

# THE LANCET

## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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# The Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis – Appendix

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**The Community-Level Interventions for Pre-eclampsia (CLIP)  
cluster randomised trials in Mozambique, Pakistan, and India:  
an individual participant data meta-analysis – Appendix**

**Supplementary Tables**

**Table S1: CLIP Trials Working Group**

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<b>CLIP Data Safety and Monitoring Board (DSMB)</b> Romano Nkumbwa Byaruhanga, Brian Darlow, Eileen Hutton, Mario Merialdi, Lehana Thabane

**Table S2: Data abstracted from the CLIP cluster randomised controlled trials (N (%) women or median [interquartile range] unless otherwise stated)**

	IPD-MA		INDIA		PAKISTAN		MOZAMBIQUE	
<b>TRIAL CHARACTERISTICS</b>								
Design	IPD MA		cRCT		cRCT		cRCT	
Study period	Feb 2014-Jan 2015 Nov 2014-Feb 2017		Feb 2014 - Oct 2014 (4 clusters) Nov 2014 - Oct 2016 (12 clusters)		Feb 2014- Jan 2015 (4 clusters) Jan 2015- Dec 2016 (20 clusters)		-	
Inclusion criteria	Pregnant women, 12–49 years who were followed-up with regards to pregnancy outcomes		Pregnant women, 15–49 years, resident in cluster for ≥6 months		Pregnant women, 15–49 years		February 2015-17 (12 clusters) Pregnant women, 12–49 years	
	<b>Intervention</b>	<b>Control</b>	<b>Intervention</b>	<b>Control</b>	<b>Intervention</b>	<b>Control</b>	<b>Intervention</b>	<b>Control</b>
Number of clusters	22	22	6	6	10	10	6	6
Estimated population per cluster	29 583 [22 487, 34 625]	29 677 [23 183, 34 593]	21 318 [20 259, 22 767]	21 554 [19 846, 23 454]	34 523 [30 672, 31 585]	33 877 [31 490, 34 900]	29 354 [23 080, 31 585]	28 817 [24 158, 35 978]
Estimated annual birth rate/cluster	22/1000	22/1000	22/1000	22/1000	14/1000	14/1000	40/1000	40/1000
N women enrolled	36,008	33,322	7839	6944	20,238	19,186	7192	7192
Withdrawn	4 (0.01%)	5 (0.02%)	0	0	3 (0.01%)	4 (0.02%)	1 (0.01%)	2 (0.03%)
Lost to follow-up	903 (2.5%)	1063 (3.2%)	0	0	747 (3.7%)	865 (4.5%)	156 (2.0%)	198 (2.8%)
Still on follow-up	2811 (7.8%)	2555 (7.7%)	931 (11.9%)	835 (12.0%)	1047 (5.2%)	967 (5.0%)	833 (10.5%)	753 (10.5%)
N women followed-up	32 290	29 698	6908	6109	18 441	17 350	6941	6239
<b>PARTICIPANT CHARACTERISTICS</b>	(N=32 290)	(N=29 698)	(N=6908)	(N=6109)	(N=18 441)	(N=17 350)	(N=6941)	(N=6239)
Maternal age (years)	26 [22,30]	26 [22, 30]	23 [20,25]	22 [20, 25]	28 [25, 30]	28 [25, 30]	24 [19, 31]	24 [19,30]
Parous	23 464 (72.7%)	21 924 (73.8%)	4398 (63.7%)	3943 (64.5%)	14 216 (77.1%)	13 665 (78.8%)	4850 (69.9%)	4316 (69.2%)
Basic education*	11 574 (35.8%)	10 670 (35.9%)	3969 (57.5%)	3377 (55.3%)	3623 (19.7%)	3000 (17.3%)	3982 (57.4%)	4239 (68.9%)
GA at enrollment (weeks)	19.0 [12.5, 26.8]	20.1 [13.2, 27.8]	10.6 [8.0, 14.6]	11.3 [8.29, 15.9]	20.2 [14.5, 27.1]	21.0 [15.1, 27.6]	26.1 [20.1, 32.7]	27.5 [21.7, 33.8]
<b>INTERVENTION</b>	(N=32 290)	(N=29 698)	(N=6908)	(N=6109)	(N=18 441)	(N=17 350)	(N=6941)	(N=6239)
Community engagement sessions	6990 group 16 691 LHW-led	-	1379 group	-	1368 group 16 691 LHW-led	-	4243 group	-
Community Health Workers trained	450	-	148	-	223	-	79	-
N POM-guided CLIP visits	138 347	-	57 561	-	54 782	-	26 004	-
Median POM-guided visits/pregnancy								
Antenatal	4 [2, 6]	-	8.0 [3.0, 12.0]	-	3.0 [2.0, 5.0]	-	4.0 [2.0, 6.0]	-
Postnatal	2 [1, 3]	-	2.0 [1.0, 4.0]	-	2.0 [1.0, 3.0]	-	2.0 [1.0, 3.0]	-
BP measurement (all visits)	137 705 (99.5%)	-	57 181 (99.4%)	-	54 721 (99.9%)	-	25,803 (99.2%)	-
Proteinuria measurement (of first and any hypertensive visit)	21 257/22 051 (96.4%)	-	6143/6652 (92.4%)	-	10 856/11 035 (98.4%)	-	4260/4369 (97.5%)	-
Complete visits that resulted in a recommendation	136 755/138 347 (98.9%)	-	56 755/57 561 (98.6%)	-	54 544/54 782 (99.6%)	-	25,456/26,004 (97.9%)	-
Pregnancies with ≥1 POM-guided CLIP visit	20 819/36 008 (57.8%)	-	6138/7839 (78.3%)	-	10 536/20 238 (52.1%)	-	4145 (52.3%)	-
Pregnancies compliant with POM-guided CLIP visit frequency	11 095 (53.3%)	-	2601 (42.4%)	-	5748 (52.1%)	-	2746 (34.6%)	-
Pregnancies offered methyldopa	181 (0.9%)	-	60 (1.0%)	-	93 (0.9%)	-	28 (0.7%)	-
<i>Accepted</i>	162 (89.5%)	-	51 (85.0%)	-	92 (98.9%)	-	19 (67.9%)	-
Pregnancies offered MgSO <sub>4</sub>	198 (1.0%)	-	67 (1.1%)	-	103 (1.0%)	-	28 (0.7%)	-
<i>Accepted</i>	133 (67.2%)	-	47 (70.5%)	-	73 (70.9%)	-	13 (46.4%)	-
Pregnancies offered referral to facility	1255 (6.0%)	-	505 (8.2%)	-	487 (4.6%)	-	263 (6.3%)	-
<i>Accepted</i>	864 (81.6%)	-	401 (86.7%)	-	305 (83.6%)	-	158 (68.4%)	-

	IPD-MA		INDIA		PAKISTAN		MOZAMBIQUE	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
<b>OUTCOMES</b>	(N=32 290)	(N=29 698)	(N=6908)	(N=6109)	(N=18 441)	(N=17 350)	(N=6941)	(N=6239)
<b>PRIMARY OUTCOME</b>								
Composite maternal and perinatal outcome†	7871 (24.4%)	6515 (21.9%)	1252 (18.1%)	1157 (18.9%)	5373 (29.1%)	4186 (24.1%)	1246 (18.0%)	1172 (18.8%)
Maternal mortality and morbidity	7871 (24.4%)	6516 (21.9%)	1252 (18.1%)	1157 (18.9%)	5373 (29.1%)	4187 (24.1%)	1246 (18.0%)	1172 (18.8%)
<i>Maternal mortality</i>	77 (0.2%, 238/100 000)	66 (0.2%, 226/100 000)	7 (0.1%)	9 (0.1%)	55 (0.3%)	50 (0.3%)	15 (0.2%)	7 (0.1%)
<i>Maternal morbidity</i>	3319 (10.3%)	2743 (9.2%)	371 (5.4%)	325 (5.3%)	2213 (12.0%)	1728 (10.0%)	735 (10.6%)	690 (11.1%)
Perinatal mortality, late neonatal death or neonatal morbidity	5618 (17.4%)	4760 (16.0%)	1010 (14.6%)	950 (15.6%)	3954 (21.4%)	3156 (18.2%)	654 (9.4%)	654 (10.5%)
<i>Stillbirth</i>	1322 (4.1%)	1269 (4.3%)	191 (2.8%)	156 (2.6%)	935 (5.1%)	951 (5.5%)	196 (2.8%)	162 (2.6%)
<i>Neonatal death</i>	1408 (4.4%)	1269 (4.3%)	179 (2.6%)	136 (2.2%)	1011 (5.5%)	962 (5.5%)	218 (3.1%)	171 (2.7%)
<i>Neonatal morbidity</i>	3463 (10.7%)	2836 (9.5%)	813 (11.8%)	790 (12.9%)	2375 (12.9%)	1684 (9.7%)	275 (4.0%)	362 (5.8%)
<b>SECONDARY OUTCOMES</b>								
Birth preparedness and complication readiness‡	15 875 (53.4%)	13 530 (45.5%)	4892 (70.8%)	5178 (84.8%)	7848 (42.6%)	5132 (29.6%)	3135 (45.2%)	3220 (51.6%)
Proportion of facility births	25 397 (85.5%)	23 282 (78.7%)	6078 (88.0%)	5335 (87.3%)	13 517 (73.3%)	12 708 (73.2%)	5802 (83.6%)	5339 (85.6%)
Birth at a CEmOC facility	14 657 (49.3%)	14 398 (48.5%)	4161 (65.5%)	3837 (67.9%)	9599 (53.7%)	9625 (57.2%)	897 (12.9%)	936 (15.0%)
<b>SAFETY OUTCOMES</b>								
SAEs unrelated to intervention	0/32 290	0/29 698	0/6908	0/6109	0/18 441	0/17 350	0/6941	0/6239
Adverse events								
Transport-related injury or death	0/864	-	0/401	-	0/305	-	0/158	-
Injection site complications after community administration of IM MgSO <sub>4</sub>	0/133	-	0/47	-	0/73	-	0/13	-
Injection site haematoma/infection after any administration of IM MgSO <sub>4</sub>	4/168 (2.4%)	1386 (3.5%)	4/168 (2.4%)	1386 (3.5%)	-¶	-¶	-¶	-¶
Respiratory depression, coma or death during transport following in-community MgSO <sub>4</sub>	0/47 (0%)	-	0/47 (0%)	-	-¶	-	-¶	-
Maternal sBP <110 mmHg on facility arrival following in-community methyldopa	1/51 (2.0%)	-	1/51 (2.0%)	-	-¶	-	-¶	-
CEmOC, comprehensive emergency obstetric care; CLIP, community-level interventions for pre-eclampsia; cRCT, cluster randomized controlled trial; GA, gestational age; IM, intramuscular; IPD-MA, individual participant data meta-analysis; MgSO <sub>4</sub> , magnesium sulfate; POM, PIERS-On-the-Move; SAEs, serious adverse events; sBP, systolic blood pressure; *Basic education defined as ≥8 years of schooling in India, ≥5 years of schooling in Pakistan and ≥ Grade 5 in Mozambique; † One/more of maternal morbidity or mortality, or perinatal mortality (stillbirth or neonatal death) or neonatal morbidity; ‡Birth preparedness, as defined in Panel 1; ¶ This was unfeasible to collect as trial surveillance was not informed by facility records.								

