Analytical plan for Birth Outcomes module

## Objectives

Primary Objective

* 1. To assess whether the level of resistance in the community affects the efficacy of SP and if so, whether a threshold level of resistance above which SP is no longer effective can be determined. This will be determined by looking at the efficacy of SP at preventing adverse maternal and infant outcomes.\*

\* Note that placental histopathology is not available from Mali

Secondary Objectives

1. To determine the relationship between time from delivery to last SP dose and maternal peripheral parasitemia (reverse *in vivo*)
2. To determine whether the timing of the final dose of SP affects maternal and infant outcomes among women who received at least 2 doses of SP
3. To determine if the resistance pattern of the isolate (as defined above) is associated with adverse maternal or infant outcomes at the individual level

## Preparation of data set

1. Participant flow (screened vs enrolled)
2. Review inclusion/ exclusion criteria for pooled analysis
   * 1. Inclusion criteria
        1. Documented HIV negative or HIV unknown in low HIV-prevalence countries where screening was not conducted
     2. Exclusion/Enrolment deviations
        1. HIV positive women
        2. SP doses received unknown
3. Variables to be included: see annex

## Definition of efficacy outcomes

1. Binomial
   * 1. Placental parasitemia (histology)- Primary maternal outcome (any infection)
        1. Active
        2. Chronic
        3. Past
        4. All
     2. Maternal peripheral parasitemia (smear)
     3. Any positive smear or RDT at delivery (maternal, placental (smear and impression smear), cord)
     4. Maternal anemia (Hb< 11 and Hb <8)
     5. Composite of LBW, Preterm, SGA- Primary neonatal outcome
     6. Birth weight (prevalence of LBW)
     7. Preterm delivery (where gestational age has been determined by Ballard)
     8. Small for gestational age (SGA)
     9. Stillbirths or late miscarriages
2. Continuous
   * 1. Haemoglobin
     2. Mean birth weight
     3. Mean gestational age

## Definition of Safety Outcomes

1. Congenital anomalies

## Definition of Resistance

1. Double mutant (dhps) 437 + 540
2. Triple mutant (dhfr) 108, 51, 59
3. Quintuple mutant
4. dhps 540 alone (proxy for quintuple mutation)
5. dhps 437 alone
6. dhps 581 mutation
7. Quintuple mutations plus dhps 581

## Statistical analysis

1. Descriptive analysis

Baseline data overall and for each site individually:

* 1. Number of IPTp doses (mean)
  2. Maternal age
  3. Gravidity- primi, secundi, multi
  4. ITN use- last night or not
  5. IRS
  6. Rural vs urban
  7. Education: Years of schooling- categorical: 0-4 years, 5-8 years, 9-12+ years, or missing
  8. Wealth status/ SES (derived by principle component analysis (PCA) at site level)

