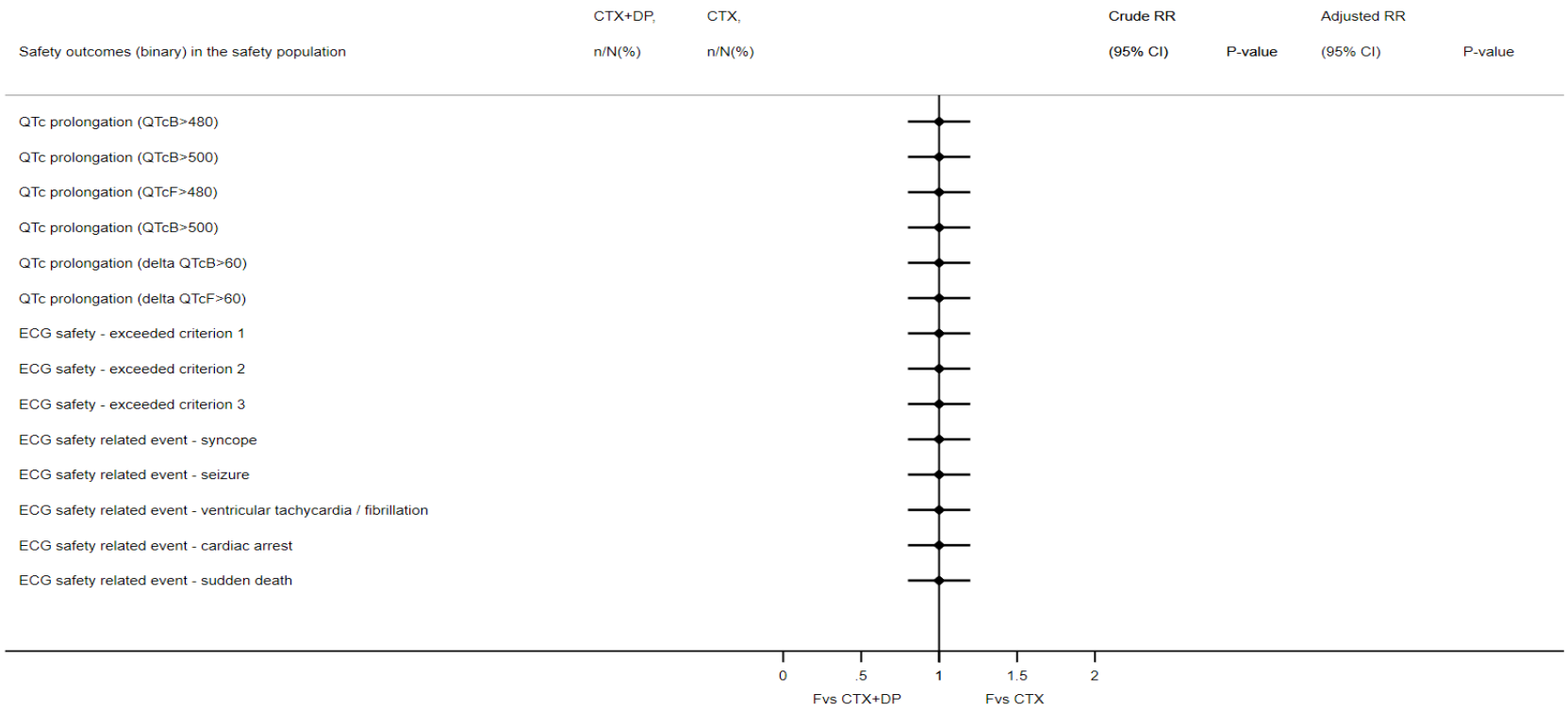
Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

† RR and p-value could not be computed because of zero events in at least one of the arms

P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure 4: Safety outcomes (binary) in the safety population



RR=Relative Risk.

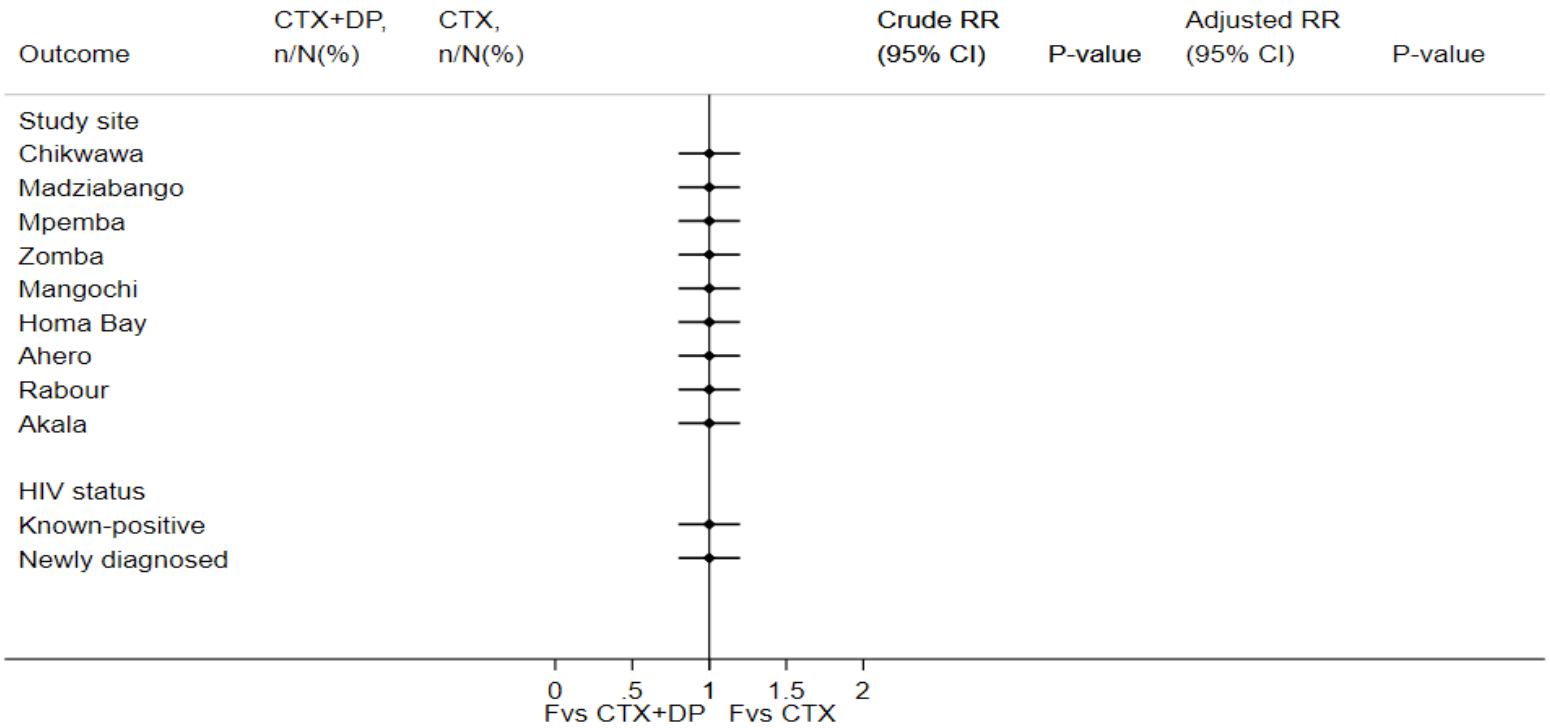
Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