**Table S3: Sensitivity analyses for the primary outcome and its components**

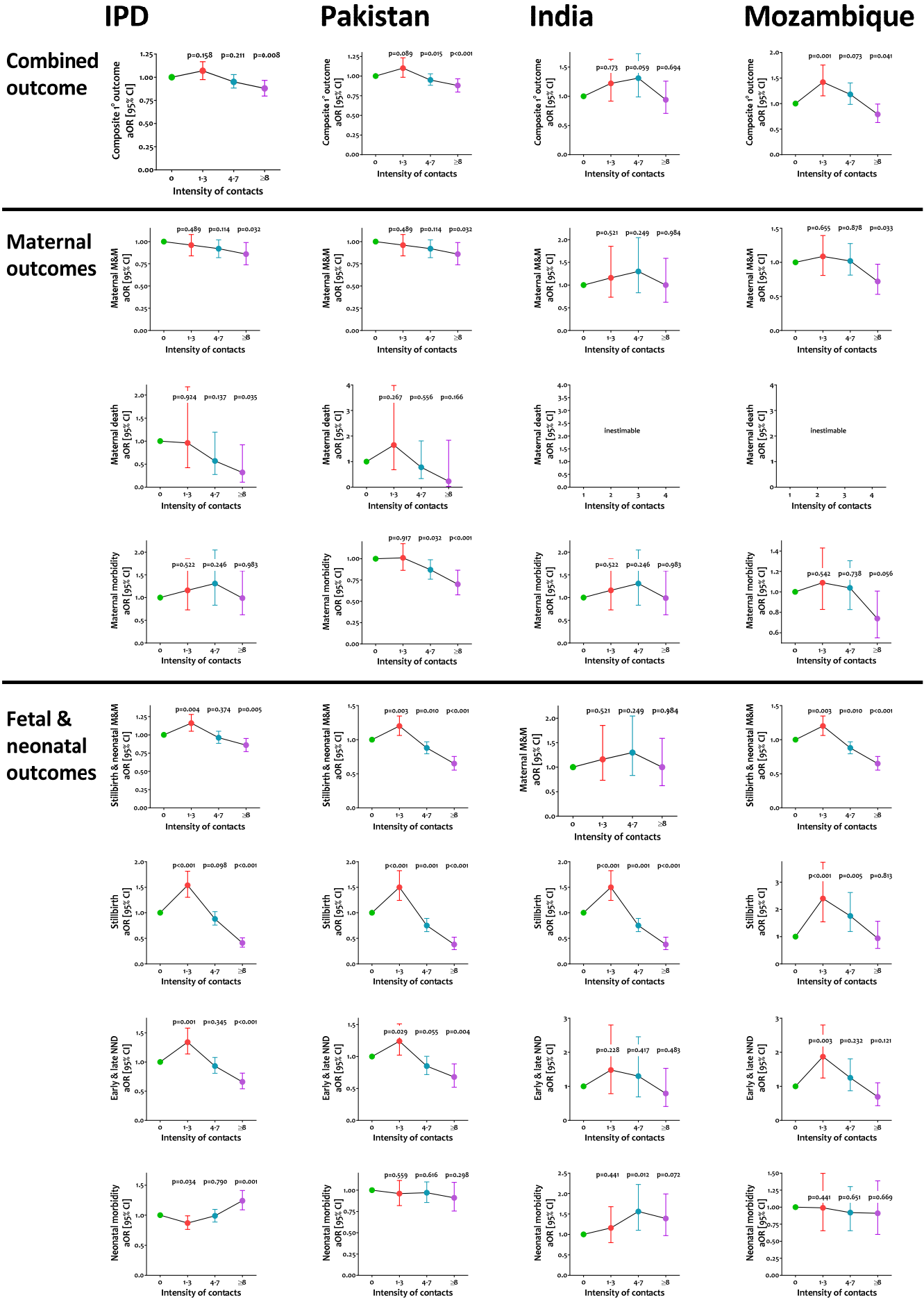
Outcome	With imputation*		Excluding pregnancies with GA<20 weeks		Restricted to women with postpartum follow-up to 42d after birth		Restricted to women with anticipated birth within trial timeline		Restricted to women with anticipated birth and 42d postpartum within trial timeline		Expanded to include women enrolled postpartum <sup>‡</sup>		Unadjusted for baseline characteristics		'On treatment' analysis (of women with at least one POM-guided CLIP visit)	
	OR (95% CI); p value	Heterogeneity <sup>†</sup>	OR (95% CI); p value	Heterogeneity <sup>†</sup>	OR (95% CI); p value	Heterogeneity <sup>†</sup>	OR (95% CI); p value	Heterogeneity <sup>†</sup>	OR (95% CI); p value	Heterogeneity <sup>†</sup>	OR (95% CI); p value	Heterogeneity <sup>†</sup>	OR (95% CI); p value	Heterogeneity <sup>†</sup>	OR (95% CI); p value	Heterogeneity <sup>†</sup>
<b>Primary outcome<sup>‡</sup></b>	1.13 (0.78, 1.63); p=0.74	Tau <sup>2</sup> = 0.04 R <sup>2</sup> =1.52	1.17 (0.91, 1.51); p=0.21	Tau <sup>2</sup> = 0.004 R <sup>2</sup> =1.05	1.17 (0.91, 1.51); p=0.21	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.05	1.17 (0.90, 1.51); p=0.48	Tau <sup>2</sup> = 0.007 R <sup>2</sup> =1.08	1.26 (0.91, 1.74); p=0.17	Tau <sup>2</sup> = 0.004 R <sup>2</sup> =1.06	1.10 (0.69, 1.76); p=0.68	Tau <sup>2</sup> = 0.08 R <sup>2</sup> =1.96	1.17 (0.91, 1.51); p=0.21	Tau <sup>2</sup> = 0.007 R <sup>2</sup> =1.08	1.12 (0.86, 1.47); p=0.40	Tau <sup>2</sup> = 0.001 R <sup>2</sup> =1.02
Maternal outcome	-	-	1.21 (0.82, 1.77); p=0.33	Tau <sup>2</sup> = 0.007 R <sup>2</sup> =1.05	1.20 (0.83, 1.74); p=0.32	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.01	1.20 (0.84, 1.73); p=0.32	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.01	1.27 (0.80, 2.01); p=0.31	Tau <sup>2</sup> = 0.000 R <sup>2</sup> =0.99	1.11 (0.72, 1.72); p=0.62	Tau <sup>2</sup> = 0.007 R <sup>2</sup> =1.05	1.21 (0.85, 1.74); p=0.30	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.01	1.06 (0.70, 1.61); p=0.79	Tau <sup>2</sup> = 0.001 R <sup>2</sup> =1.00
<i>Maternal mortality</i>	-	-	1.13 (0.76, 1.67); p=0.55	Tau <sup>2</sup> = 0.002 R <sup>2</sup> =1.29	1.06 (0.68, 1.64); p=0.81	Tau <sup>2</sup> = 0.001 R <sup>2</sup> =1.24	0.90 (0.50, 1.60); p=0.71	Tau <sup>2</sup> = 0.03 R <sup>2</sup> =1.58	1.13 (0.76, 1.67); p=0.55	Tau <sup>2</sup> = 0.000 R <sup>2</sup> =1.01	0.87 (0.53, 1.42); p=0.59	Tau <sup>2</sup> = 0.008 R <sup>2</sup> =1.22	1.07 (0.67, 1.70); p=0.77	Tau <sup>2</sup> = 0.002 R <sup>2</sup> =1.24	0.89 (0.55, 1.46); p=0.65	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.25
<i>Maternal morbidity</i>	-	-	1.21 (0.83, 1.75); p=0.32	Tau <sup>2</sup> = 0.002 R <sup>2</sup> =1.01	1.20 (0.83, 1.74); p=0.32	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.00	1.20 (0.83, 1.74); p=0.32	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.01	1.27 (0.79, 2.02); p=0.32	Tau <sup>2</sup> = 0.000 R <sup>2</sup> =1.00	1.12 (0.72, 1.73); p=0.62	Tau <sup>2</sup> = 0.007 R <sup>2</sup> =1.04	1.21 (0.85, 1.73); p=0.30	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.00	1.06 (0.70, 1.62); p=0.79	Tau <sup>2</sup> = 0.001 R <sup>2</sup> =1.00
Fetal or neonatal adverse outcome	-	-	1.10 (0.89, 1.37); p=0.38	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.06	1.10 (0.89, 1.37); p=0.38	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.06	1.10 (0.89, 1.37); p=0.37	Tau <sup>2</sup> = 0.004 R <sup>2</sup> =1.07	1.14 (0.85, 1.54); p=0.38	Tau <sup>2</sup> = 0.012 R <sup>2</sup> =1.16	1.11 (0.87, 1.43); p=0.40	Tau <sup>2</sup> = 0.09 R <sup>2</sup> =1.19	1.11 (0.90, 1.37); p=0.35	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.06	1.09 (0.88, 1.36); p=0.35	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.06
<i>Stillbirth</i>	-	-	1.03 (0.89, 1.19); p=0.72	Tau <sup>2</sup> = 0.006 R <sup>2</sup> =1.42	1.03 (0.89, 1.19); p=0.69	Tau <sup>2</sup> = 0.005 R <sup>2</sup> =1.39	1.04 (0.90, 1.21); p=0.60	Tau <sup>2</sup> = 0.005 R <sup>2</sup> =1.45	1.02 (0.86, 1.21); p=0.82	Tau <sup>2</sup> = 0.007 R <sup>2</sup> =1.59	1.00 (0.85, 1.18); p=0.99	Tau <sup>2</sup> = 0.005 R <sup>2</sup> =1.45	1.05 (0.91, 1.21); p=0.50	Tau <sup>2</sup> = 0.003 R <sup>2</sup> =1.00	1.04 (0.88, 1.25); p=0.62	Tau <sup>2</sup> = 0.01 R <sup>2</sup> =1.65
<i>Neonatal mortality</i>	-	-	1.10 (0.96, 1.27); p=0.18	Tau <sup>2</sup> = 0.005 R <sup>2</sup> =1.43	1.10 (0.96, 1.27); p=0.17	Tau <sup>2</sup> = 0.005 R <sup>2</sup> =1.44	1.11 (0.96, 1.28); p=0.16	Tau <sup>2</sup> = 0.005 R <sup>2</sup> =1.44	1.07 (0.92, 1.25); p=0.37	Tau <sup>2</sup> = 0.004 R <sup>2</sup> =1.43	1.08 (0.91, 1.29); p=0.38	Tau <sup>2</sup> = 0.007 R <sup>2</sup> =1.53	1.11 (0.96, 1.27); p=0.16	Tau <sup>2</sup> = 0.005 R <sup>2</sup> =1.44	1.12 (0.96, 1.30); p=0.15	Tau <sup>2</sup> = 0.006 R <sup>2</sup> =1.47
<i>Neonatal morbidity</i>	-	-	1.09 (0.73, 1.62); p=0.69	Tau <sup>2</sup> = 0.026 R <sup>2</sup> =1.10	1.09 (0.73, 1.62); p=0.69	Tau <sup>2</sup> = 0.025 R <sup>2</sup> =1.12	1.09 (0.73, 1.61); p=0.69	Tau <sup>2</sup> = 0.025 R <sup>2</sup> =1.12	1.08 (0.59, 1.99); p=0.80	Tau <sup>2</sup> = 0.073 R <sup>2</sup> =1.27	1.08 (0.89, 1.67); p=0.22	Tau <sup>2</sup> = 0.000 R <sup>2</sup> =0.99	1.09 (0.75, 1.59); p=0.64	Tau <sup>2</sup> = 0.025 R <sup>2</sup> =1.12	1.04 (0.69, 1.57); p=0.84	Tau <sup>2</sup> = 0.026 R <sup>2</sup> =1.10

CI, confidence interval; GA, gestational age; OR, odds ratio; \* The data from the individual country Imputation models were used for this analysis. Imputation was performed only for the primary outcome overall; †Tau<sup>2</sup> was estimated as the variance term of the random effect for treatment in the mixed effect model and R<sup>2</sup> was computed as the ratio of the standard errors of the treatment effect from a model with fixed slope and one with a random slope. ‡Defined as one/more of maternal morbidity or mortality, stillbirth, neonatal mortality, or neonatal morbidity; the primary outcome in the CLIP Trials.

**The Community-Level Interventions for Pre-eclampsia (CLIP)  
cluster randomised trials in Mozambique, Pakistan, and India:  
an individual participant data meta-analysis – Appendix**

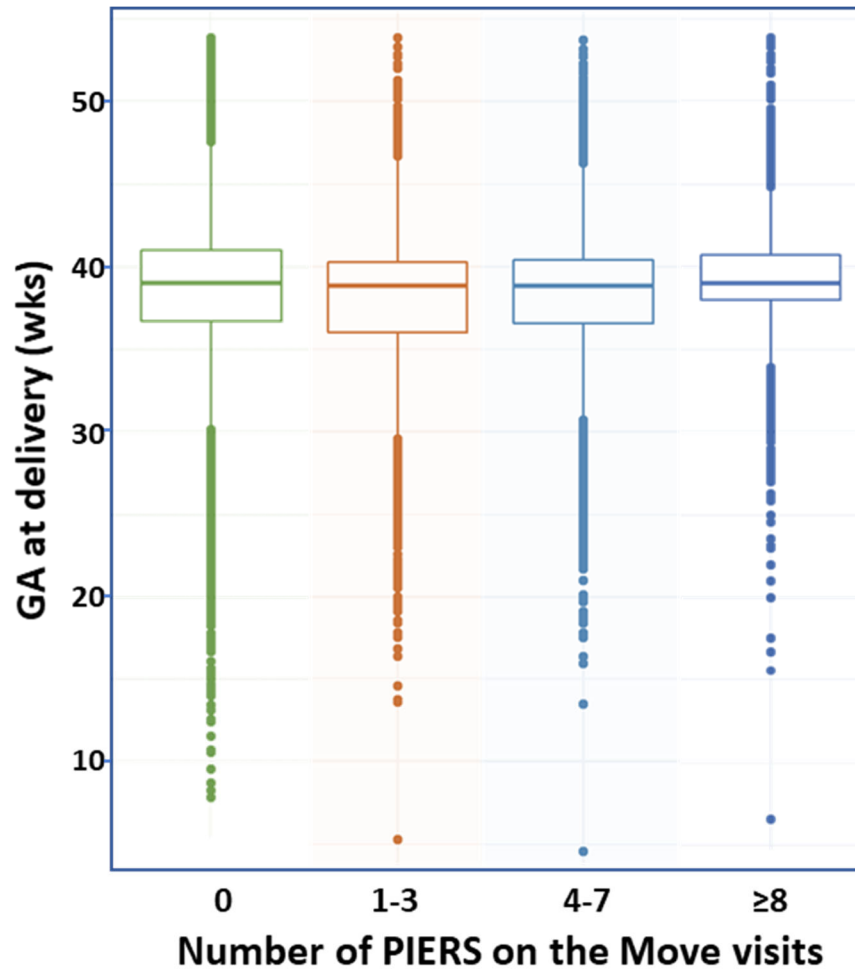
**Supplementary Figures**





**Figure S1: Dose-response by country and within individual participant data meta-analysis**

aOR, adjusted odds ratio; CI, confidence interval; IPD, individual participant data meta-analysis; M&M, morbidity and mortality; NND, neonatal death



**Figure S2: Gestational age at delivery by number of PIERS on the Move visits**  
GA, gestational age

**The Community-Level Interventions for Pre-eclampsia (CLIP)  
cluster randomised trials in Mozambique, Pakistan, and India:  
an individual participant data meta-analysis – Appendix**

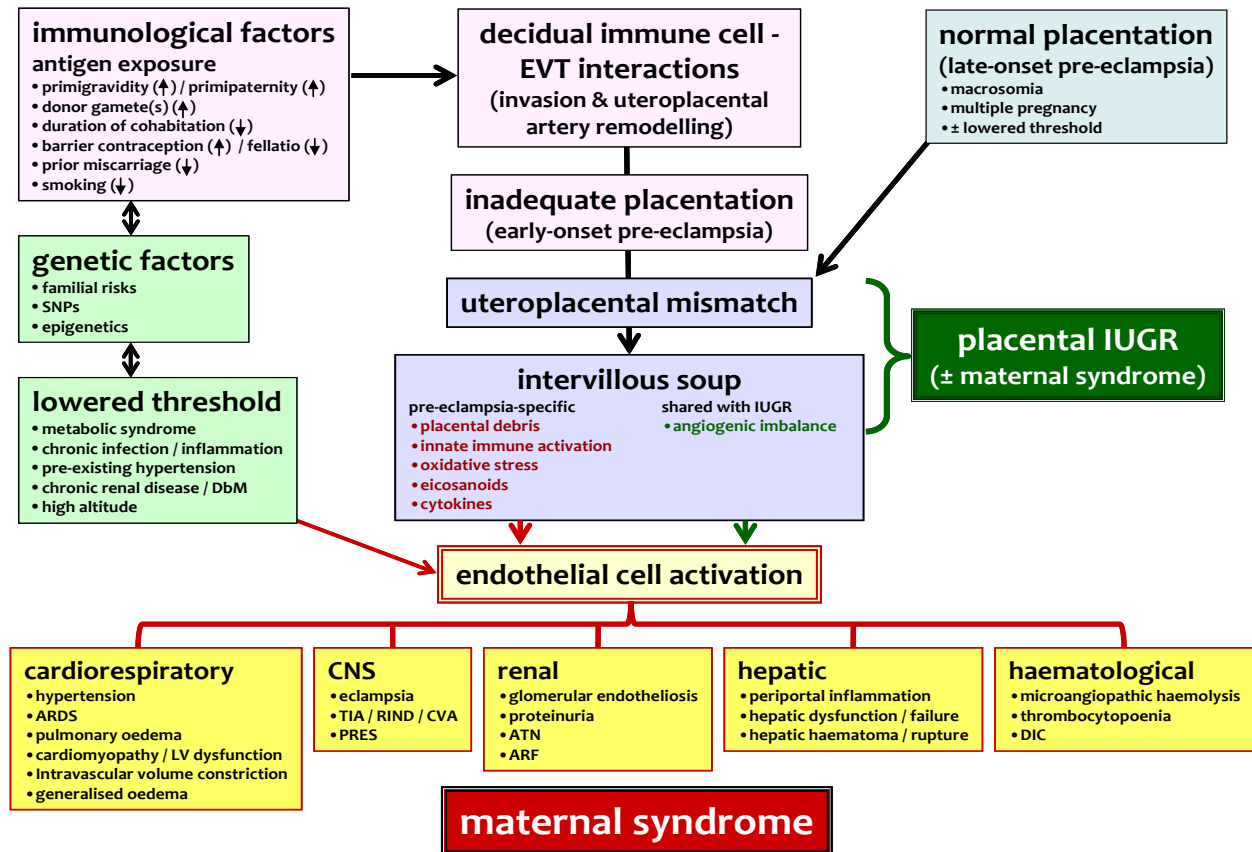
**CLIP Trial Protocol**

# THE CLIP (COMMUNITY LEVEL INTERVENTIONS FOR PRE-ECLAMPSIA) CLUSTER RANDOMIZED CONTROLLED TRIAL

## SECTION 1: BACKGROUND

### 1.1 WHAT IS THE PROBLEM TO BE ADDRESSED?

Pre-eclampsia remains a leading cause of maternal and perinatal mortality and morbidity<sup>1</sup>. It is a pregnancy-specific disease characterised by *de novo* development of endothelial dysfunction resulting in the most common diagnostic features, concurrent hypertension and proteinuria, sometimes progressing into a multiorgan cluster of varying clinical features (Figure 1)<sup>1</sup>. Poor early placentation is especially associated with early-onset disease<sup>1</sup>. Predisposing cardiovascular or metabolic risks for endothelial dysfunction, as part of an exaggerated systemic inflammatory response, might dominate in the origins of late onset pre-eclampsia<sup>1</sup>. Because the multifactorial pathogenesis of different pre-eclampsia phenotypes has not been fully elucidated, prevention and prediction are still not possible, thus symptomatic clinical management should be focussed on the prevention of maternal morbidity (e.g., eclampsia) and mortality.



**Figure 1** The origins and consequences of pre-eclampsia

**ARDS** acute respiratory distress syndrome; **ARF** acute renal failure; **ATN** acute tubular necrosis; **CVA** cerebrovascular accident; **DbM** diabetes mellitus; **DIC** disseminated intravascular coagulation; **EVT** extravillous trophoblast; **IUGR** intrauterine growth restriction; **LV** left ventricular; **PRES** posterior reversible leukoencephalopathy syndrome; **RIND** reversible ischaemic neurological deficit; **SNPs** single nucleotide polymorphisms; **TIA** transient ischaemic attack

Expectant management of women with early-onset disease to improve perinatal outcome should not preclude timely delivery - the only definitive step to initiate cure<sup>1</sup>. Pre-eclampsia foretells raised rates of

cardiovascular and metabolic disease in later life, which could be a reason for subsequent lifestyle education and intervention <sup>1</sup>.

Globally, pre-eclampsia is the second-leading cause of maternal mortality, resulting in an estimated 76,000 maternal deaths annually. In addition, 500,000 fetal and newborn lives are lost annually due to the perinatal consequences of pre-eclampsia. Over 99% of these deaths occur in low and middle income countries (LMICs), primarily in South Asia and Sub-Saharan Africa <sup>2</sup>.