1. Examination of possible confounders
   1. Gravidity- assess effects of gravidity both by inclusion in model with interaction term for gravidity and SP dose and stratification
   2. Adjustment for confounders through propensity matching
   3. Age (5 year window)
   4. ITN use (last night)
   5. IRS
   6. Education
   7. SES
   8. Rural vs urban
   9. Type of facility
   10. Season/ calendar time
   11. Folate dose
   12. Site level variables to be included
       1. Site variable to take into account all the unmeasured confounders
       2. Level of resistance at the site (pre SP)
          1. dhps 540 alone (proxy for quintuple mutation)
          2. Quintuple mutations
          3. Quintuple mutations plus dhps 581
       3. Transmission intensity – 2010 MARA map
2. Estimation of propensity scores
   1. Fit predictive model to estimate probability of treatment assignment
      1. Outcome: number of SP doses
         1. Ideally treat as ordinal
         2. If ordinal not feasible, then try it as binary- need to minimize number of comparisons so restrict to:
            1. 0, 1 vs 2, 3
            2. 0 vs 2
      2. Predictors: Anything that might affect the probability of receiving SP, will consider all of the following to find best model to predict SP doses
         1. Age (5 year window)- possibly related to SP- definitely related to outcome
         2. ITN use (last night)- possibly be related to SP- related to outcome
         3. IRS- unlikely related to SP- related to outcome
         4. Education- likely related to SP- possibly related to outcome
         5. SES- likely related to SP- possibly related to outcome
         6. Rural vs urban - likely related to SP- possibly related to outcome
         7. Type of facility- likely related to SP- possibly related to birth outcomes
3. Matching/weighting
   1. Patients will be matched at site level, prior to pooling
   2. Options:
      1. Match without replacement participants with similar propensity scores (e.g., < 0.1) and omit those without a comparable match from analyses.
      2. Control for propensity score(s) as covariates in analyses and include all participants.
      3. Weight participants based on propensity score using inverse probability treatment weighting (IPTW) or similar method (allows incorporation of all data points as opposed to exact matching which excludes all unmatched observations). [Ref: Curtis and Mini-Sentinel papers]
   3. Notes/potential challenges
      1. If SP dose is treated as ordinal, analysis will require a multinomial model, e.g., cumulative logit or proportional odds. With ordinal outcome, multiple propensity scores will be created. The added dimension of having multiple scores can make matching difficult (see Spreeuwenberg et al., Med Care 2010; 48: 166-74).
      2. Same will be true for IPTW, i.e., creating weights when there are multiple propensity scores is not straightforward. There appear to be methods designed for this situation (e.g., Hong, Psychol Methods 2012; 17: 44-60).
      3. Controlling for propensity scores in analysis may not be as effective as matching. Stuart has studies which showed including propensity scores in models does not remove bias, though Spreeuwenberg et al. promote this approach.
4. Modelling of Efficacy
   1. Dose dependency- SP dose as ordinal variable: 0, 1, 2, 3+ doses

Use contrast statements in SAS in order to look at difference in efficacy with stepwise increase in number of doses

* + - 1. 0 vs. 1, 1 vs. 2, 2 vs. 3+
      2. 0 vs. 1, 0 vs. 2, 0 vs. 3+
      3. 0, 1 vs. 2, 3+ (SP dose dichotomized)
      4. 0, 1, 2 vs. 3+
  1. Utilize hierarchical linear and non-linear models to account for different effects of individual (gravidity, age, ITN use, timing of delivery (relation to malaria transmission season)) and site level variables (resistance levels, transmission level, site level variable to account for other, unmeasured differences)
     1. Binomial outcomes- log binomial regression/ poisson regression
     2. Risk differences for binomial outcomes- poisson regression
     3. Continuous outcomes- ANOVA
  2. Adjusted analysis

Include all relevant variables not included in propensity score such as gravidity, study site, resistance at site (defined from either in vivo or OPD data), transmission intensity at site; include interaction term for gravidity and SP dose, ITN and SP-dose, and also for resistance and SP dose

1. Gravidity as primigravidae/secundigravidae (G1-2) versus multigravidae (G3+)Effect of timing of final dose among those who received 2 doses of SP
2. Examine risk of positive smear at delivery with last SP dose as a continuous variable and at 7 day intervals
3. ”Survival” analysis going backwards from delivery looking at risk of positive smear at delivery versus timing of last SP dose.

## References

* Brookhart et al., Am J Epidemiol 2006; 163: 1149-56
* Hong, Psychol Methods 2012; 17: 44-60).
* Spreeuwenberg MD, Bartak A, Croon MA, Hagenaars JA, Busschbach JV, Andrea H, Twisk J, Stijnen T. The Multiple Propensity Score as Control for Bias in the Comparison of More Than Two Treatment Arms An Introduction From a Case Study in Mental Health. Med Care 2010;48: 166–174
* Stuart EA. Matching Methods for Causal Inference: A Review and a Look Forward. Statistical Science 2010, 25 (1): 1–21
* Cook AJ, et al. MINI-SENTINEL METHODS DEVELOPMENT STATISTICAL METHODS FOR ESTIMATING CAUSAL RISK DIFFERENCES IN THE DISTRIBUTED DATA SETTING FOR POSTMARKET SAFETY OUTCOMES Curtis LH, et al. Using Inverse Probability-Weighted Estimators in Comparative Effectiveness Analyses With Observational Databases. *Med Care* 2007;45: S103–S107