† RR and p-value could not be computed because of zero events in at least one of the arms

P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure 5: Subgroup analysis of the effect on the primary outcome in the mITT population (stratification variables)



RR=Relative Risk.

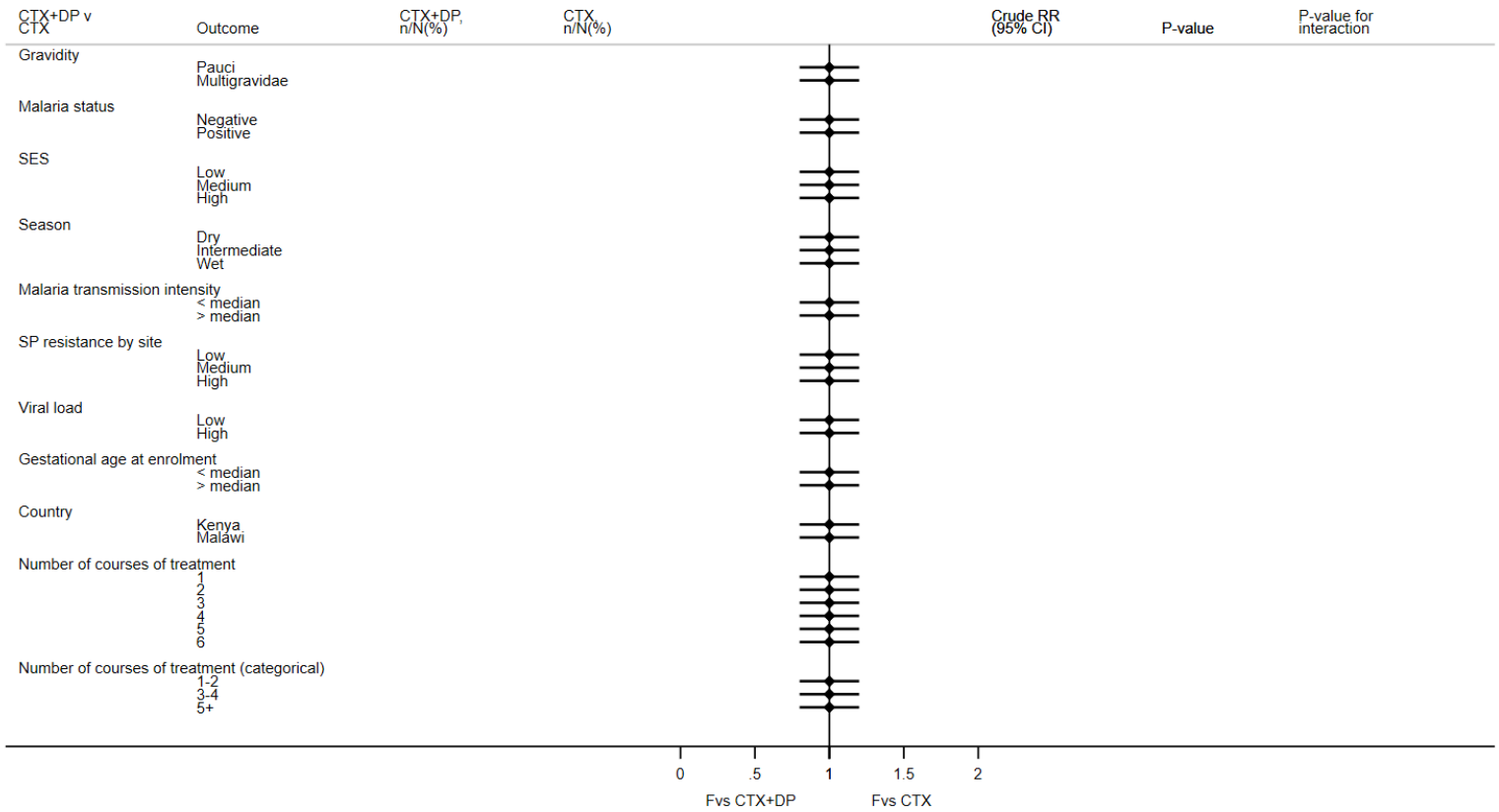
Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

† RR and p-value could not be computed because of zero events in at least one of the arms

P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure 6: Subgroup analysis of the effect on the primary outcome in the mITT population (other variables)



RR=Relative Risk.

Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

† RR and p-value could not be computed because of zero events in at least one of the arms

Figure 7: Cumulative incidence of malaria (primary outcome) and other malaria infection related secondary outcomes in the per-protocol population

RR=Relative Risk; IRR=Incident Rate Ratio.

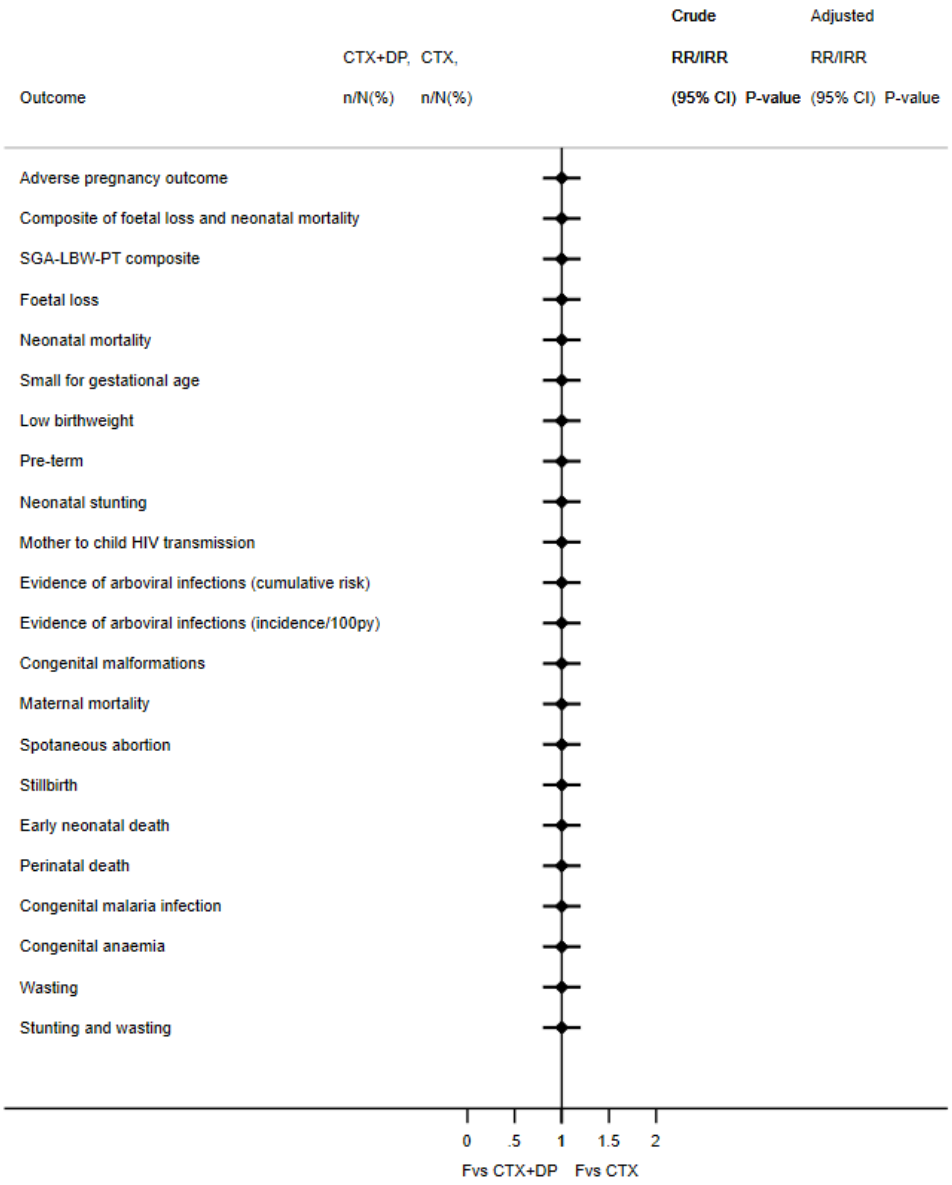
Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

† RR and p-value could not be computed because of zero events in at least one of the arms