As a result of the focus on postpartum haemorrhage (PPH; the leading cause of maternal death) over the past decade, rates of PPH-related maternal mortality are falling. This fall in PPH-related maternal mortality is driving the improvements in the maternal mortality ratio (MMR; maternal deaths per 100,000 live births) observed in countries such as Bangladesh and Pakistan. Therefore, the proportional contribution of pre-eclampsia-related mortality to the MMR is increasing. It may be that some of the residual PPH-related mortality arises from the consumptive coagulopathy of severe pre-eclampsia, especially when complicated by abruption <sup>1</sup>.

Clearly, improvements in PPH-related outcomes have no direct impact on perinatal mortality as the woman is delivered before she bleeds. However, we recognise that maternal death places infants at a 6-fold increased risk of infant mortality.

In general, previous research in this field has focussed on institutional level interventions with MgSO<sub>4</sub> (eclampsia prevention and treatment <sup>3-6</sup>) and the treatment of severe pregnancy hypertension <sup>7</sup>. However, if we limit ourselves to studying inpatient, facility-level, interventions with fully assessed treatment options, many women will die or be irreversibly affected by pre-eclampsia (e.g., either moribund or having suffered a stroke) prior to arriving at the inpatient facility.

Of all the Millennium Development Goals (MDGs), MDG 5 (a 75% reduction in maternal mortality from 1990 levels by 2015) is that which is proving hardest to achieve. Maternal lives lost from pre-eclampsia and eclampsia result from delays in triage, transport and treatment. As such, the solution has to reside in getting care to women in the community as current health systems either never see affected women (who die either in their community or en route to formalised care) or receive women who are moribund and beyond salvage regardless of the quality of care being offered.

Currently, Bangladesh is one of the few countries on target to achieve MDG 5; however, the remaining issues to be addressed (such as pre-eclampsia) will be harder to achieve – partly because women with pre-eclampsia feel well until they are critically ill. It is probable that in Nigeria, Mozambique, Pakistan and India, MDG 5 will not be achieved.

The CLIP trial is a singular step towards addressing the excess maternal and perinatal mortality that derive from the failure to identify and rapidly manage pre-eclampsia and eclampsia at the community level in LMICs.

## 1.2 WHAT ARE THE PRINCIPAL RESEARCH QUESTIONS TO BE ADDRESSED?

### **Hypothesis**

That implementing community-level evidence-based care will reduce pre-eclampsia-related maternal and perinatal mortality and major morbidity by addressing ‘three delays’ in triage, transport, and treatment.

### **Objective**

To reduce pre-eclampsia-related, and all-cause, maternal and perinatal mortality and major morbidity by 20% or more in intervention clusters in Ogun State (Nigeria), Maputo and Gaza Province (Mozambique), Sindh Province (Pakistan) and in Karnataka State (India).

### 1.3 RELEVANT CONVERGENT ACTIVITIES

#### ***Pre-requisite knowledge: CLIP Feasibility Study (co-PIs: P von Dadelszen & R Qureshi)***

The Feasibility Study is being conducted in Nigeria, Mozambique, Pakistan, and India in preparation for the CLIP cluster randomised controlled trial (cRCT; CW UBC REB # H12-00132). In Pakistan we are building on the previous community- and primary health centre (PHC)-level perinatal intervention studies and trials led by Professor Bhutta<sup>8-12</sup>. A process evaluation may be conducted in all the sites to provide information on mechanisms of impact and delivery of intervention.

The purpose of each national CLIP Feasibility Study is to understand the health care system, explore key methodological issues for CLIP, and engage in a dialogue with the key stakeholders (to inform the development of culturally appropriate tools and educational materials for use in CLIP).

The *health care system organisation and infrastructure capacity* must be clear, related to antenatal care models and pre-eclampsia/eclampsia monitoring, triage, management, referral and maternal transfer, and PHC and referral facility pre-eclampsia/eclampsia treatment.

*Key methodological issues for CLIP* include: community demographics, pre-eclampsia/eclampsia prevalence rates and rates of associated maternal and perinatal morbidity and mortality; data collection methods and informational systems for population surveillance; specific barriers to conducting a cRCT, including recruitment feasibility, capacity to implement community intervention, and accurate data collection; and cost identification to conduct the CLIP trial and an adequately powered cRCT in the identified country.

Finally, we must receive input from *key community stakeholders* (cultural and/or community beliefs/practices/influences/attitudes), *community-based health care providers (cHCP)* (professional scope of practice regulations and/or legal barriers and potential for task shifting), *facility care providers* (provider knowledge and competency related to pre-eclampsia/eclampsia and resource/informational capacity for provider training), and *key decision-making stakeholders* (support, commitment, and financial/schedule feasibility to remedy identified barriers). By engaging relevant stakeholders from the beginning of the trial planning process, we will work towards long term sustainability of the intervention, should it prove to be effective.

Each national Feasibility Study is using a mixed methods approach (quantitative, participatory, and formative, with community mapping) based on the normalization process model and will utilize literature reviews, target interviews, focus groups, and survey tools. Target interviews and focus group data are being recorded and transcribed; observations and assessments written up as field notes. The core approach is similar across the four study sites, but will allow for tailoring according to individual setting and cultural context. We are drawing on models of how interventions are embedded in practice (e.g., the normalisation process<sup>13-15</sup> and psychological theory<sup>16</sup>) as frameworks for this assessment.

A summary of key findings from the Feasibility Studies to date, including stakeholders engaged and information on health care system organisation and current scope of practice of cHCPs can be found in Appendix A of this document.

#### ***Tools & Funding: PIERS On the Move (POM) (co-PIs: JM Ansermino & P von Dadelszen [funded by Saving Lives at Birth])***

Risk stratification using the miniPIERS model aims to address three delays that lead to the increased incidence of maternal mortality in LMICs: delays in triage, transport, and treatment (adapted from Thadeus and Maine)<sup>17</sup>.

The *delays in triage* relate to the presentation of women late in the clinical course of their hypertensive disorder of pregnancy (HDP) and the failure to have the nature and potential severity of their condition recognised. In many settings, women receive no antenatal care; therefore achieving some degree of practical oversight and getting a triage mechanism into the hands of women and their immediate caregivers is a priority. Often, immediate care is given by cHCPs and at PHCs. Once women enter the formal health care system [hospitals providing either basic or comprehensive emergency obstetric care (EmOC)], the miniPIERS and fullPIERS models will identify those most at risk of adverse outcomes so that they can receive appropriate interventions in the timeliest manner possible<sup>18;19</sup>.

To identify women for whom *transport* is a particular priority, cHCPs and the nurses, medical assistants, and physicians staffing PHCs need to have available to them tools that risk stratify women with pre-eclampsia; the miniPIERS model will do this.

Testing the *hypothesis* that the PIERS models, based on a combination of maternal and fetal predictors, will accurately identify women at incremental risk of maternal complications of pre-eclampsia, we have developed the fullPIERS model (see below) in eight tertiary academic centres in Canada, United Kingdom, New Zealand, and Australia<sup>19</sup>; and developed and validated the miniPIERS model in five LMICs (see below). The fullPIERS model identifies risk most accurately over the following 48h, but also for up to 7 days. The miniPIERS model performs with less accuracy, but may have greater impact as it is more generalisable to all levels of care in high, middle, and low income settings. Only miniPIERS will be utilised as a triage tool in the CLIP trial, as we anticipate that a model solely derived from, and validated in, LMICs will be the most accurate and have greatest validity for the CLIP trial.

**The fullPIERS model (Figures 2 & 3)** In the fullPIERS data set, we have identified those women with pre-

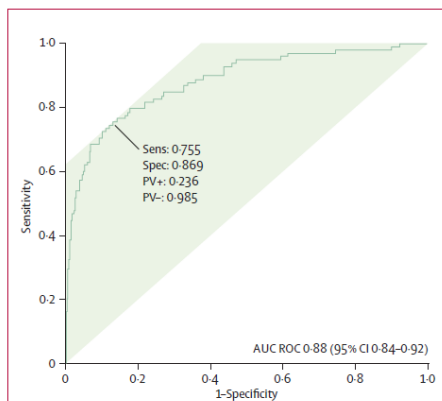


Figure 2: Performance of the fullPIERS model

Combined adverse maternal outcomes predicted within 48 h of eligibility on the basis of only data recorded before the outcome (an online tool to calculate fullPIERS probabilities is available on the study website). AUC ROC=area under the curve of the receiver operating characteristic. PV+—negative predictive value. PV+—positive predictive value. Sens=sensitivity. Spec=specificity.

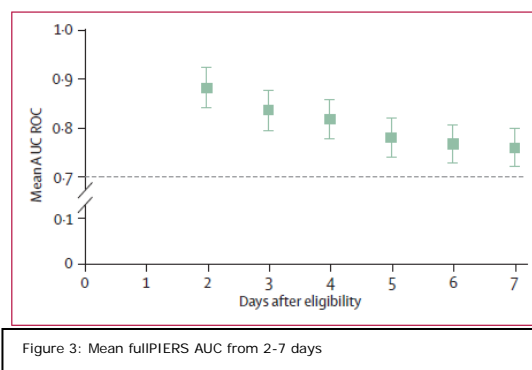


Figure 3: Mean fullPIERS AUC from 2-7 days

Error bars show 95% CIs. AUC ROC=area under the curve of the receiver operating characteristic.

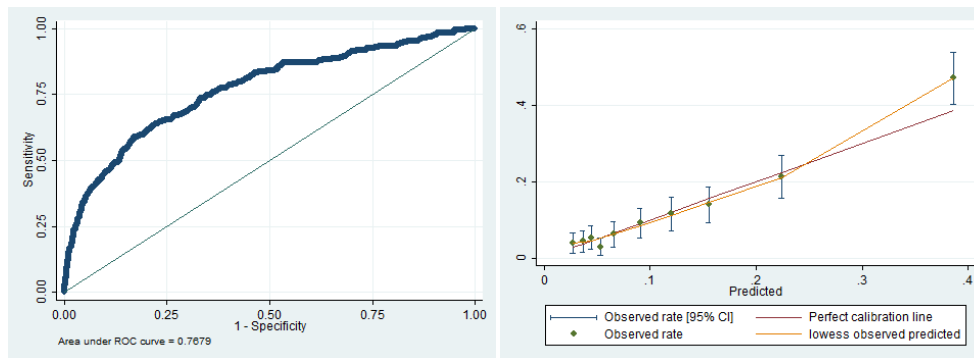
eclampsia who are at increased risk of maternal complications and have been able to grade this risk<sup>18-28</sup>.

The independent predictors of adverse maternal outcome are: gestational age at eligibility, chest pain/dyspnea, SpO<sub>2</sub>, creatinine, aspartate transaminase (AST), and platelet count. fullPIERS assesses risk up to 7 days after eligibility (AUC ROC 0.76 [95% CI 0.72, 0.80]<sup>19</sup>).

An ancillary, and cost neutral, benefit of this project will be to externally validate the fullPIERS model in LMIC settings.

**The miniPIERS model (Figures 4 & 5)** Based on data from 2081 women admitted to a miniPIERS centre in Brazil, South Africa, Uganda, Pakistan and Fiji, the miniPIERS model predicts adverse maternal events in women with any HDP. The components of the miniPIERS model are: parity (multiparity vs. nulliparity)

gestational age at identification; symptoms (Y/N) of headache/ visual disturbances, chest pain/ dyspnoea, or abdominal pain with vaginal bleeding; systolic blood pressure (sBP); and dipstick proteinuria. The AUC ROC is 0.8788 [95% CI 0.4744, 0.80], decreasing to 73 on internal validation.



**Figures 4 & 5:** miniPIERS model ROC curve and calibration curve

Using funds from within the wider PRE-EMPT grant, miniPIERS modelling (development and validation) was completed in September 2012. The final model is a prerequisite for development of the management algorithms for the CLIP cRCT. miniPIERS will be a component of the CLIP trial hosted on a mobile platform.

In Mozambique and Pakistan an additional component to the miniPIERS mobile phone application will be the use of a low-cost mobile phone adapted pulse oximetry sensor to measure blood oxygen saturation (SpO<sub>2</sub>) in the pregnant population under study. This sensor is being provided by our industry partner LionsGate Technologies (LGT) Medical. LGT Medical developed and manufactures a low-cost audio-port enabled pulse oximetry sensor, called the audio oximeter, for use with mobile phones and tablets. The raw photoplethysmogram (PPG) will be recorded to facilitate the optimal estimation of hearth rate, heart rate variability, pulse pressure variation, oxygen saturation and other parameters that may be used to optimize future signal quality estimates and to develop novel methods to characterize and display the information contained in the PPG. These waveform characteristics may be combined with other waveform or clinical information.

The raw pressure waveforms will be recorded during the measurement of blood pressure to estimate the optimal thresholds for future therapeutic decisions, to optimize future signal quality estimates and to develop novel methods to characterize and display the information contained in the non-invasive pressure waveform. These waveform characteristics may be combined with other waveform or clinical information

Using data from both the miniPIERS and fullPIERS studies we have previously demonstrated that blood oxygen saturation <93% is associated with significantly increased risk for the mother (OR fullPIERS: 18.0 95% CI 8.1 – 40.1; miniPIERS: 30.7 95% CI 13.9 - 67.7). Addition of SpO<sub>2</sub> as a variable in the miniPIERS model significantly improves the model sensitivity and has the potential to further improve risk stratification in the CLIP trial. Testing this modified model in two countries will allow us to determine if the added value in model sensitivity translates to real improvements in maternal outcomes compared to use of the original miniPIERS triage tool.

The miniPIERS mobile phone application to be used by chCPCs in the CLIP trial: (i) provides local, rapid and accurate risk assessment, referral, and treatment advice for pre-eclampsia, and (ii) transmits information to referral centres for co-ordination of triage, transportation, and treatment.

By harnessing the processing and battery power of the phone and widespread availability of cellular services



in Africa and South Asia, we will empower cHCPs to rapidly and reliably assess a woman’s risk of pre-eclampsia complications in real-time, and to take action before complications arise.

**Tools & pre-requisite knowledge: Blood pressure monitoring in LMICs (PI: A Shennan)**

Using parallel funding from the Bill and Melinda Gates Foundation (BMGF), and building on two decades’ experience, we have identified the optimal automated sphygmomanometers for use in LMIC settings, the Microlife BP 3AS1-2 and the Microlife CRADLE VSA, developed for Professor Shennan’s parallel CRADLE (Community blood pressure monitoring in Rural Africa: Detection of underLying pre-Eclampsia) research programme in South Africa and Tanzania. Through his relationship with Microlife, Professor Shennan has arranged for us to bulk purchase 900 machines that have been purpose-modified for CLIP. See Appendix E for details on the validation study for the Microlife BP 3AS-2 and the Microlife CRADLE VSA.

As part of our collaboration with Microlife and Dr. Shennan, we will undertake qualitative analysis relating to the use of this tool in CLIP. Plans for qualitative evaluation fall within the CRADLE research programme and are funded separately from CLIP. Qualitative analysis plans are outlined in Appendix E of this protocol.

**Pre-requisite knowledge: Oral antihypertensive therapy for severe pregnancy hypertension - review (PI: LA Magee)**

Traditionally, severe hypertension (usually defined as sBP≥160mmHg and/or dBP≥110mmHg) has been treated with short-acting parenteral antihypertensive agents, most frequently, intravenous (i.v.) hydralazine or labetalol<sup>29</sup>. Parenteral agents require more resources than do oral antihypertensive agents, in terms of equipment (i.e., i.v. tubing, syringes, and needles) and personnel (as administration is by nurses or doctors). Also, parenteral agents require more monitoring and supervision as they are rapidly-acting and have the potential to lower BP quickly and cause maternal hypotension and fetal compromise.

Oral antihypertensive therapy is used for hypertensive urgencies in pregnancy in some jurisdictions, with apparently good effect. In the regional pre-eclampsia guidelines from Yorkshire, UK, labetalol 200 mg is administered orally before i.v. access is secured, with a repeat dose given if no response is seen after 30 minutes<sup>30</sup>. The UK National Institute for Health and Clinical Excellence (NICE) Hypertension in Pregnancy guideline recommends oral labetalol or nifedipine for the treatment of severe hypertension in critically ill women during pregnancy or after birth<sup>31</sup>.