## Tables and figures

**Table 1. Baseline characteristics of enrolled women by site**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Site 1** | **Site 2** | **Site 3** | Overall |  |
|  | **N** |  |  |  |  | p-value |
| **IPTp doses** | Mean (Std.) |  |  |  |  |  |
| **Maternal age** | Mean (Std.) |  |  |  |  |  |
| **Gravidity** | **Primi** |  |  |  |  |  |
| **Secundi** |  |  |  |  |
| **Multi** |  |  |  |  |
| **ITN** | **Used last night** |  |  |  |  |  |
| **IRS** |  |  |  |  |  |  |
| **Rural / Urban** |  |  |  |  |  |  |
| **Years of schooling** | **0-4 years** |  |  |  |  |  |
|  | **5-8 years** |  |  |  |  |
|  | **9+ year** |  |  |  |  |
| **Wealth status** | **Below average** |  |  |  |  |  |
| **Average** |  |  |  |  |
| **Above average** |  |  |  |  |

**Table 2. Baseline characteristics of enrolled women by number of SP doses**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **0 dose** | **1 dose** | **2 doses** | **3+ doses** |  |
|  | **N** |  |  |  |  | p-value |
| **IPTp doses** | Mean (Std.) |  |  |  |  |  |
| **Maternal age** | Mean (Std.) |  |  |  |  |  |
| **Gravidity** | **Primi** |  |  |  |  |  |
| **Secundi** |  |  |  |  |
| **Multi** |  |  |  |  |
| **ITN** | **Used last night** |  |  |  |  |  |
| **IRS** |  |  |  |  |  |  |
| **Rural / Urban** |  |  |  |  |  |  |
| **Years of schooling** | **0-4 years** |  |  |  |  |  |
|  | **5-8 years** |  |  |  |  |
|  | **9+ year** |  |  |  |  |
| **Wealth status** | **Poorest** |  |  |  |  |  |
| **Average** |  |  |  |  |
| **Richest** |  |  |  |  |

**Table 3. Maternal and infant outcomes by number of SP doses (also look at SP doses as 0, 1, 2, 3+)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **0-1 SP doses** | **2 or more SP doses** | **p-value** |
| **N** |  |  |  |  |
| **Any placental infection** |  |  |  |  |
| **Active placental infection** |  |  |  |  |
| **Chronic placental infection** |  |  |  |  |
| **Past placental infection** |  |  |  |  |
| **Maternal smear positive** |  |  |  |  |
| **Placental smear positive** |  |  |  |  |
| **Cord smear positive** |  |  |  |  |
| **Maternal hemoglobin (mean)** |  |  |  |  |
| **Maternal anemia (Hb <11 gm/dl)** |  |  |  |  |
| **Moderate- severe maternal anemia (Hb <8 gm/dl)** |  |  |  |  |
| **Composite (LBW, SGA, preterm)** |  |  |  |  |
| **SGA** |  |  |  |  |
| **LBW** |  |  |  |  |
| **Preterm** |  |  |  |  |
| **Mean birth weight (grams)** |  |  |  |  |
| **Mean gestational age (weeks)** |  |  |  |  |
| **Stillbirths** |  |  |  |  |
| **Delivery complications** |  |  |  |  |
| **Physical abnormality\*** |  |  |  |  |

**Table 4. Maternal and infant outcomes by number of SP doses, stratified by gravidity (also look at SP doses as 0, 1, 2, 3+)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **G1/2** | | | **G3+** | | |
|  | **0-1 doses of SP** | **2 or more doses SP** | **p-value** | **0-1 doses of SP** | **2 or more doses SP** | **p-value** |
| **N** |  |  |  |  |  |  |
| **Any placental infection** |  |  |  |  |  |  |
| **Active placental infection** |  |  |  |  |  |  |
| **Chronic placental infection** |  |  |  |  |  |  |
| **Past placental infection** |  |  |  |  |  |  |
| **Maternal smear positive** |  |  |  |  |  |  |
| **Placental smear positive** |  |  |  |  |  |  |
| **Cord smear positive** |  |  |  |  |  |  |
| **Maternal hemoglobin (mean)** |  |  |  |  |  |  |
| **Maternal anemia (Hb <11 gm/dl)** |  |  |  |  |  |  |
| **Moderate- severe maternal anemia (Hb <8 gm/dl)** | |  |  |  |  |  |
| **Composite (LBW, SGA, preterm)** |  |  |  |  |  |  |
| **SGA** |  |  |  |  |  |  |
| **LBW** |  |  |  |  |  |  |
| **Preterm** |  |  |  |  |  |  |
| **Mean birth weight (grams)** |  |  |  |  |  |  |
| **Mean gestational age (weeks)** |  |  |  |  |  |  |
| **Stillbirths** |  |  |  |  |  |  |
| **Delivery complications** |  |  |  |  |  |  |
| **Physical abnormality\*** |  |  |  |  |  |  |