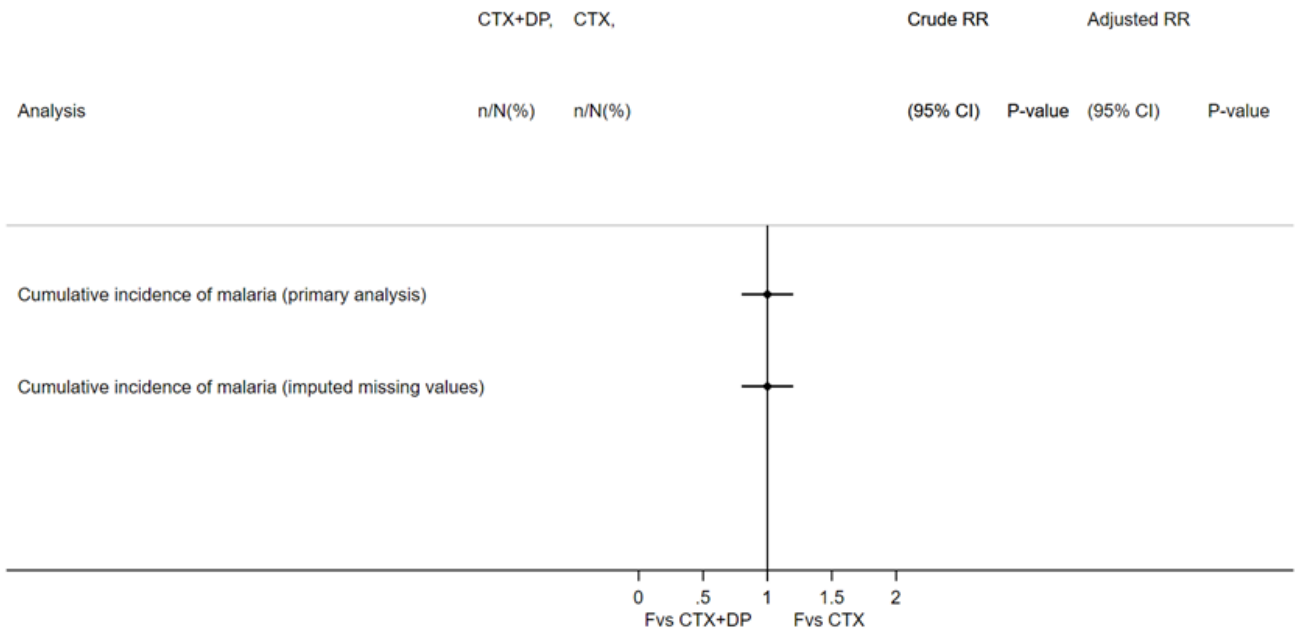
P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure 8: Impact on pregnancy and newborn outcomes in the per protcol population



RR=Relative Risk; IRR=Incident Rate Ratio.
Crude RR/IRR adjusted for site and HIV status as per stratification factors.
Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.
† RR and p-value could not be computed because of zero events in at least one of the arms
P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

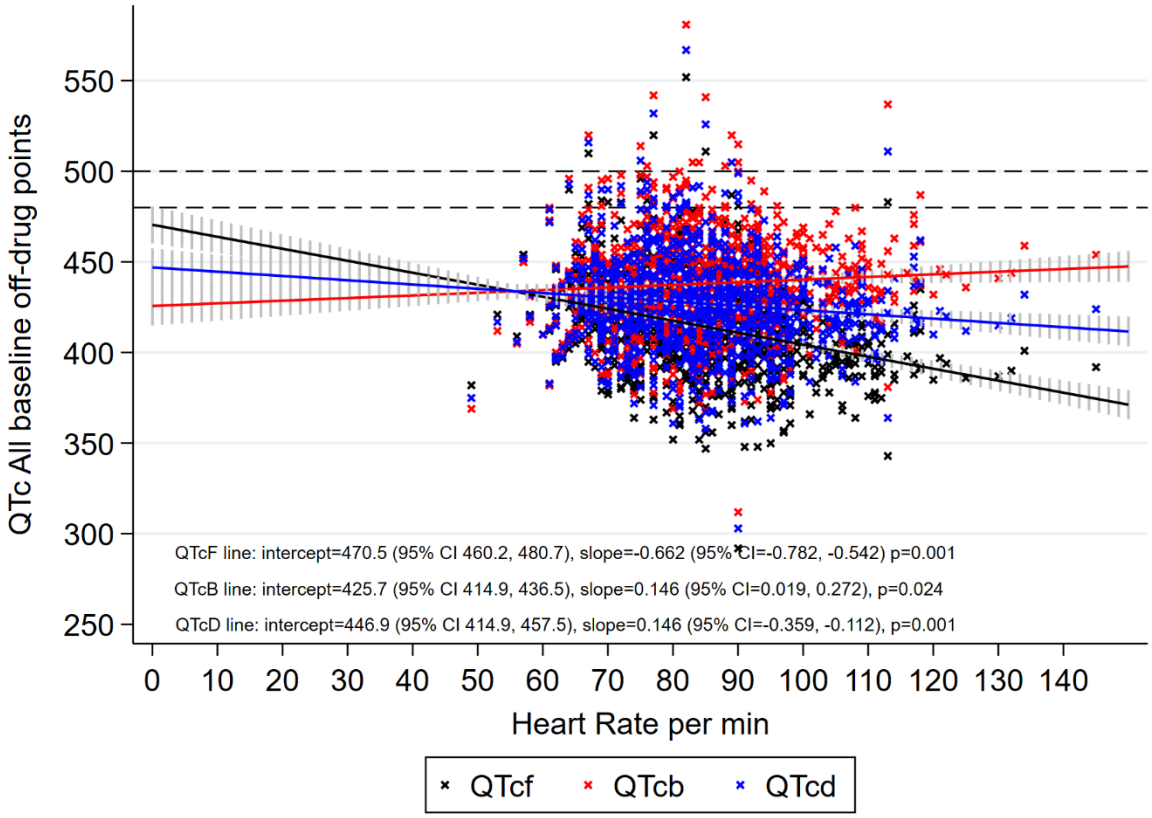
Figure 9: Sensitivity analysis of the primary outcome comparing the primary analysis (complete case analysis) vs analysis with missing outcomes imputed



RR=Relative Risk.