In our literature review of oral antihypertensive therapy for severe hypertension in and outside pregnancy, we identified 15 RCTs (915 women) in pregnancy, one postpartum and 34 outside pregnancy (Firoz *et al*; manuscript in preparation). Most trials in pregnancy compared oral/sublingual (SL) nifedipine capsules (8-10mg) with another agent, usually parenteral hydralazine or labetalol. 84-100% of women achieved successful treatment with nifedipine with less than 1% experiencing hypotension. Target BP was achieved ~50% of the time with oral labetalol and methyldopa, suggesting that each may be a reasonable alternative to nifedipine. Outside pregnancy, most trials compared short-acting nifedipine with SL captopril (6 trials, 251 subjects) with similar rates of success (88% vs. 76%). The results are presented in detail in Appendix B.

In our review of the pharmacokinetics of antihypertensive agents found commonly on the essential medicines lists of LMICs (Lalani *et al. JOGC*), the onset, peak, and duration of action of agents were very similar (Table 1).

**Table 1** Oral antihypertensives for severe pregnancy hypertension

Drug	Dosage	Onset	Peak	Duration
Atenolol	25 – 50 mg	1hr	2-4hr	24hr (dose dependent)
Labetalol	200 mg	20min – 2hr	1-4 hr	8-12hr (dose dependent)

Methyldopa	500 mg – 2 g	40 min	3-6hr	12-24hr
Nifedipine intermediate-acting	10 mg	30min	4hr	12hr
Nifedipine capsule	5 -10 mg	5-10min	30min	6.5hr

In summary, 750mg (alpha-)methyldopa has been chosen as the optimal antihypertensive to treat severe pregnancy hypertension in CLIP for several reasons: (i) it has been well-studied in RCTs in pregnancy for non-severe hypertension, and more limited RCT data for severe hypertension suggest that the drug is effective; (ii) it has an acceptable onset, peak, and duration of action for treatment of severe hypertension; (iii) there is a high level of comfort with methyldopa due to its long history of use as an antihypertensive of first choice in pregnancy, making it an acceptable choice to most practitioners; (iv) it is likely to face fewer barriers in terms of acceptability during implementation as it does not interact with MgSO<sub>4</sub>, whereas unfounded misconceptions persist about a nifedipine-magnesium interaction<sup>32</sup>; (v) it is widely available on nearly all LMIC essential medicines lists, and it is affordable, which speaks to feasibility during post-trial implementation and scale-up; and (vi) as an oral treatment it is more acceptable for administration by cHCPs than complex intravenous medications.

**Pre-requisite knowledge: Options for safe community administration of MgSO<sub>4</sub> (PI: LA Magee)**

We have reviewed the current literature that pertains to intramuscular (i.m.)-only administration of a MgSO<sub>4</sub> loading dose at the community level (Gordon *et al*; JOGC [in press]). We have determined that a single 10g i.m. dose of MgSO<sub>4</sub> would be safe (even in the presence of anuria) and would achieve therapeutic Mg<sup>2+</sup> levels within 45 minutes and result in sustained levels for 4-6 hr (Figure 6)<sup>33</sup>. A more thorough description of the results of this systematic review is provided in Appendix B.

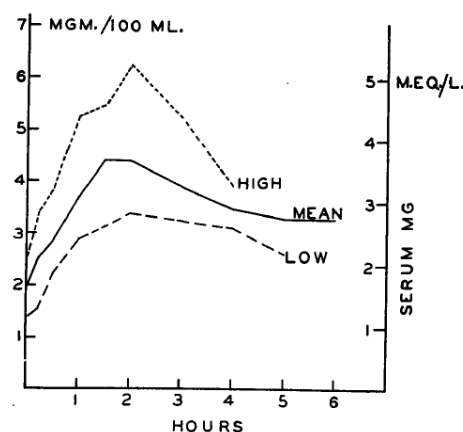


Figure 6 Effect of 10g IM MgSO<sub>4</sub> loading dose on serum Mg<sup>2+</sup> concentration

**Pre-requisite knowledge: Current CLIP-related maternity services provision in Nigeria, Mozambique, Pakistan & India (PI: P von Dadelszen)**

We have reviewed the current availability of CLIP-relevant personnel, drugs, devices and interventions at all levels of the public, NGO and private health care systems in Nigeria, Mozambique, Pakistan and India.

Table 2 CLIP-related maternity care service provision	Nigeria	Mozambique	Pakistan	India
Community-based care				
HOME-BASED CARE				
cHCPs	Community Health Extension Workers (CHEWs; cover 2500 population each) Health Assistants (HAs)	Agente Comunitarios de Saude (APEs; cover 500-2000 population each)	Lady Health Workers (LHWs; cover 1000 population each)	Auxiliary Nurse Midwives (ANMs; cover 3000-5000 population each) Accredited Social Health Activists (ASHAs; cover 1000)

<b>Table 2</b> CLIP-related maternity care service provision	<b>Nigeria</b>	<b>Mozambique</b>	<b>Pakistan</b>	<b>India</b>
				population each)
<b>Delivery in the home</b>	70% births at home	30% births at home	40% births at home	5-10% births at home
<b>PHC-based care</b>				
<b>Medical officers</b>	Sometimes	No	Yes	Yes
<b>Nurses</b>	Yes	Yes	Yes	Yes
<b>cHCPs</b>	CHEWs, Health Assistants (HA)	ACSS	LHWs	ANMs, Lady Health Visitors (LHV)
<b>BP device</b>	Yes (93%)	Yes	Yes (100%)	Yes (100%)
<b>Urine dipsticks</b>	Sometimes (20%)	Yes	Few (37%)	Yes (90%)
<b>Laboratory testing</b>	Sometimes (11%)	Some	Yes (100%)	No
<b>Ultrasound</b>	Sometimes (5%)	No	Sometimes	No
<b>Methyldopa</b>	Yes (purchased by patient at pharmacy)	Yes	Yes	Yes
<b>MgSO4</b>	Availability of some anticonvulsant (82%)	Yes	Sometimes (38%)	Sometimes (56%)
<b>Attend deliveries</b>	Yes	Yes	Yes	Yes
<b>BEmOC</b>	Varies	No	Yes	No
<b>Hours of available care</b>	Information pending	Information pending	Day time only	Some services are 24/7
<b>Facility-based care</b>				
<b>Number of facilities serving CLIP clusters</b>	936 (32 public, 904 private)	56	12 (3 public, 9 private)	96
<b>BEmOC in CLIP clusters</b>	Information pending	10	17 (14 public, 3 private)	Information pending
<b>CEmOC in CLIP clusters</b>		1	12	Majority
<b>General practitioners/ medical officers</b>	Yes	Yes	Yes	Yes
<b>Specialists</b>	Rarely	Rarely	At some highest level facilities	Yes
<b>Nurses</b>	Yes	Yes	Yes	Yes
<b>cHCPs</b>	Yes	Yes	No	ANMs
<b>BP device</b>	Yes	Yes	Yes (100%)	Yes (100%)
<b>Urine dipsticks</b>	Yes	Yes	Sometimes	Yes
<b>Laboratory testing</b>	Yes	Yes	Yes (100%)	Yes
<b>Ultrasound</b>	Yes	Yes	Yes	Yes
<b>Fetal heart assessment</b>	Pinard; US	Pinard, Doppler, US	Pinard, CTG, US	Pinard, Doppler, CTG, US
<b>Methyldopa</b>	Sometimes (30%)	Yes	Yes	Yes
<b>Other antihypertensives</b>	Sometimes (7%)	Yes	Yes	Yes
<b>MgSO4</b>	Sometimes (20% stock outs)	Yes	Some	Yes

**ANM** auxiliary nurse midwife; **APE** agente polivalente elementares; **ASHA** accredited social health advocate; **BEmOC** basic emergency obstetric care; **BP** blood pressure; **CEmOC** comprehensive EmOC, **cHCP** community health care provider; **CHEW** community health extension worker; **CTG** cardiotocograph; **LHW** lady health worker; **MO** medical officer; **PHC** primary health centre; **US** ultrasound

## SECTION 2: THE CLIP TRIAL

### 2.1 THE CLIP TRIAL DESIGN

We have designed a two-phased community (including PHC-level) cRCT encompassing both rural and urban settings to be fully powered in each of:

- Ogun State, Nigeria
- Maputo and Gaza Province, Mozambique
- Hyderabad and Matiari districts in Sindh Province, Pakistan.
- Belgaum and Bagalkot districts in Karnataka State, India

The trial will be phased from the Pilot CLIP trial to Definitive CLIP trial on the basis of a satisfactory rate of use ( $\geq 50\%$ ) of the CLIP ‘package of care’ in appropriate women in all countries but Mozambique (see section 2.2 intervention for details on the ‘package of care’). Mozambique will be unique in that they will rely on an extended period of feasibility to pilot test all Trial systems and tools before directly beginning a definitive trial. Foregoing the Pilot in Mozambique was felt to be appropriate based on their experience with community-based surveillance and will ensure timelines of the trial are met within a manageable budget.

For all other countries, use of the package in the Pilot phase will be defined as appropriate referral (urgent or non-urgent) to a facility able to provide comprehensive emergency obstetric care (CEmOC) in appropriate women during the first six months of the Pilot CLIP trial (Figure 2). This accelerated transition from Pilot CLIP trials to Definitive CLIP trials will: (i) save resources in the long term as the research infrastructure will be maintained in all countries and, thereby, start-up costs will be reduced as will core infrastructure costs at UBC, and (ii) deliver more rapidly the primary CLIP research question, does the CLIP community intervention improve outcomes for mothers and babies?

Full details of the sample size calculation for both Pilot and Definitive trial phases can be found in Table 3.

Monitoring during the Pilot phase of the trial to determine rate of use of the CLIP package of care will be performed by the cHCPs using the POM mobile application in an ongoing manner after the Pilot trial begins. In the Pilot Trial, if the percentage use of the CLIP ‘package of care’ is  $< 50\%$  in any given jurisdiction at 6 months after the trial start date, but climbing, we plan to re-assess at 7, 8, and 9 months before making a decision whether or not to continue the Trial. Similarly, if there is an identifiable barrier or number of barriers found then we will attempt to overcome the barrier(s) and reassess, deferring the commencement of the Definitive CLIP trial in that jurisdiction, while proceeding in the others. All decision will be made in consultation with the Bill & Melinda Gates Foundation (sponsor), after reviewing the advice of the CLIP trial Data Safety Monitoring Board (DSMB), and complying with relevant REB/ethical board guidance. The rationale for continuing the Pilot CLIP trial beyond the initial nine months is to beta-test the whole Trial process through at least two household surveillance cycles, as well as testing and validating any tools designed specifically for use in the Definitive CLIP trial but not related to the primary outcome.

All tools related to the Definitive CLIP trial primary outcome will be field-tested prior to the Pilot CLIP trial.

#### **For CLIP Pilot and Definitive trials**

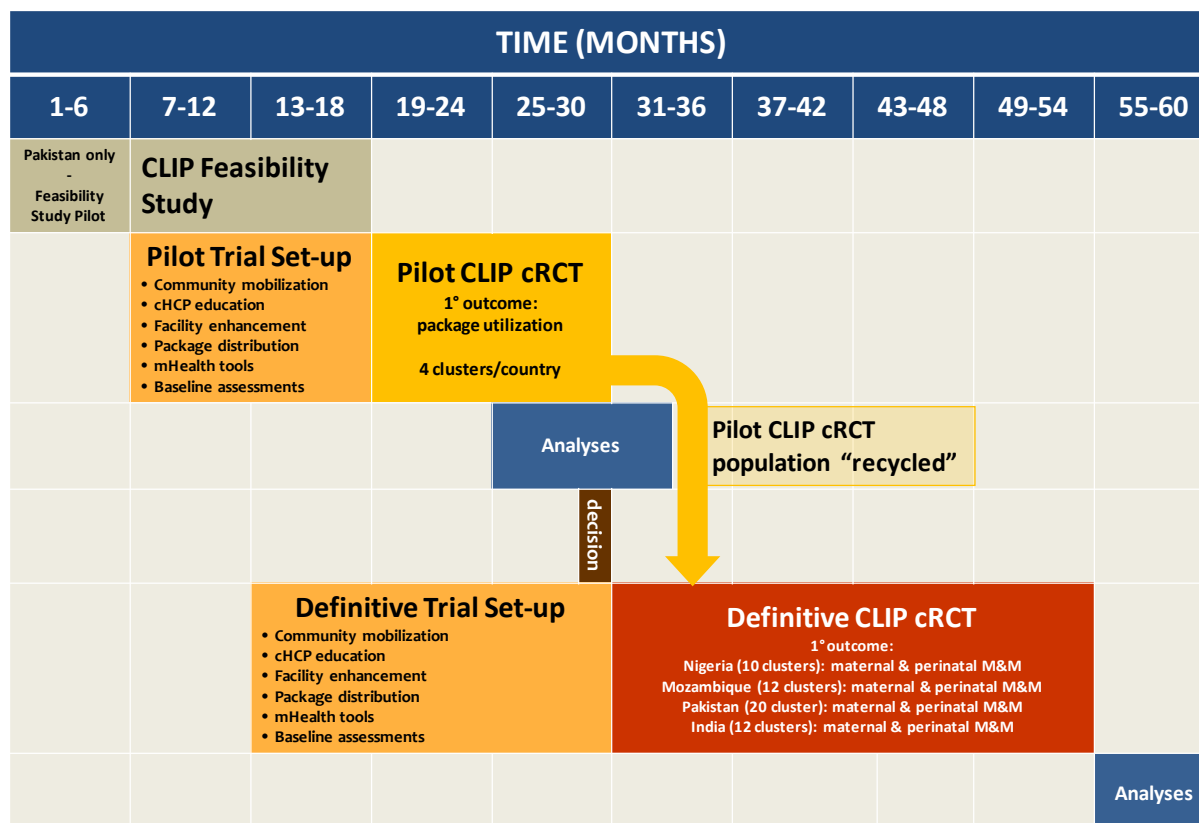
**Control clusters** Women receive the current pattern of care

**Intervention clusters** Women and their communities receive the CLIP intervention

The primary implementers of the CLIP intervention will be cHCPs, the nature of whom will differ between countries. In Nigeria, these are Community Health Extension Workers (CHEWs) and Health Assistants (HAs); in Mozambique, these are Agente Polivalente Elementares (APEs); in Pakistan, these are Lady

Health Workers (LHWs); and in India, these are Accredited Social Health Advocates (ASHAs) and Auxiliary Nurse Midwives (ANMs). Unless context-specific, we will use the term cHCP to describe these cadres of health providers for simplicity. The training and experience of these groups are described in Table 2.

As the primary outcome changes between the Pilot and Definitive Trials, the women in the Pilot Trials will contribute to the sample size of the Definitive Trials. We plan that each pair of Pilot and Definitive CLIP Trials will span 48 months (36 months’ recruitment) as shown in Figure 7 below. In India, the Pilot phase



will be shorter due to the difference in surveillance process as described later in this protocol.