**Table 5. Modelling effect of SP dose on prevalence of placental infection**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Prevalence of placental infection | PR | Confidence Limits | p-value | |
| **2 or more doses of SP among G1** |  |  |  |  | |
| **Less than 2 doses of SP among G1** |  | ref | | |
| **2 or more doses of SP among G2+** |  |  |  |  | |
| **Less than 2 doses of SP among G2+** |  | ref | | |
| **Maternal age < 25 years** |  |  |  |  | |
| **Maternal age > 25 years** |  | ref | | |
| **Used net last night** |  |  |  |  | |
| **Did not use net last night** |  | ref | | |
| **SP resistance (presence of quintuple, i.e. mutant in >50% of samples)** |  |  |  |  |  |
| **No SP resistance** |  | ref | | |  |

Adjust for education, rural vs urban, SES, site

**Table 6. Modelling effect of SP dose on prevalence of composite birth outcome among infants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Prevalence of composite birth outcome | PR | Confidence Limits | p-value | |
| **2 or more doses of SP among G1** |  |  |  |  | |
| **Less than 2 doses of SP among G1** |  | ref | | |
| **2 or more doses of SP among G2+** |  |  |  |  | |
| **Less than 2 doses of SP among G2+** |  | ref | | |
| **Maternal age < 25 years** |  |  |  |  | |
| **Maternal age > 25 years** |  | ref | | |
| **Used net last night** |  |  |  |  | |
| **Did not use net last night** |  | ref | | |
| **SP resistance (presence of quintuple mutant in >50% of samples)** |  |  |  |  |  |
| **No SP resistance** |  | ref | | |  |

Adjust for education, rural vs urban, SES, site

**Table 7. Dose dependent effect of SP doses\* adjusted for other factors as above**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Placental infection** | | | **Composite birth outcome** | | | **Composite birth outcome among G1/2** | | |
|  | **PR** | **95% CI** | **p-value** | **PR** | **95% CI** | **p-value** | **PR** | **95% CI** | **p-value** |
| **Effect of 1 dose vs 0** |  |  |  |  |  |  |  |  |  |
| **Effect of 2 doses vs 1** |  |  |  |  |  |  |  |  |  |
| **Effect of 3+ doses vs 2** |  |  |  |  |  |  |  |  |  |

**Figure1. Prevalence of any histologically confirmed placental infection stratified by gravidity**

**Figure 2. Prevalence of the composite birth outcome stratified by gravidity**

**List of variables to be included in merged delivery dataset**

**From delivery form Socioeconomic Form**

* Date Interview - Years of school completed?
* First pregnancy - Level of school completed?
* Prior pregnancies - Complete asset index
* Delivery age based on LMP
* Age
* Live (rural/ urban)
* Use a bednet?
* Used a bednet last night?
* Bednet impregnated?
* Last treated?
* Where did you get it?
* IRS?
* Total doses of IPTp
* Dates of IPTp administration (1st, 2nd, 3rd, 4th, 5th)
* Where did you get the SP?
* Other medicines used for malaria or fever?
* Any other medicines?
  + Iron?
  + Folate?
* Any transfusion?
* Axillary temperature
* Systolic BP
* Diastolic BP
* Date of delivery
* Place of delivery
* Who performed the delivery
* Type of delivery
* Delivery induced/ spontaneous
* Delivery complications?
* Birth outcome?
* For stillbirths, was the baby moving at start of labor?
* Baby born dead or alive?
* Baby’s sex?
* Birthweight?
* Gestational age based on ballard?
* Physical abnormality of infant?
* HB
* HIV
* Syphilis
* Lab results (all results):
  + Maternal smear
  + Placental smear
  + Cord smear