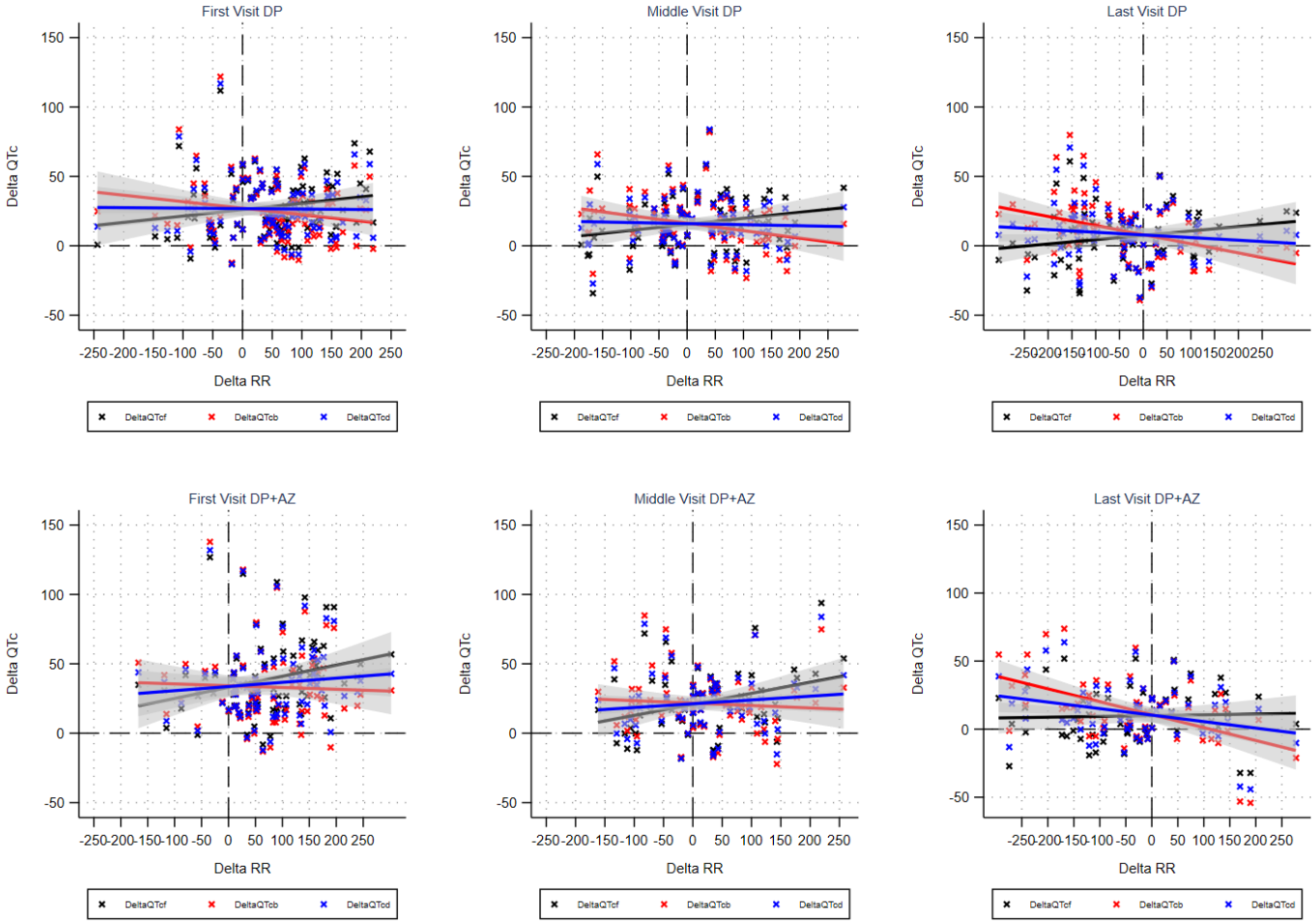
Crude RR/IRR adjusted for site and HIV status as per stratification factors.
Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.
† RR and p-value could not be computed because of zero events in at least one of the arms
P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure 10: QTc plotted against Heart Rate in the safety population



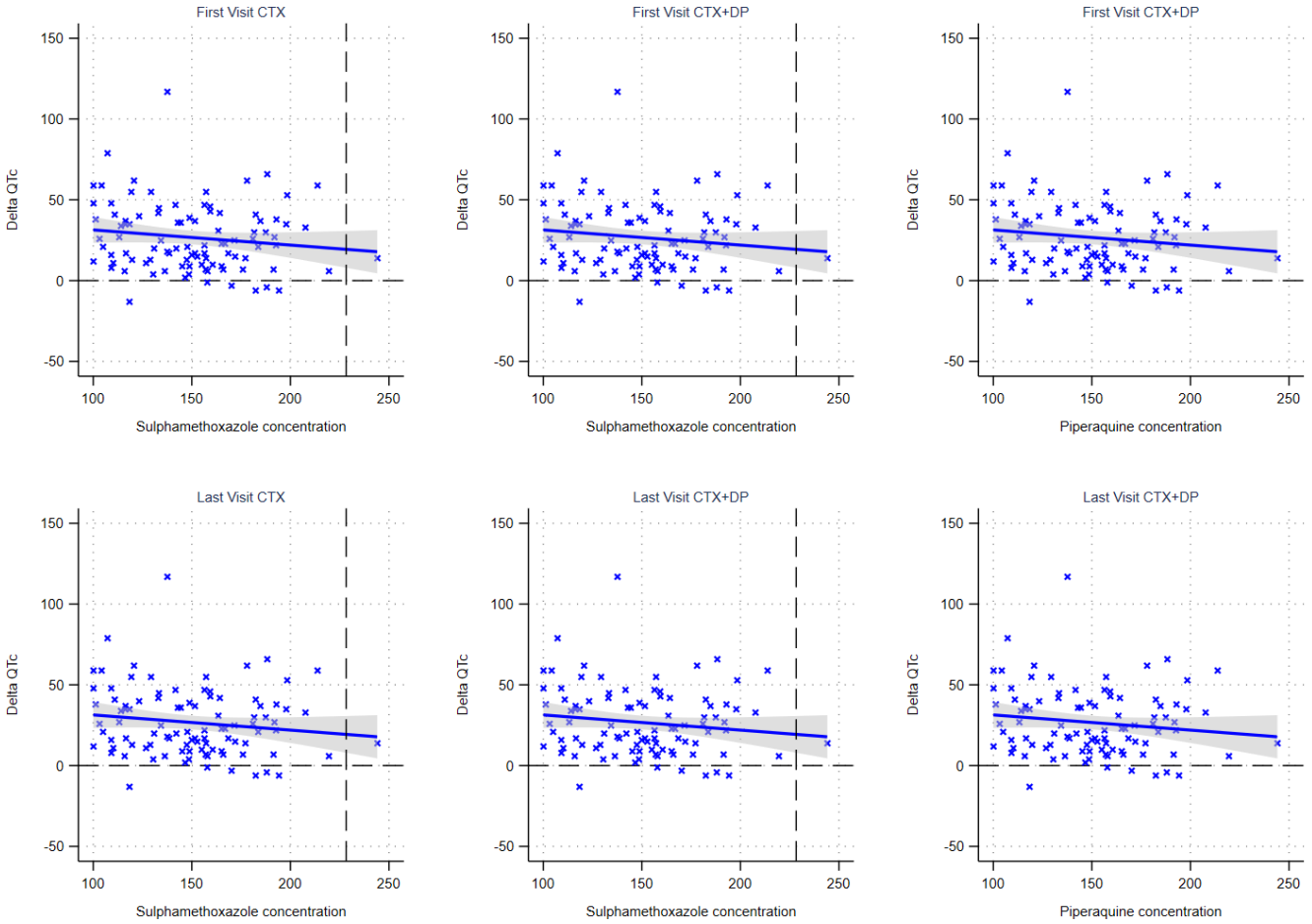
QTc interval on ECG corrected using the Fridericia method (in black), Bazett's method (in red), or study specific correction factor (in blue). The solid line depicts the liner regression line for Fridericia's method (black), Bazett's method (red) and study specific method (in blue). It shows that better rate correction is achieved with Bazett's method, whose slopes are very close to 0. P-value is probability regression line differs from 0, note that for all methods this is statistically significant. 95% Confidence Interval are shown as shading around fitted lines. Results are taken from dose 0 time 0 (i.e. before any treatment given) only.