**Figure 7:** CLIP trial timeline

cHCP community health care provider, cRCT cluster randomised controlled trial, mHealth mobile health

## 2.2 INTERVENTIONS

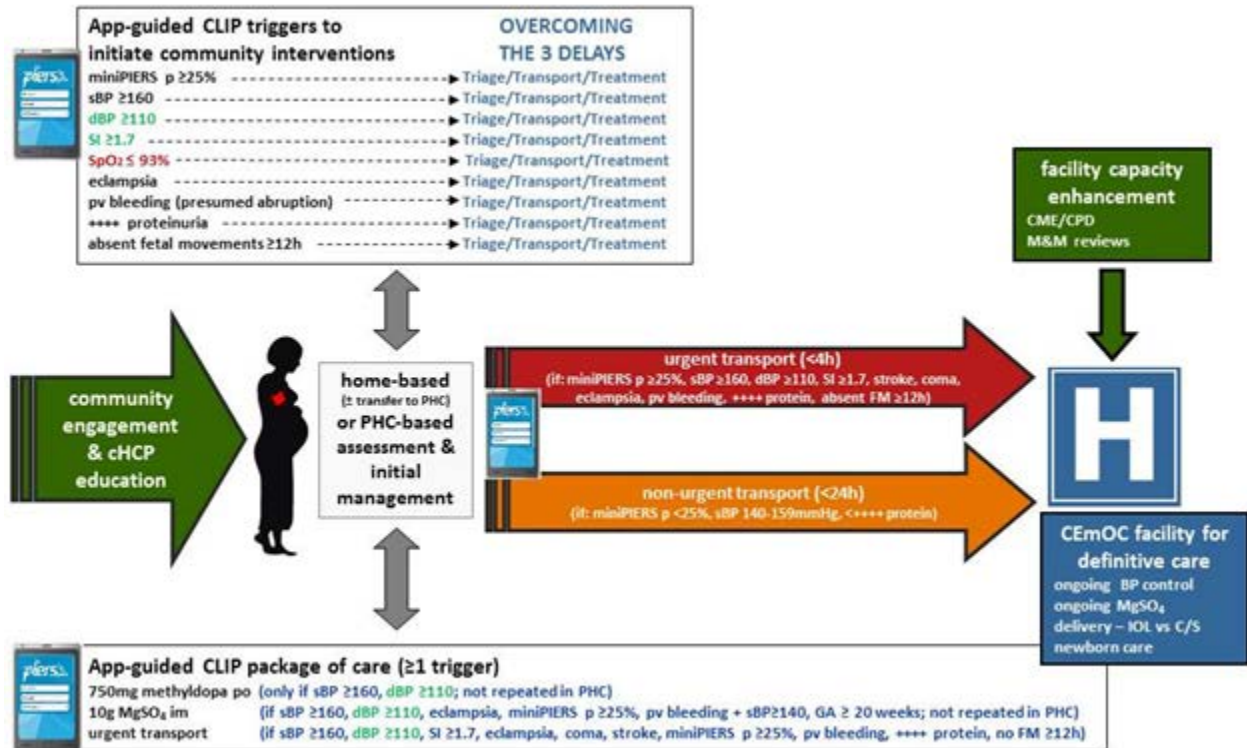
The interventions will be:

**Control group:** current practice (around antenatal care, referral to facility, and initiation of therapy).

**Study group:** The CLIP intervention consists of (i) *community engagement* including community leaders, the women of the communities themselves, and their mothers, husbands, and mothers-in-law, regarding pre-eclampsia, its origins, symptoms, signs, and potential consequences, pre-permissions for maternal transport, and fundraising activities around transport and treatment costs; (ii) *provision of HDP oriented antenatal care through CLIP visits and use of CLIP POM tool* (for risk stratification), and (iii) *use of the CLIP package for women with a CLIP ‘trigger’* (i.e., oral antihypertensive therapy when indicated, intramuscular (i.m.) MgSO<sub>4</sub> when indicated; and appropriate referral to an CEmOC facility when indicated) (Figure 8). cHCPs will assess pregnant women with a target frequency of every 4 weeks at a

minimum, and according to protocol (Appendix C: CLIP cHCP Working Protocol). These visits can occur in the home or PHC as both are considered part of the community for the purpose of the CLIP Trial. They will be trained to enquire about women's symptoms (using country-specific pictograms), take women's BP (using sBP as it more closely reflects the risk for hypertensive stroke than does dBP<sup>11;12</sup>), and check urine for protein using dipstick on the first visit or on any subsequent visits for sBP  $\geq 140$  mmHg. This will inform the diagnosis and risk assessment of women with pre-eclampsia.

**Both groups:** CEmOC facility enhancement to promote evidence-based care of women with pre-eclampsia/eclampsia who are referred to CEmOC facilities, focussing on the WHO guidelines<sup>34</sup>.



**Figure 8:** CLIP intervention diagram

CEmOC comprehensive emergency obstetric care, cHCP community health care provider, CME/CPD continuous medical education/professional development, C/S Caesarean section, FM fetal movements, im intramuscular, IOL induction of labour, i.v. intravenous, M&M morbidity and mortality, p probability, PHC primary health centre, po by mouth, pv vaginal, sBP systolic blood pressure. In green (for Nigeria), there are additional triggers for severe diastolic hypertension and shock. In red (Mozambique and Pakistan), there is an additional trigger for SpO<sub>2</sub>  $\leq 93\%$ .

### Component 1: Community engagement

The primary objective of the community engagement activities in CLIP will be to create awareness and action around the prevention of maternal morbidity and mortality due to pre-eclampsia/eclampsia. Community engagement involves the collective action of individuals, families, religious leaders, policy makers, health care providers and community members toward the creation of meaningful and sustainable change. Studies indicate that successful health behaviour change occurs when interventions create positive social, individual, and environmental conditions. Furthermore, community-based interventions that

include women's and men's support groups, education, counselling, home visits, emergency transport initiatives and fundraising activities, have shown significant improvements in maternal and perinatal morbidity and mortality.

For each of the CLIP trials, a community engagement strategy will be developed with the participation of local stakeholders and community members that aims to be culturally and contextually appropriate, meaningful, sustainable, and effective in improving maternal health in CLIP intervention communities.

The first step is to determine what past and current activities related to community engagement around maternal health are occurring in control and intervention clusters. A specific tool has been developed for the purposes of identifying these community engagement activities so that the CLIP trial strategy can build upon them (Appendix C).

The second step follows the community mapping exercise. A community-specific engagement strategy will be developed, with direct input from community members, for the purpose of creating awareness and action around pre-eclampsia/eclampsia and the prevention of the associated maternal and perinatal morbidity and mortality, including but not limited to:

The CLIP community engagement activities must include (but are not limited to) the following nine topics:

1. Warning symptoms and signs of pregnancy complications, particularly pre-eclampsia & eclampsia
  - Relate the association of danger symptoms/signs with the occurrence of pre-eclampsia/eclampsia, using the warning symptoms of pre-eclampsia and eclampsia pictograms.
  - Identify the need for referral when danger symptoms/signs associated with pre-eclampsia/eclampsia occur.
  - Considering discussing postpartum haemorrhage (PPH), a 'visible' cause of maternal death, as a segway into discussion of pre-eclampsia/eclampsia as a 'silent' killer of pregnant/ postpartum women
2. Permission for women to seek care
  - Recognise the need for decision-making power and/or prior permissions in the event of obstetric emergencies.
  - Discuss how women can obtain prior permission to seek that care
3. Identification of skilled birth attendant
4. Identification of facility for delivery
5. Transport and treatment funds
  - Recognise the need to develop plans for financial resources when required in emergency conditions associated with pre-eclampsia/eclampsia. Funds may be personal or from the community. The community engager should facilitate the individual communities to form a plan for transport and treatment funds.
  - Encourage the identification of existing community resources (if applicable) and the development of community funds for seeking emergency care. The community should be told that CLIP will supplement any existing funds, but fund-raising activities must build on those funds to make this sustainable
  - Identify available and appropriate modes of transport, the associated costs, and the means by which these modes can be accessed in emergencies.
6. Feedback mechanisms about adverse outcomes and 'great saves'
  - Country-specific CLIP Team could request that families of sufferers share their experiences with the community



7. CLIP protocol (brief)

- The description should be brief, and focus on who is eligible and the CLIP intervention (of which community engagement is an important component)

8. CLIP visits and the CLIP triggers for treatment and transport (brief)

- Review the frequency of the visits, assessments to be done as part of each visit, and the ‘triggers’ that will prompt the cHCP to recommend treatment and transport to facility.

9. Discussion about, and trouble-shooting designed to address, the barriers identified in the country-specific CLIP Feasibility Study.

Community engagement strategies used in the CLIP trial intervention clusters may take many forms and will be unique to the culture and context of each community as well as the community’s resources and constraints. The CLIP team aims to utilise knowledge gained from an update to the Cochrane systematic review of the literature on community mobilisation in LMICs (being led by Susan Munabi-Babigumira), in co-ordination with the results of community mapping, and direct community input, to develop a community engagement strategy that is both evidence-based and tailored to the unique needs of CLIP intervention clusters.

It is recognised that sustainable community engagement activities more frequently involve an element of fund raising activity, than activities that are not sustained<sup>35-38</sup>. Therefore, the focus on transport and treatment fundraising activities is a singularly important element of the community engagement activity, and one that the CLIP Trial will pump prime funds so that every intervention cluster community has access to funds as the Trial commences to support the transport and care of women from the initiation of trial activity in that cluster. Maintenance and strengthening of that funding pool will be the responsibility of the intervention cluster communities.

### ***Component 2a: cHCP training in home-based maternity surveillance***

We will develop an intervention package that involves the relevant main providers of primary maternal care in the community: LHWs (Pakistan), CHEWs and HAs (Nigeria), ANMs and ASHAs (India), and APess (Mozambique). These health care providers are termed cHCPs for this protocol. A description of the current scopes of practice in maternity care for these cHCPs is provided in Appendix A. In addition, in all countries, PHC-based health workers will be included in formal CPD activities provided in parallel to the CEmOC facilities to which women will be referred (see immediately below).

The cHCPs will be encouraged to identify pregnant women in their area, and will have pregnant women referred to them when identified by the surveillance team during regular surveillance cycles. The regular CLIP visits will occur approximately: 4-weekly during pregnancy until 28 weeks, fortnightly from 28-35 weeks and weekly thereafter, within 24 hours of birth, and on approximately days 3, 7, and 14 after delivery. 4-weekly visits over the course of a pregnancy in women enrolled in the study will be considered a minimum standard for exposure to this aspect of the intervention; anything less than 4-weekly will be recorded as non-compliance with the intervention. These visits are not meant to supplement regular ANC clinical visits, but will be performed in coordination with those existing programs to achieve the frequency as previously described. At each of those visits, the CLIP assessment will place women in one of three care trajectories: (i) usual antenatal care, (ii) non-urgent referral (within 24hr), or (iii) urgent referral (within 4 hr) to a CEmOC facility. Visits may occur in the woman’s home or at the nearest PHC.

The CLIP intervention package (including the oral antihypertensive, MgSO<sub>4</sub> and all relevant safety and

disposal devices) will be provided to the cHCPs in addition to incentives for the increased workload. Relevant incentives (e.g., monetary, gifts, or plaques) will be determined in conjunction with national site investigators.

For cHCP training in Pakistan, the enhanced education module will be developed as an adjunct to the regular LHW training programme; this module will be developed in collaboration with either the Sindh Ministry of Health or national Directorate of Health (depending on which entity has responsibility for the LHW programme after the current devolution to provinces is complete). In Nigeria, India and Mozambique, we will undertake parallel processes in collaboration with our local partners and relevant Ministries of Health.

This enhanced education module will include information about:

1. Understanding pre-eclampsia and eclampsia
2. Overview of the CLIP Trial
3. Basics of effective communication
4. Consent taking procedures
5. CLIP protocols
  - a. CLIP materials
  - b. CLIP visit schedule and protocols
    - i. Counselling of women about:
      1. Warning signs of pre-eclampsia/eclampsia (involving use of pictograms)
      2. Advanced permission to seek care
      3. Transport plan
    - ii. Proteinuria measurement
    - iii. Blood pressure measurement using Microlife AS1-2 device in Mozambique, Pakistan and India and using the Microlife CRADLE VSA in Nigeria
    - iv. SpO<sub>2</sub> measurement using the LGT Medical audio oximeter connected to the mobile phone (Mozambique and Pakistan only)
    - v. Estimating gestational age
    - vi. Assessment of warning signs of pre-eclampsia/eclampsia utilizing pictograms
  - c. CLIP treatment
    - i. Triggers for treatment
    - ii. Administration of methyldopa
    - iii. Administration of MgSO<sub>4</sub>
    - iv. Appropriate referrals, utilizing the referral form
    - v. Recognizing adverse events
    - vi. Triggers for treatment and appropriate medication administration
  - d. Use of PIERS on the Move application
6. Contact Information

We anticipate that CLIP training will take an initial 2-3 days with an extra day for refresher training every six months or as needed.

Training of cHCPs will be evaluated at the initial training session, at each subsequent refresher session and throughout the CLIP Trial. Remedial action will be offered in the case of substandard performance with the evaluation. This evaluation will include pre and post assessment of both competence and self-efficacy on each training objective by means of demonstration of CLIP skills and completion of a survey.

## **2b: Diagnosis & triage – miniPIERS & CLIP POM**

The final miniPIERS cohort used for analysis included 2081 women. The worst clinical values within the first 24hr after admission were used to develop the model. Variables included in the final miniPIERS model are parity (multiparity vs. nulliparity), gestational age on admission (or delivery if assessing a postpartum woman), the symptoms of chest pain and/or dyspnoea, headache and/or visual disturbances, vaginal bleeding with abdominal pain, and right upper quadrant pain; sBP; and dipstick proteinuria. The AUC ROC for this model was 0.6876868 (95% CI 0.37353 – 0.18011) which demonstrates a great ability to discriminate between women with and without adverse maternal outcomes. The stratification capacity of the model is good. Using a predicted probability cut-off of 25% resulted in a positive likelihood ratio of 5.09 [4.12, 6.29] and classified women with 85.0% accuracy, suggesting moderate utility of the model as a rule-in test for adverse maternal outcomes. The CLIP version of the PIERS on the Move tool (CLIP POM) integrates the miniPIERS predictive score and a clinical data collection system into a single application. cHCPs will assess women according to the visit protocol (Appendix D), entering clinical data into the CLIP POM mobile application. The application will provide recommendations for care according to Figure 9 below, as per this protocol. Triggers identified that will indicate treatment and/or transport (urgently, defined as within 4hrs) to a CEmOC facility are as follows:

1. Unconsciousness (MgSO<sub>4</sub> if sBP ≥160 mmHg and gestational age is equal to or greater than 20 weeks (GA≥20 weeks) [to be reasonably sure that the unconsciousness is associated with severe pre-eclampsia and not due to obstetric sepsis], urgent transport)
2. Signs of recent stroke or seizure (methyldopa if sBP ≥160 mmHg [to ensure BP is not lowered too much], MgSO<sub>4</sub> (if GA≥20 weeks) urgent transport)
3. Significant vaginal bleeding (MgSO<sub>4</sub> if sBP ≥140 mmHg and GA≥20 weeks [presumed abruption associated with severe pre-eclampsia] , urgent transport).
4. No fetal movements felt in the previous 12 hrs (urgent transport [a threshold for identifying at risk fetuses that are alive at the time of screening] <sup>39</sup>)
5. sBP ≥160 mmHg (or dBP ≥ 110 mmHg in Nigeria only) (methyldopa, MgSO<sub>4</sub> (if GA≥20 weeks) urgent transport [consistent with severe pre-eclampsia])
6. Heavy proteinuria (≥4+ by dipstick – predictive of stillbirth in miniPIERS cohort, urgent transport)
7. miniPIERS predicted probability ≥25% (MgSO<sub>4</sub> (if GA≥20 weeks)urgent transport)
8. Shock index ≥ 1.7 in Nigeria only (the Shock index is a ratio of pulse/sBP; high shock index is an indication of poor prognosis in women with postpartum haemorrhage)

Non-urgent transport (by non-ambulance services), meaning assessment at a CEmOC facility within 24 hours, will be advised for all women with non-severe hypertension (sBP 140-159 mmHg) who do not meet criteria for one of the above 7/8 triggers.

In Mozambique and Pakistan additional CLIP triggers based on use of the audio oximeter will also be included in the POM decision aid. As with the original miniPIERS model, the enhanced model including SpO<sub>2</sub> uses a risk threshold of ≥25% predicted probability to identify high-risk cases. Recommendations based on the updated miniPIERS model will include treatment with MgSO<sub>4</sub> and urgent referral. An additional independent trigger of SpO<sub>2</sub>≤93% will also be used in Mozambique and Pakistan to indicate urgent referral.

In Nigeria where the updated Microlife CRADLE VSA blood pressure device is being used additional triggers will be included for severe diastolic blood pressure or severe shock index to coincide with the traffic light warning signs included in this device (see Appendix E).

There will be *three models of referral* within the Pilot and Definitive CLIP Trials, depending on the country. In Nigeria and Pakistan, women, their families and communities will be responsible for identifying and paying for transport to the CEmOC facility unless the woman is found in critical condition. In these cases an emergency trial transport fund will be made available to ensure no undue harm comes to women found in critical condition during a CLIP visit. The related fundraising activity will be a focus of the community engagement, particularly in these two countries to ensure in non-urgent situations women can get to care. In Mozambique, women, their families and communities will be responsible for identifying and paying for transport to the nearest PHC, where i.m. MgSO<sub>4</sub> will be administered (if relevant) and where women will be transferred by ambulance (free service provided 24/7) to a CEmOC facility. In Belgaum and Bagalkot Districts, Karnataka, India, there is a functioning ambulance service available free of charge 24/7. Women will be taken from their home or local subcentre (if ANM not available to go to their home) directly to the CEmOC facility.