Figure 11: QTc plotted against RR in the safety population



Note: Results in this figure are normalised to no change in HR in each group

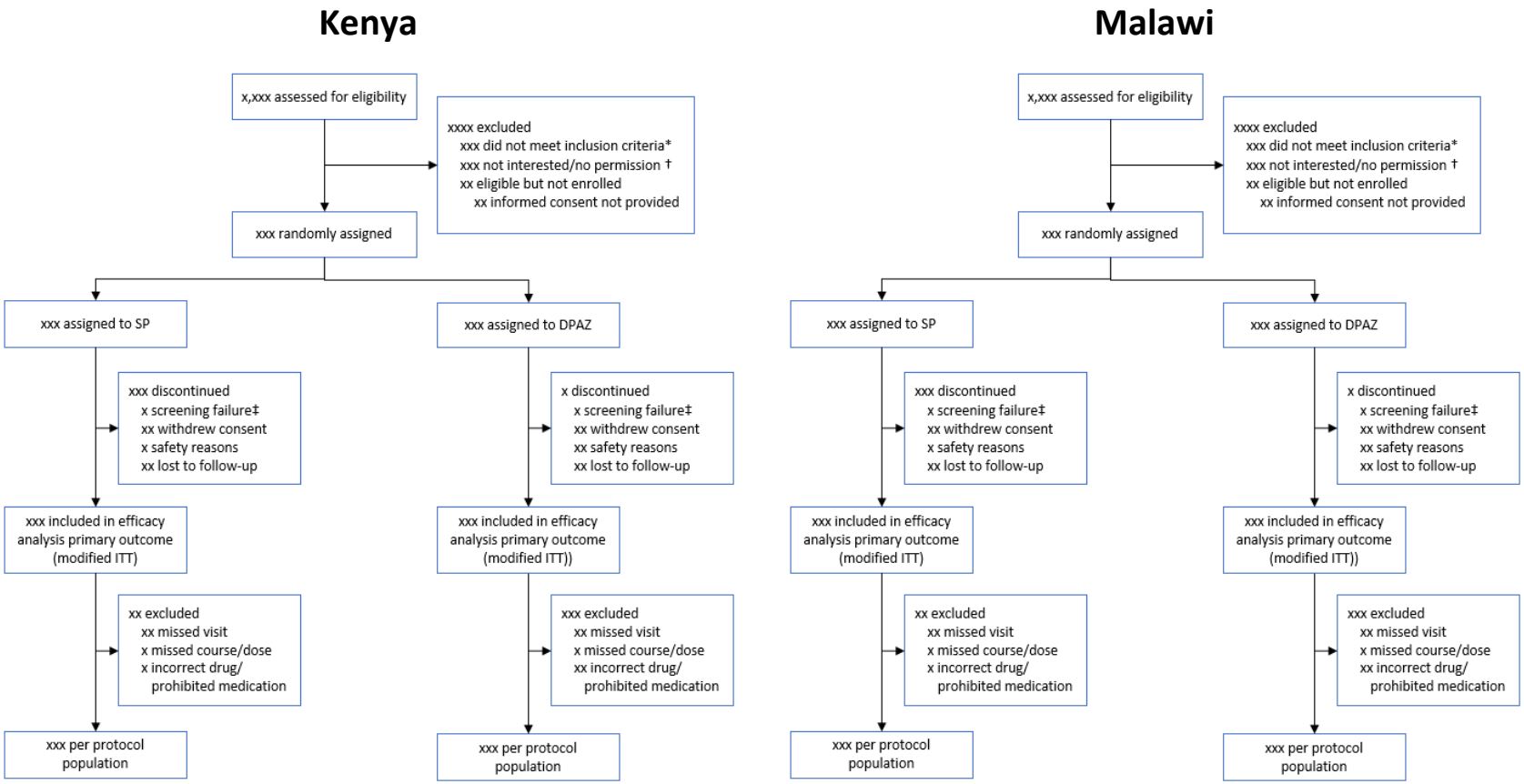
Figure 12: QTc plotted against drug concentration in the safety population



Note: Results in this figure are normalised to no change in HR in each group

12.2.2 Figure Shells by country

Figure S1: Trial profile by country



CTX=cotrimoxazol. DP=dihydroartemisinin-piperaquine. ITT=intention to treat population.