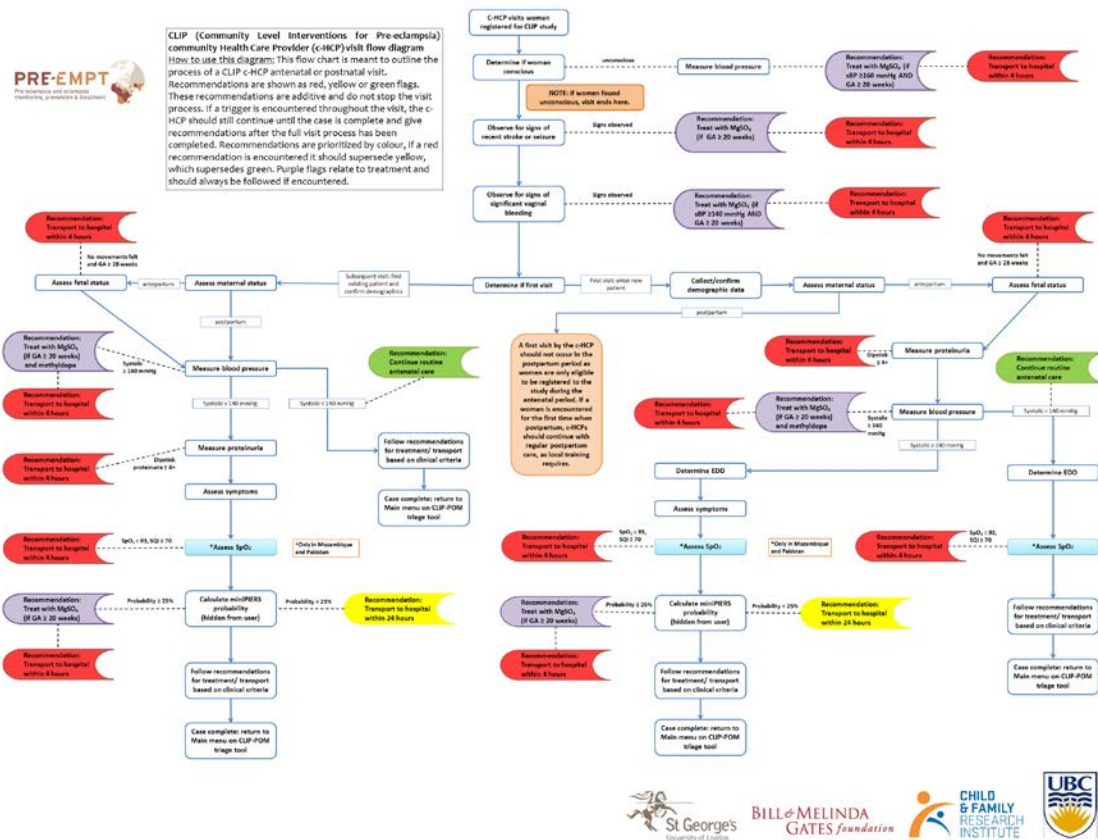


Figure 9 CLIP POM decision model for use in the mobile application for the CLIP trial

## 2c: Lowering severe hypertension – oral methyldopa

In the absence of a clearly preferred oral agent, we have opted for **methyldopa 750mg**. Our rationale is that oral methyldopa has been well-studied in pregnancy hypertension RCTs, and although possibly less effective than some agents<sup>5</sup>, is less likely to cause hypotension<sup>5</sup>, has no common medical contraindications, and can be administered orally<sup>5</sup>. Also, methyldopa is readily available on nearly all LMIC essential medicines lists and it is cheap and acceptable for use by most practitioners [Lalani *et al.* JOGC]. As shown in the decision tree (Figure 9), methyldopa will be administered to women when:

- sBP is  $\geq 160$  mmHg, or dBP  $\geq 110$  mmHg (in Nigeria only)

Women will be given methyldopa if identified as having severe hypertension as defined above regardless of current medication use. This means that any woman encountered in the community who is already taking an antihypertensive should still be given a full dose of methyldopa if severe hypertension is measured.

Women will not receive further methyldopa until they reach a CEmOC facility. As part of facility enhancement, personnel at CEmOC facilities will be educated about how to deal with those women enrolled in CLIP who are transported to facilities. As part of these enhancement activities described below, we will encourage facility staff to provide further antihypertensive therapy if at least 40 minutes has passed and sBP has not started to decrease; if so, clinicians will be advised to wait and monitor BP until the peak effect of methyldopa occurs (between 3 and 6 hr). Otherwise, additional antihypertensive therapy (such as oral nifedipine or i.v. hydralazine) may be administered.

## **2d: Preventing & treating eclampsia – intramuscular MgSO<sub>4</sub>**

MgSO<sub>4</sub> is the treatment of choice to prevent and manage eclampsia in high, middle, and low income countries<sup>3;40-43</sup>. In the International Eclampsia and Magpie Trials, the loading dose was either: (i) 4g i.v. given over 10-15 minutes plus 10g i.m. (followed by i.m. maintenance therapy of 5g i.m. every 4 hr), or (ii) 4g i.v. (followed by i.v. maintenance therapy at the rate of 1g/hr).

We have elected to use only **10g MgSO<sub>4</sub> via the i.m. route**. Our rationale for this is as follows. First, the choice of a 10g loading dose is supported by the WHO (Integrated Management of Pregnancy and Childbirth, 2009), where, in the absence of i.v. access, the expert committee advised loading with only 10g i.m. of MgSO<sub>4</sub><sup>44</sup>. Second, the use of i.v. medication by cHCPS is not feasible and the i.m.-only regimen results in therapeutic serum Mg<sup>2+</sup> concentrations by 45 minutes after i.m. administration<sup>33</sup>. Third, although there are limited RCT data for this regimen, there is substantial regional experience with i.m. loading dose administration in the community (Hall & Theron, personal communications) as well as with 10g total loading dose regimens<sup>45-51</sup>. Professors Hall and Theron have over 10 years' experience with community i.m. MgSO<sub>4</sub> loading in the Cape Flats, Cape Town, South Africa, without apparent maternal harm. In Shahjadpur, Bangladesh, the ICDDR,B community-level (community skilled birth attendants) intervention for women with eclampsia includes a total 10g loading dose (4g i.v. and 6g i.m.) based upon the Dhaka protocol<sup>45;46;52;53</sup>. Currently, in our study areas in India and Pakistan, ANMs and LHWs are administering i.m. dexamethasone within the context of an RCT ([clinicaltrials.gov/ct2/showNCT01084096](http://clinicaltrials.gov/ct2/showNCT01084096) [accessed 28 Jan 2013]) which shows capacity for skill training in this area.

Based on the approach used in the successful Eclampsia and Magpie Trials, we will develop '**pre-eclampsia boxes**' for use by cHCPS. These boxes will include single doses of oral methyldopa (750mg) and i.m. MgSO<sub>4</sub> (10g in two 5g vials of 50% solution), along with all necessary supplies and disposal measures. Women will not receive further MgSO<sub>4</sub> until they reach a CEmOC facility. There, they will receive a further dose according to local protocols. As part of facility enhancement, personnel at CEmOC facilities will be educated about how to deal with those women enrolled in CLIP who are transported to facilities. Through these enhancement activities, described below, we will encourage standardised dosing regimens in line with international guidelines such as 2g i.v. MgSO<sub>4</sub> over 10-15 minutes for recurrent eclampsia (that occurred en route or at facility). Through CPD activities, we will suggest optimal treatment protocols for CLIP women referred to facilities. **Following administration of 10g i.m. of MgSO<sub>4</sub> in the community:**

- Women will not receive further MgSO<sub>4</sub> therapy until they have reached a CEmOC facility
- At the CEmOC facility, these women will receive more MgSO<sub>4</sub> ONLY after at least 4 hr have passed since their initial 10g i.m. MgSO<sub>4</sub> loading dose given in the community.

- If women arrive at the CEmOC facility 4-6hr after receiving a 10g i.m MgSO<sub>4</sub> loading dose in the community, these women should receive MgSO<sub>4</sub> maintenance therapy, consisting of either: (i) 5g i.m. every 4hr, or (ii) 1g/hr i.v.
- If women arrive at the CEmOC facility >6hr after receiving a 10g i.m MgSO<sub>4</sub> loading dose in the community, these women should receive another loading dose of MgSO<sub>4</sub> following by maintenance therapy, as follows: (i) 10g i.m. plus 4 g i.v. loading dose, followed by 5g i.m. every 4 hr as maintenance therapy, or (ii) 4g i.v. loading dose, followed by 1g/hr i.v. maintenance therapy.

### **Component 3: Facility enhancement**

We will undertake enhancement activities at facilities able to provide EmOC, to ensure a minimum standard of care will be provided to all inpatient women in both intervention and control clusters. In addition, although health workers based in PHCs are care providers at the community level, their training and experience mandates that they receive their CLIP-related training within the context of facility-based continuous professional development.

In India and Pakistan, EmOC facilities may be shared by intervention and control clusters, whereas they are distinct in Nigeria and Mozambique.

Facility enhancement activities will be undertaken in collaboration with local and international partners (e.g., MCHIP, RCOG, SOGC). The objectives of facility enhancement are to:

- 1) Provide facilities with **general HDP-related educational resources**, including WHO guidelines on pre-eclampsia and eclampsia<sup>34</sup>, textbooks, and posters.
- 2) Provide health providers with **special clinical training in basic and intermediate care of women with HDP**
  - a. CLIP protocol (including nature of cHCP CLIP visits with respect to counselling provided, tasks performed, and medications administered) and how to appropriately manage these women once they reach a facility
  - b. Warning signs of pre-eclampsia/eclampsia
  - c. BP measurement
  - d. Proteinuria measurement
  - e. miniPIERS assessment on admission
  - f. Management of severe hypertension
  - g. Management of severe pre-eclampsia and eclampsia, including MgSO<sub>4</sub> and timing of delivery
- 3) Enhance health provider **respectful communication skills** with women, their families, and other maternity care providers
- 4) Inform **adverse outcome identification** related to the CLIP intervention. Through this mechanism, we will use facility-level (and, therefore, more accurate) information for all women in the CLIP Trials to assess the accuracy of data collected through the household surveillance approach. This comparative analysis will be important as a validation exercise should the planned difference in adverse outcome rates be achieved.

## **2.3 RISKS TO THE SAFETY OF PARTICIPANTS**

The main risk of the CLIP intervention is that it may lull cHCPs, families, and the women themselves into a false sense of security, thereby delaying the initiation of transport for definitive and life-saving treatment. It is for this reason that the CLIP package of care will include education about appropriate transport to facility,

as well as instructions about how quickly that transport should occur.

For methyldopa safety, we will identify the percentage of women with an 'out of target' BP on admission to facility (i.e., sBP  $\geq$ 160mmHg indicating lack of effect, or sBP  $<$ 110mmHg indicating excessive effect).

MgSO<sub>4</sub> toxicity is not a major concern. Mg<sup>2+</sup> is renally cleared but even if a woman were anuric, one 10g i.m. loading dose of MgSO<sub>4</sub> would not result in serum Mg<sup>2+</sup> concentrations sufficient to cause neuromuscular blockade<sup>54</sup>. However, given that repeat doses would have the capacity to do so, no repeat doses of i.m. MgSO<sub>4</sub> will be given in the community by cHCPs (or at a PHC with only BEmOC capabilities), even if the indication for therapy persists. Practically, we will assess MgSO<sub>4</sub> injection site haematomas, infections and pain using standardised assessment tools in women who received the particular intervention. cHCPs will be trained in proper methods of administration of i.m. injections and all women who receive an injection will be referred to a local facility for follow-up in order to minimize any risks related to these side effects.

## 2.4 METHOD OF RANDOMISATION

### **Clusters**

The unit of randomisation will be defined by criteria relevant to each setting.

In Nigeria, the unit of randomisation will be Local Government Areas (LGAs). Each has a Department of Health headed by a Medical Officer of Health. All villages and PHCs within the LGA will be included in that cluster.

For the pilot phase, we will include four LGAs.

For the definitive phase, we will include 10 (5 intervention and 5 control) clusters in the trial with a public and private sector referral facility in the Ogun area. The four pilot trial clusters will remain in their assigned groups.

In Mozambique, the unit of randomisation is the Administrative Post. All villages and PHCs within the unit of randomisation will be included in that cluster.

There will be no Pilot phase in Mozambique. For definitive phase, we will include 12 (6 intervention and 6 control) clusters in the trial with a public and private sector referral facility in the provinces of Maputo (3 de Fevereiro, Maluana/Maciana, Ilha Josina/Calanga, Magude) and Gaza (Xilembene, Chicumbane, Nhancutse, Chibuto, Macia, Chissano, Mazivila, Messano)..

In Pakistan, the unit of randomisation will be defined by their union council. The villages and PHCs within that union council will be included in the cluster. We will recruit in the catchment area of adjacent union councils of Hyderabad and Matiari, Sindh, Pakistan.

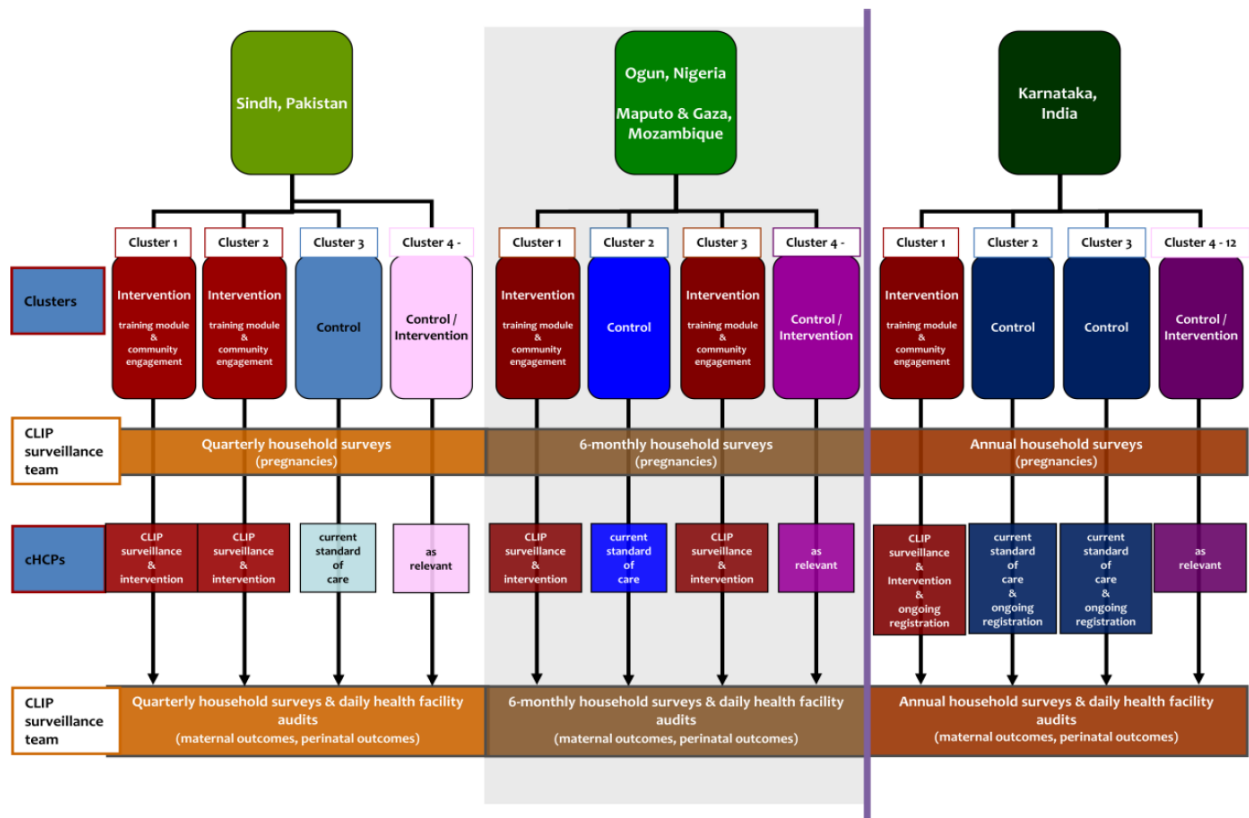
For the pilot phase, we will include four union councils.