* The reasons for not meeting the exclusion criteria included: Kenya: <16 or >28 weeks pregnant (n=XXX); fetal abnormality or non-viable pregnancy (US) (n=XXX); plans to relocate outside study area/resides outside study area (n=XXX); history of allergy to study drugs (n=XX); HIV negative or not willing to be tested (n=XXX); history of heart disease (n=XX); multiple pregnancies (e.g. twins) (n=XX); committed/enrolled in another study (n=XX); negative pregnancy test or ultrasound (n=X); not switching to DTG-based antiretrovail therapy (n=XXX), other (n=XX).

Malawi: <16 or >28 weeks pregnant (n=XXX); fetal abnormality or non-viable pregnancy (US) (n=XXX); plans to relocate outside study area/resides outside study area (n=XXX); history of allergy to study drugs (n=XX); HIV negative or not willing to be tested (n=XXX); history of heart disease (n=XX); multiple pregnancies (e.g. twins) (n=XX); committed/enrolled in another study (n=XX); negative pregnancy test or ultrasound (n=X); not switching to DTG-based antiretrovail therapy (n=XXX), other (n=XX). †The full eligibility criteria could not be assessed in a further X,XXX pregnant women (Kenya: X,xx), Malawi: X,xx) who either expressed hesitation to join a study, or whose spouse/husband, or another family member discouraged them from joining research studies. ‡ Screening failures include participants who were found not to fulfil the eligibility criteria after enrolment (e.g. Kenya: HIV-negative (n=X), twin pregnancy (n=X), already enrolled in another study (n=X), etc.; Malawi: HIV-negative (n=X), twin pregnancy (n=X), already enrolled in another study (n=X), etc.).

Figure-S2a: Cumulative incidence of malaria (primary outcome) and key secondary outcomes in the mITT population – Kenya

RR=Relative Risk; IRR=Incident Rate Ratio.

Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

† RR and p-value could not be computed because of zero events in at least one of the arms

P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure-S2b: Cumulative incidence of malaria (primary outcome) and key secondary outcomes in the mITT population – Malawi

RR=Relative Risk; IRR=Incident Rate Ratio.

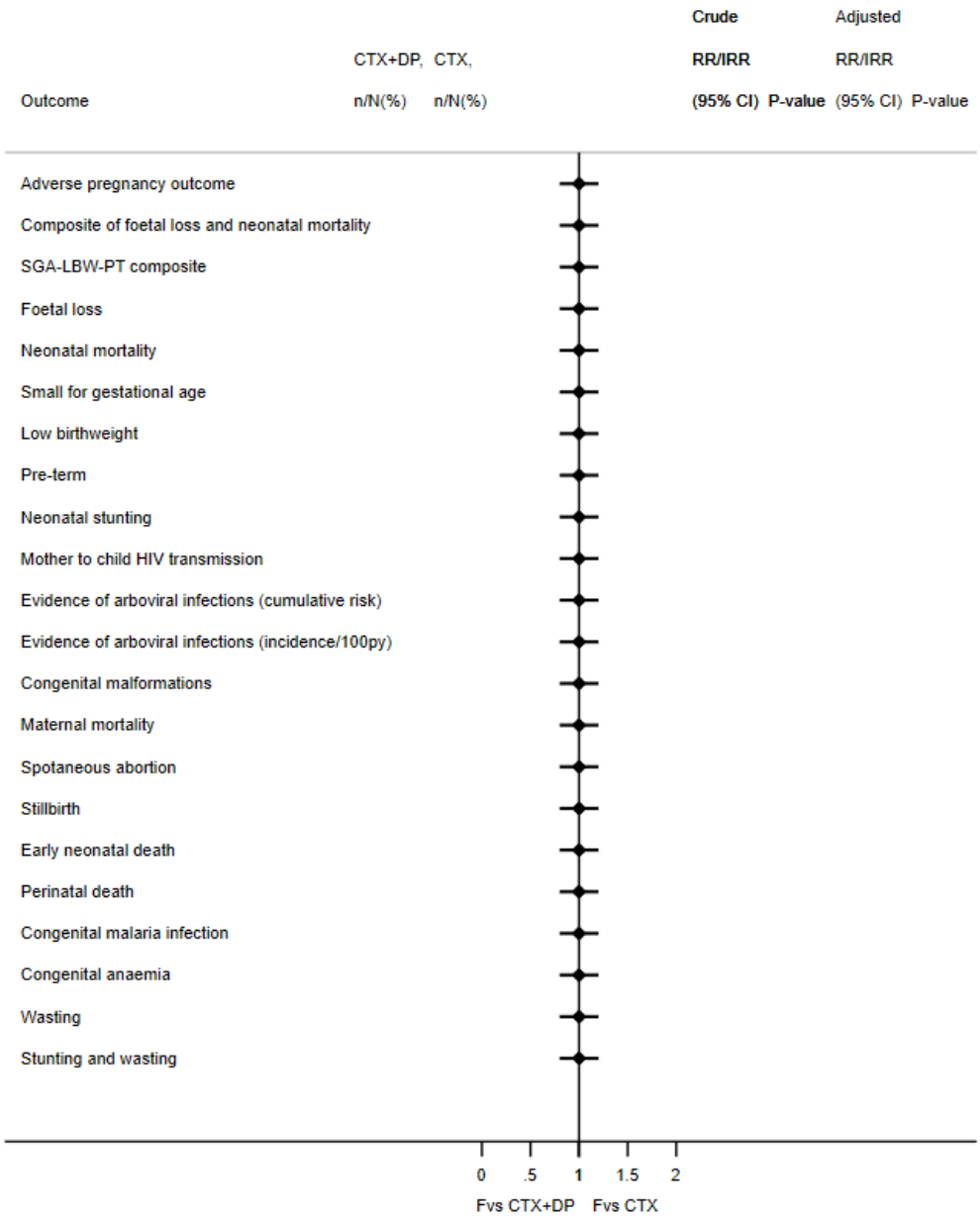
Crude RR/IRR adjusted for site and HIV status as per stratification factors.

Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.

† RR and p-value could not be computed because of zero events in at least one of the arms

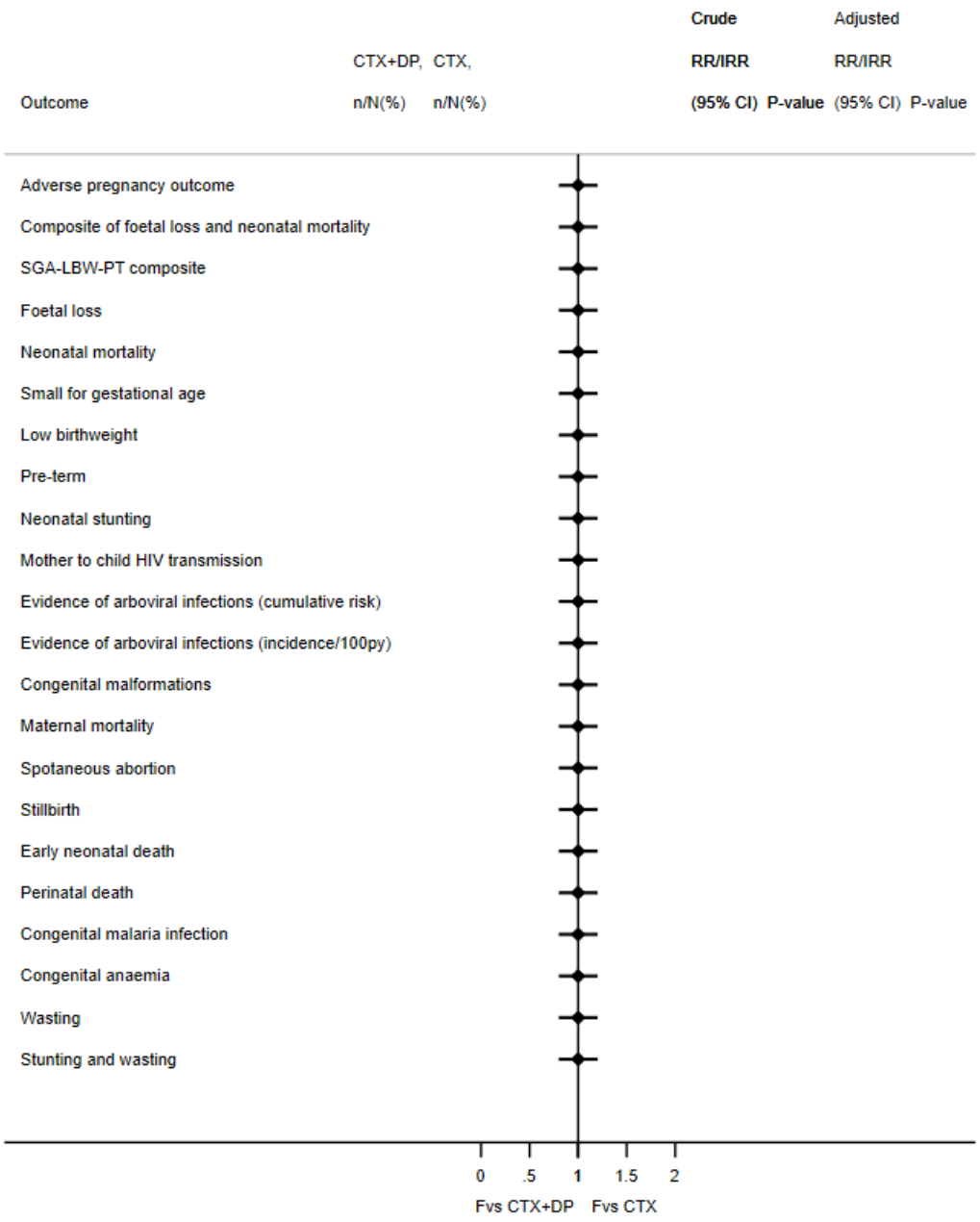
P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure-S3a: Impact on pregnancy and newborn outcomes in the MITTpopulation (Kenya)



RR=Relative Risk; IRR=Incident Rate Ratio.
Crude RR/IRR adjusted for site and HIV status as per stratification factors.
Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.
† RR and p-value could not be computed because of zero events in at least one of the arms
P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.

Figure-S3b: Impact on pregnancy and newborn outcomes in the MITTpopulation (Malawi)



RR=Relative Risk; IRR=Incident Rate Ratio.
Crude RR/IRR adjusted for site and HIV status as per stratification factors.
Adjusted RR/IRR is adjusted for the stratification factors site and HIV status and the other covariates gravidity, malaria status, SES, season, and malaria transmission intensity by site.
† RR and p-value could not be computed because of zero events in at least one of the arms
P-values and the widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity, so the values should not be used to infer definitive treatment effects.