For the definitive phase, we will include 20 (10 intervention and 10 control) clusters in the trial with a public and private sector referral facility in the area adjacent to Hyderabad and Matiari (the latter to give patients choice in terms of referral options beyond the rural health centres (RHCs)). The four pilot trial clusters will remain in their assigned groups.

In India, the unit of randomisation will be the PHC. All villages within the PHC catchment area will be included in that cluster.

For the pilot phase, we will include four PHCs.

For the definitive phase, we will include 12 (6 study and 6 control) clusters in the trial with a public and private sector referral facility in the area adjacent to Belgaum and Bagalkot. The four pilot trial clusters will remain in their assigned groups.



**Figure 10 Trial organisation by country and clusters CHCP community health care provider**

To ensure reasonable balance between the two groups, we will use restricted, stratified randomisation to allocate clusters to the intervention and control groups<sup>12</sup>. We will be using only one continuous stratification variable for the randomization of clusters in each country. For all countries this will be Population size. The randomization algorithm ensures adequate balance on the stratification variable over the Intervention arm and the Control arm. Allocations that fail any of the balance criteria will be excluded, and only allocations that meet all criteria are eligible for consideration. The final allocation scheme is a random selection from the list of eligible allocations.

The current algorithm is implemented using R Programming and can consider the following balance criteria:

1. Means ratios: the mean value over intervention clusters and the mean value over control clusters have a ratio no less than 0.9 and no greater than 1.1 (10%).
2. Mean relative to overall mean: the overall mean is the mean over all clusters; mean value in each arm is within 10% of overall mean.
3. Absolute difference in sums: the absolute difference between sums in the two arms is within 10,000.
4. Wilcoxin rank sum: Allocations where the Wilcoxin rank sum test have p-value <0.01 will be excluded.



5. Kolmogorov-smirnov test: Allocations where the Kolmogorov-smirnov test have p-value  $<0.01$  will be excluded.

In the pilot phase of the trial we randomize 4 clusters per country, except Mozambique where no Pilot phase is occurring. When we approach the definitive phase of the trial, these 4 clusters will be included in the randomization algorithm together with the new clusters, and their previous allocations will serve as an additional requirement for the algorithm. The set of eligible allocations will be those that meet the list of balance criteria and the pilot-allocation requirement.

We may or may not use all of the balance criteria listed, and the cut-points listed may be modified. These are common criteria and cut-points used in the literature, but adjustments may be needed if the resulting number of eligible allocations is deemed inadequate.

At the stage of analysis other cluster level factors identified as having an impact on the outcome will be adjusted for, including those used for stratification, such as (i) cHCP density by cluster, (ii) population density, (iii) distance to referral facilities (public or private), (iv) home birth numbers, (v) skilled birth attendant numbers, and (vi) mortality data. Once the decision has been made to proceed to the Definitive Trial phase the population numbers will be re-confirmed for all remaining non-Pilot clusters and the stratification and randomization process will be performed as described above. Clusters participating in the Pilot Trial phase will not be re-randomised for the Definitive Trial phase but will retain their Pilot Trial phase designation of intervention or control.

## 2.5 PROTECTING AGAINST BIAS

We will *not* undertake a hospital level implementation trial, but rather, focus on community-level (i.e., cHCP and PHC) interventions. It is at those levels that the burden of disease-related risk lies. However, informed by the results of the Feasibility Study in each country, we will have determined that, at first level inpatient facilities (BEmOC) and the CEmOC facilities, both: (i) effective antihypertensive therapy is used in  $>80\%$  of women with severe hypertension (sBP  $\geq 160$ mmHg and/or dBP  $\geq 110$ mmHg), and (ii) MgSO<sub>4</sub> is on formulary and used in  $>90\%$  of women with eclampsia. Ensuring a standard and consistent level of care across both intervention and control clusters will reduce any bias that may have existed due to variability in facility based quality of care at study baseline.

### ***Specifying and selecting study clusters***

No cluster will have participated (or be currently participating) in either antenatal intervention trials or community mobilisation.

### ***Execution of the intervention***

#### ***Contamination bias***

Communities in control clusters will not be engaged in any community engagement activities.

cHCPs in control clusters will receive no additional training about pre-eclampsia/eclampsia diagnosis or management, or the CLIP protocol. At present, cHCPs in these jurisdictions do not measure both BP and proteinuria and in Pakistan, they measure neither. cHCPs in control clusters will not be taught how to measure BP or proteinuria because their measurements are components of the miniPIERS risk stratification tool, an important element of the CLIP intervention. cHCPs in control clusters will have access to neither the mHealth tools or the CLIP intervention package.

There is no risk of contamination at the CEmOC facility level as both intervention and control clusters will be engaged in capacity enhancement activities at CEmOC facilities in order to ensure that women who are transported to a CEmOC facility with pre-eclampsia/eclampsia will receive standardised care. This is an important element as it is anticipated that the CLIP intervention will result in more women sent to facility, because of diagnosis and treatment of pre-eclampsia/eclampsia that either: would not have been otherwise made (and could have resulted in death or morbidity that went unrecognised because they did not go to facility), or would have been made at a later stage of their disease (at which point these women would have been transferred to facility). PHC workers in the intervention clusters (not those in control clusters) will be educated within the BEmOC and CEmOC capacity enhancement.

### **Compliance bias**

We will assess cHCP compliance with administration of the intervention using the mHealth technology.

### **Measurement bias**

We will reduce the risk of measurement bias by using measurement tools tested for validity and reliability during the CLIP Feasibility Studies or by others in unrelated studies (Appendix D).

BP measurement will be standardised through use of a standard protocol and an automated measurement device (Microlife BP 3AS-2).

## **2.6 INCLUSION / EXCLUSION CRITERIA**

Participants will be **all consenting pregnant women aged 15-49 (except in Mozambique where reproductive age begins at 12)** identified by the cHCPs assigned to their community. No such pregnant women will be excluded from the analysis which will be by intention-to-treat.

In Nigeria and Mozambique, all women in both control and intervention clusters will give written consent for surveillance (head of household/women of reproductive age) and verbal consent for the secondary visits for the entire CLIP trial. In India, consent will be written. In Pakistan, all women in both control and intervention clusters will give: verbal consent to participate in the quarterly household surveillance, and written consent (personal or proxy [if obtunded]) for administration of the intervention package, if indicated.

## **2.7 PROPOSED DURATION OF TREATMENT**

The **community engagement** aspect of the CLIP intervention will be applied from the time of randomisation of the clusters until completion of recruitment to the Trial.

The **provision of HDP-oriented antenatal care through CLIP visits and use of the CLIP POM tool**, as well as use of the **CLIP package for women with a 'trigger'**, will be applied from the identification of each woman's pregnancy (and her consent to participate in CLIP), through transport to an CEmOC facility (as indicated), and until six weeks postpartum. From the time of diagnosis of a CLIP trigger consistent with pre-eclampsia, women may remain pregnant for an average 10-14 days depending on the gestational age at diagnosis<sup>1</sup>. After diagnosis all women are referred to care at a local facility where they will receive the standard of care in place at that facility. The standard that we will promulgate through our facility enhancement rounds will specify that induction of labour (or semi-elective Caesarean if obstetrically indicated) will be offered routinely to women at or beyond 37<sup>+0</sup> weeks' gestation<sup>55</sup>.

## **2.8 FREQUENCY AND DURATION OF FOLLOW-UP**

Clinically, women will be followed up by cHCPs up to 14 days postpartum. In addition, women will be

followed until 42 days after their delivery by CLIP research staff. In all clusters, this research follow-up will be by means of regular household survey over the 18 months of the trial (i.e., baseline and 9 follow-up surveys) and daily facility audit (as outlined in Figure 10).

## 2.9 OUTCOMES

### • **Pilot CLIP Trials**

The **primary outcome** for the Pilot CLIP Trials will be common for all participating countries, and will be appropriate use of the CLIP package of care (methyldopa and/or MgSO<sub>4</sub> and urgent/non-urgent transport to CEmOC facility) in women with the appropriate CLIP trigger. To justify continuing on with the Definitive CLIP Trial, by 8 months into the 12 month Pilot (with the exception of India where assessment will occur at 6 months), at least 50% of eligible women (i.e., with a trigger) should have received the package of care.

The Pilot CLIP Trials will recruit for 12 months, primarily to field test: application of the CLIP intervention, data collection, and research infrastructure through four quarterly surveillance cycles (in Pakistan).

The **secondary outcomes** for the Pilot CLIP Trials will be the adverse maternal and perinatal outcomes described below for the Definitive CLIP Trials.

The **other outcomes** will be the secondary and other outcomes described below for the Definitive CLIP Trials.

As the primary outcome will change between the Pilot and Definitive CLIP Trials, women recruited to the Pilot Trial will be included in the total sample analysed for the Definitive Trial.

### • **Definitive CLIP Trials**

The **primary outcome** will be a combined maternal and/or perinatal outcome (either maternal, fetal or neonatal death, or severe morbidity for the mother or baby). We have chosen a combined maternal and/or perinatal outcome as powering a trial for maternal death alone would require a prohibitively large sample size.

**Maternal death** (defined as the number of deaths during pregnancy or within 42 days of pregnancy (or last contact day if contact not maintained to 42 days) / 1,000 identified pregnancies), termed Maternal Death Rate. We have not chosen the classical WHO maternal mortality ratio (MMR) definition of events per 100,000 live births because we hope that the CLIP intervention will reduce stillbirth in women with pre-eclampsia. If so, the MMR per 100,000 live births would fall artificially as the proportion of live born infants increased, without any absolute change in the maternal adverse event rates (per pregnancy). We will be basing the number of pregnancies on the household surveys; although the timing of public declaration of pregnancy varies between cultures (first trimester in India and up to 20-24 weeks in Pakistan, Nigeria, and Mozambique), the manner of identifying pregnancies will be similar between control and intervention clusters in each country.

**Maternal morbidity** (defined as the number of women with one or more life-threatening complications of pregnancy during pregnancy or within 42 days of pregnancy or last contact day if contact not maintained to 42 days) / 1,000 identified pregnancies). These are the serious end-organ complications of pre-eclampsia, other major causes of maternal mortality, or life-saving interventions related to one of the aforementioned:

**Serious end-organ complications of pre-eclampsia:**

- *Eclampsia*: occurrence of generalised convulsions during pregnancy, labour or within 42 days of

delivery in the absence of epilepsy or another condition predisposing to convulsions

- *Stroke*: hemiparesis and/or blindness developed during pregnancy or in the 42 days postpartum lasting greater than 48 hours
- *Coma*: prolonged unconsciousness  $\geq 12$  hours
- *Antepartum haemorrhage*: vaginal bleeding  $\geq 15$  mL with or without pain before the onset of labour
- *Disseminated intravascular coagulation (DIC)*: abnormal bleeding from mucosa (mouth and/or ears)

Other major causes of maternal mortality:

- *Obstetric sepsis*: In the community, defined as fever and one of: abdominal/uterine tenderness, foul smelling vaginal discharge/lochia, productive cough and shortness of breath, dysuria or flank pain, headache and neck stiffness. In the facility, defined as presence of fever ( $>38^{\circ}\text{C}$ ), a confirmed or suspected infection (e.g., chorioamnionitis, septic abortion, endometritis, pneumonia) and at least one of the following: heart rate  $>90$ /min, respiratory rate  $>20$ /min, leukopenia (total leukocyte count [TLC]  $<4 \times 10^9$ /L) or leukocytosis (TLC  $>12 \times 10^9$ /L)
- *Vesicovaginal or rectovaginal fistula*: continuous loss of urine and/or faeces after delivery

Life-saving interventions:

- *Cardiopulmonary resuscitation*: a set of emergency procedures including chest compressions and lung ventilation applied in cardiac arrest victims
- *Dialysis*: haemodialysis and/or peritoneal dialysis
- *Mechanical ventilation* (other than for Caesarean section): intubation and ventilation not related to anaesthesia
- *Blood transfusion*:  $\geq 1$  unit
- *Interventions for major postpartum haemorrhage*: brace sutures, external and internal uterine compression, anti-shock garment use, internal iliac artery ligation and/or hysterectomy with or without transfusion

**Perinatal & late neonatal death** (defined as stillbirth [ $\geq 20^{+0}$  and/or  $\geq 500\text{g}$ ], early neonatal mortality [d 0-7 of postnatal life] and late neonatal mortality [d 8-28 of postnatal life] / 1,000 identified pregnancies), or

**Neonatal morbidity** (defined as occurrence of a primary neonatal morbidity<sup>30</sup> during d 0-28 of postnatal life / 1,000 identified pregnancies). The following are the primary neonatal morbidities:

- **Feeding difficulty**
  - Including inability to suckle normally or latch on to the mother's breast to feed even if the mother's milk is not let down
- **Breathing difficulty**
  - Including grunting and in-drawing of the abdomen under the ribs
- **Seizure**
  - Occurrence of any seizure event (fits)
- **Lethargy**
  - Baby not appearing normally wakeful after activities such as feeding or sleeping
- **Coma**
  - Not medically induced period of unconsciousness of any length
- **Hypothermia**

- *Cold to touch*
- ***Umbilical cord infection***
  - *Characterized by discharge from and redness around the umbilical stump*
- ***Skin infection***
  - *Any appearance of abnormally red, black, swollen and blistered skin with pus*
- ***Bleeding***
  - *From anywhere*
- ***Jaundice***
  - *Yellow skin and eyes*
- ***Central nervous system related morbidity***
  - *Abnormal amount of vomiting as defined by the parents or caregiver with bulging or sunken fontanelle*

**Secondary outcomes** for the Definitive CLIP Trials have been defined to measure the impact of the CLIP intervention on the delays around triage and transport. The effect of the CLIP intervention on treatment delays will be determined by the primary outcome and does not need further evaluation as a secondary outcome.

*Birth preparedness and complication readiness* as measured by any three of the following: (1) arranged for transport; (2) obtained prior permission for transport should emergency arise; (3) saved money for obstetric care; (4) identified skilled birth attendant; (5) identified facility for delivery. This will evaluate the success of community engagement.

*Number of women presenting for care at a CEmOC facility and number of facility births*: This number should increase if triage (using the miniPIERS risk stratification and POM) is effective, and if there is compliance with transport to CEmOC facility.

**Other outcomes** will be evaluated such as knowledge of pre-eclampsia/eclampsia among women of reproductive age; total number of seizures; number of pre-admission and post-admission seizures; adverse events; functional disability; and cost-effectiveness of the CLIP intervention. In addition, other outcomes for the perinatal morbidities are neonatal fever, congenital anomaly and birth injury.

*Functional disability for any reason*: Inability to perform usual daily duties at specific points in time during the postpartum period that would be acceptable and expected culturally (we are determining these normal limits through local focus group discussions; these will be defined for each country prior to the commencement of each Pilot CLIP Trial)

## 2.10 MEASURING THE OUTCOME MEASURES AT FOLLOW UP

In total, 54 village and urban clusters will be identified and randomised in the four countries (Nigeria: 10; Mozambique: 12; Pakistan: 20; India: 12). Each cluster will contain a health unit or regional health centre which has provided the training base for the corresponding cHCPs. Subsequently, the 27 clusters chosen to receive the intervention will be analysed against 27 control clusters.

A **baseline household and facility survey** is being carried out within the context of the CLIP Feasibility Study in all trial clusters to assess their socioeconomic characteristics and baseline maternal, perinatal, and neonatal mortality rates. In all countries except India this will be performed based on retrospective information on pregnancies occurring in the previous year. In India, the baseline data will draw from the

existing prospective Maternal and Neonatal Health Registry (MNH Registry). In Nigeria, due to the large cluster populations we will perform baseline surveillance on a random sample of households while in all other countries all households will be surveyed. This addresses the human resource constraints identified in Nigeria during the CLIP Feasibility study.

Subsequent **cross-sectional surveys of all households** will be conducted at varying frequency depending on current registration and surveillance activities in the relevant country: quarterly (Pakistan), 6-monthly (Nigeria and Mozambique), while in India, household surveys will continue prospectively using the MNH Registry. Although the cHCPs will routinely record information on maternal/perinatal births and deaths, the cross-sectional surveys will be conducted by a separate team to collect data on births, deaths, and care-seeking behaviour in the preceding study epoch. In Nigeria, due to population sizes and human resource constraints the cross-sectional surveys will focus on collection of maternal/perinatal mortality and morbidity for all households and a random sample of these households will receive a more in-depth survey including questions around birth preparedness, care-seeking and pre-eclampsia knowledge. The cross-sectional surveys will be considered the gold standard for the Trial as they will be applied equally between control and intervention clusters.

These surveys will permit us to accrue outcome data about women who had a CLIP primary outcome but who did not seek care at a CEmOC facility. These data will be necessary for us to understand fully the impact of the CLIP intervention on mothers and babies. It is our hope that the CLIP intervention will cause women from the intervention clusters to be treated earlier in the course of their disease and, as a result, have less complicated clinical courses and lower rates of severe morbidity. As such, fewer women may die unknown to the formal health care system but more such women may be referred to the PHC and both BEmOC and CEmOC hospital levels. If that referral occurs in a timely fashion, then it is our hope that women will receive more timely, evidence-based, care (given facility enhancement). As such, it is hoped that overall, maternal and perinatal mortality and morbidity will be decreased. However, it is plausible that despite identification, triage, community treatment, and transport of women with a CLIP trigger, and despite EmOC facility enhancement about pre-eclampsia/eclampsia care, the number of inpatient pre-eclampsia-related maternal and perinatal deaths may rise if women and/or fetuses who previously would have died in their community might now reach hospital moribund and beyond help.

Information on referrals will be collected from the cHCPs and community health committees by the surveillance teams. Surveillance teams will carry out **verbal and social autopsies of maternal deaths, stillbirths, neonatal deaths**, and similarly constructed reviews of maternal and neonatal morbidity.

In the event of significant barriers to application of the CLIP package or unforeseen events, focus group discussions and/or in-depth interviews and/or surveys will be conducted to better understand relevant barriers or events, in an effort to remedy the situation. Case analysis may also be employed on a select number of maternal or perinatal morbidities or mortalities to uncover greater detail of context of the outcome.

A final aspect of follow-up will be **facility-based chart audit** of pregnant women admitted to CEmOC facilities in both intervention and control clusters, throughout the Trial will occur in all but India where the MNH registry system already incorporates a facility chart review for each registered woman. This will allow for triangulation of mortality and morbidity data collected through the the cHCPs and cross-sectional household surveys.

### **Data collection using mHealth technology**

We will develop three mHealth applications to support the CLIP trial. The first will be used in all countries and the second and third will be used in Nigeria, Mozambique and Pakistan during the definitive trial phase.

The first application will be mobile phone-based while the other two will use a tablet-based device.

For intervention clusters only, the first mHealth application is the CLIP POM (described in detail, previously). This will be used to collect routine antenatal visit data and miniPIERS variables. These data will be entered into an integrated decision guide to give real-time advice to cHCPs in terms of appropriate patient management and decisions for interventions (e.g., appropriateness and timing of transport to CEmOC facility, and community initiation of antihypertensive and MgSO<sub>4</sub> therapy, as discussed above). Women will be identified both by demographics information and by unique surveillance IDs to enhance identification through the system.

For both intervention and control clusters, the second mHealth application will be a tablet device used by the field team for routine data collection during household surveys (see above). In this way, survey data will be automatically synchronised with a centralised data warehouse, and collected efficiently (given no double handling of paper forms and efficient enforcement of complete data entry). GPS co-ordinates will be provided in real-time to confirm the place and time of each survey event.

For both intervention and control clusters, the third mHealth application will be a tablet device used by an independent team of skilled interviewers who will conduct a detailed verbal and social autopsy / morbidity review when the quarterly surveys reveal the occurrence of an adverse maternal and/or perinatal event (death or major morbidity). The application will be adapted from that developed by the WHO.

Each CLIP site will participate in the design and development of mHealth tools and will conduct usability testing of the final application prototypes before the trial begins in order to ensure acceptability and usability of the tools by users (cHCPs and surveillance teams). Post-trial evaluation of health worker and stakeholder perspectives on the acceptability and usability of the mHealth tools will be performed.

Data on individual women entered into all mHealth applications will be linked using a unique identifier code. This code will be provided to each woman after they consent for the trial on a study ID card. The key for these unique identifiers will be developed after the baseline survey by the Data Manager in each country and will not be shared with the Trial Coordinating Centre at UBC, ensuring privacy and confidentiality of the women is maintained at all times.

Patient data security is at all times of utmost importance, and will thus be maintained throughout mHealth system operations.

- Valid usernames and passwords will be used to limit unauthorized access to device data as well as access to the database and central document archives. The relevant password rules and encryption protocols will be applied.
- Encryption of data is required for any form of storage or transmission between devices and systems.
- Data validation will be performed at every stage of data input as well as on all data access requests to minimize false scripting.

In addition, all safety regulations pertaining to medical diagnostic and monitoring tools will be upheld. Any interfaces between patient, device and user will have the necessary protection systems to ensure the safety of the patient and operator.

## 2.11 SAMPLE SIZE CALCULATIONS

Each country is independently powered to assess the chosen primary outcome. The data upon which the estimates have been made are routinely at the conservative end of the published or available range, and were generally provided by the site investigators. However, these calculations will be revisited once the CLIP Feasibility Study maternal and perinatal morbidity and mortality data are in hand. We have planned an individual patient data (IPD) meta-analysis at the completion of each of the individual country trials to

ensure adequate power for an analysis of maternal mortality and morbidity.

**Table 3** Sample size calculations (Mozambique to be determined)

Country	Nigeria	Mozambique	Pakistan	India
Unit of randomization	LGA	AP	Union Council	PHC
Population per unit of randomization	70,000	25,000	32,000	27,000
Annual birth rate (/1000/yr)	16	40	14	22
Births/2yr	2240	2000	900	1200
MMR (/100,000 live births)	800	388	267	150
Intra-cluster co-efficient	0.006 <sup>†</sup>	0.002 <sup>‡</sup>	0.002*	0.001**
Incidence of maternal & perinatal/neonatal M&M				
control clusters	28.8%	14.0%	9.6%	5.4%
intervention clusters	23.0%	11.1%	7.7%	4.3%
Number of clusters (total)	10	12	20	12
Number of births in Definitive CLIP Trial (2 years)	22,400	24,405	18,000	13,000
Additional births from Pilot CLIP Trial (4 clusters/1 year)	4480	n/a	1800	2400
Total number of births (Pilot & Definitive Trials)	26,880	24,405	19,800	19,200
Expected referrals at month 6 of Pilot Trial assuming 5% incidence of HDP	112 [92, 132]	100 [81, 119]	45 [32, 58]	60 [45, 75]
Number of women to be referred at month 6 of Pilot Trial to meet 50% use target	56	50	23	30
Number of health facilities (total)				
PHC/RHC	120	44	42	22
EmOC	10	10		22
Number of cHCPs (total)	250 CHEWs & 45 HAs	170	400 LHWs	60 ANMs & 360 ASHAs

ANM: assistant nurse midwife; AM: Administrative Posts; ASHA: accredited social health activist; CHEW: community health extension worker; cHCPs: community health care providers; CHW: community health worker; EmOC, emergency obstetric care; LGA: Local Government Area; LHW: Lady Health Worker; M&M: morbidity and mortality; MMR: maternal mortality ratio; PHC: Primary Health Centre; RHC, rural health centre.

\* calculated from Sindhi miniPIERS facility data. <sup>†</sup> assumes 3-fold increase in ICC over Sindh; <sup>‡</sup> assumes same ICC as Sindh (urban population in Maputo); \*\* assumes half the ICC of Sindh. In these calculations, we have used risks at the lower end of the published ranges for that risk and milieu.

#### Assumptions

- 10% loss of individual women to follow-up
- no loss of clusters to follow-up
- alpha of 0.05, power  $\geq 0.80$
- anticipated effect size of a 20% reduction in all cause maternal and perinatal/neonatal morbidity and mortality
- Also, we have assumed a ratio of maternal morbidity : mortality of 5:1 (may be as high as 10:1), and a ratio of perinatal/neonatal : maternal events of 5:1 (may be as high as 10:1 – permits overlap in outcomes)
- All sample sizes will be supplemented by the data collected in each single country Pilot CLIP Trial.

The combined Definitive CLIP Trials cohort of 878787,480 deliveries in 56 clusters over 2 years (+16 cluster years in Pilot CLIP Trial), averaging 1376 deliveries per cluster per year, will provide the following power for the IPD meta-analysis:

*Maternal & perinatal/neonatal mortality & morbidity*: assuming a 20% effect size (incidence reduced from 15.6% to 12.4%), we would have 80% power with an ICC of 0.015.

*Maternal mortality & morbidity* (primary outcome for the IPD meta-analysis): assuming a 20% effect size (incidence reduced from 2.6% to 2.1%), we would have 80% power with an ICC of 0.001.



Alternatively, assuming a 30% effect size (incidence reduced from 2.6% to 1.8%), we would have 80% power with an ICC of 0.004. We hope to reduce the adverse maternal event rate by  $\geq 30\%$ , primarily through community mobilisation and antenatal care by cHCPs.

Finally, we will pool adjusted results for the individual CLIP Trials using the generic inverse variance method developed by the Cochrane Collaboration.

This sample size will be supplemented by the women recruited during the pilot phase (primary outcome: package utilisation), who will be 'recycled' into the Definitive Trial phase.

## 2.12 RECRUITMENT RATE

Given the populations in these centres and the fertility rates in these communities, we are confident that the sample size will be achieved in a 24 month period (see section 2.11, above) and the Trials will complete recruitment by March 2017. We will pilot the use of *contact tools* to maintain contact, with quarterly contact maintenance rate reports (e.g., birthday cards and newsletters). Thus, we will maintain a group of mothers and children available for piloting further assessment of the impact of the CLIP intervention at school age (funding for follow-up studies will be sought).

## 2.13 COMPLIANCE WITH THE CLIP INTERVENTION

Through the trial, we will measure **compliance with community mobilisation** in terms of the number of community meetings held around pre-eclampsia/eclampsia content, prior permission to seek care, and/or community transport plans/funds.

Throughout the trial period, we will measure **compliance with the CLIP visits, use of the POM tool, and use of the CLIP package for women with a CLIP trigger** based on the following criteria: (i) appropriate frequency of CLIP visits by the cHCP (i.e.,  $4 \pm 2$  weeks); (ii) N (%) of women who had a CLIP trigger and who were administered treatment as indicated (methyldopa and/or  $\text{MgSO}_4$ ); (iii) N (%) of women who had a CLIP trigger and were referred for transport as appropriate, and (iv) N (%) of women who were seen at an CEmOC facility within the appropriate period of time after referral advice given (i.e., 4hr for urgent transport or 24hr for non-urgent transport).

We have assumed a non-compliance rate in appropriate use of the intervention package of 10% in our power calculation. The primary reason for this will be lack of confidence by the cHCP in administering the intervention. We believe this to be a probable overestimate given the existing experience in Sindh where compliance with more technically challenging protocols exceeded 90%.

## 2.14 LOSS TO FOLLOW-UP

We have assumed a 10% loss to follow-up in our power calculations. The primary reason for this will be women leaving the marital home in one community for their childhood home in another community for labour and delivery.

## 2.15 TYPES OF ANALYSES/STATISTICAL PLAN

Note that this is an intent-to-treat analysis; all analyses will include all patients randomised. A detail of analysis plan is included in the CLIP cRCT Statistical Analysis Plan.

### **Trial information and patient disposition**

The following information will be presented:

- Number of patients randomised
- Number of patients completing each visit of follow-up
- Median follow-up time
- Frequency table for the reasons for going off-study
- Frequency table for loss to follow-up

### **Baseline and demographic variables**

Summary statistics such as the mean, median, standard deviation, minimum, maximum and inter-quartile range for continuous variables and the number and percentage of patients with various levels of categorical variables will be calculated for *all subjects randomised within each treatment group for each country* for variables such as:

- Demographics: maternal age, parity, gestational age at diagnosis, distance from facility
- Socioeconomic status (measured by poverty index), level of education
- Cluster level variables: cHCP density, population density
- Interventions: number of antenatal visits, type of care provider, route of birth, medications given

All summary statistics will be calculated for each treatment group individually as well as for all treatment groups combined.

### **Primary outcome**

The primary outcome is the proportion of pregnancies resulting in at least one of maternal death, stillbirth, neonatal death, or severe morbidity in the mother or child.

#### **Primary analysis**

A hierarchical regression model will be used to take into account the clustering of women within the units of randomisation. The model will take into account key determinants of outcome, as defined by the investigators, at both the individual and cluster level.

#### **Sensitivity analyses**

We will use multiple imputation to account for those lost to follow-up and examine whether this has any impact on the between-group comparisons.

### **Secondary outcome**

Similar methods will be applied to the individual components of the primary outcome. In addition, the proportion of women achieving birth preparedness and complication readiness will be compared as will be the proportion of women presenting for care at an EmONC facility, and the proportion of facility births.

### **Other outcomes**

Knowledge of pre-eclampsia and eclampsia; total number of seizures or number of pre-admission and post-admission seizures and cost-effectiveness of the intervention.

### **Safety data**

**Adverse events** will be tracked in intervention and control clusters related to:

- **Methyldopa** administration in the community: relative maternal hypotension on arrival at facility (defined as sBP < 110 mmHg)
- **MgSO<sub>4</sub>** administration in the community: either respiratory depression, coma or death during transport, as diagnosed upon arrival at facility

- **Transport:** Transport-related injury (life or limb) or death during transport
- injection site haematoma or infection (following either community or facility administration of i.m. MgSO<sub>4</sub>)
- ≥ 20% of women referred to facility being sent back to their communities without follow-up (monitoring community engagement and the CLIP POM).
- The following will be presented by treatment group: number of adverse events (overall and by type), number of women with one or more adverse event(s) (overall and by type).

## **Additional methodological details**

### ***Statistical tests***

All statistical tests will be two-sided, with significance levels of 0.05. Comparisons will be by means of risk ratios and mean differences with 95% confidence intervals for each site.

### ***Software to be used***

SAS / R / S-plus.

### ***Individual patient data meta-analysis (IPD)***

Each country will be analysed separately, with a planned IPD meta-analysis (conducted at UBC) after the completion of all four trials. For the IPD meta-analysis, we will analyse data for women recruited at ≥20 weeks, to standardise data to the latest public declaration of pregnancy (i.e., 20 weeks in Pakistan).

### ***Economic analyses***

An economic evaluation of the intervention and its impact will be performed alongside the trial from a societal perspective (accounting for both costs to health care system and families) to guide health services decision-making for post-trial programme scale-up in the selected countries. The cost to the health care system will comprise both direct and in-direct cost of patient care borne by health system, cost of the CLIP package of interventions, and follow-up household visits by cHCP. The cost to the families of pregnant women will comprise out-of-pocket expenses for patient care, transport, and cost of lost productivity resulting from morbidity or mortality of patients with or without paid jobs. The information about individual level resource/service utilization will be prospectively collected alongside the trial; whereas, secondary data sources (i.e., budgetary reviews) will be utilized to estimate the unit cost for each resource/service utilized in both intervention and control clusters. Besides, the qualitative focus group sessions will be conducted with women identified at risk of HDP, their husbands, community level health care providers, referral health facility care providers and district level health decision/policy makers to inform the design of cost modeling and interpret cost-benefit from community perspectives. (Full details of this plan are provided in Appendix F).

Economic analysis will be performed to calculate incremental cost-effectiveness ratio (ICERs) to compare the cost per unit maternal deaths/adverse pregnancy outcomes averted when switching from standard care to the CLIP package of interventions. Given the uncertainties involved in calculating the costs and trial outcomes, we will use simplistic sensitivity analysis to plot cost-effectiveness ratios. The confidence region surrounding the cost-effectiveness ratio will be estimated using appropriate statistical methods, including bootstrap and Monte-Carlo analyses. The qualitative data will be analyzed using QSR NVivo v10 software, and responses will be coded to form similar categories. Thematic analyses will be performed to underscore trial implementation challenges, perceptions of cost-benefit, strategies for knowledge translation and policy advocacy to be able to interpret the economic impact from societal perspective.

### ***Geo-temporal analyses***

We will develop and test a location sensitive maternal health risk index (development funded by CIHR). This index will chart risk for adverse maternal outcomes across multiple communities with different geographic characteristics. We will use Geographical Information Systems to identify ‘resilient’ communities and individuals and then link environmental correlates related to maternal health with pockets of resilience. Likewise, we will use environmental correlates and outcome data to identify areas and individuals who have poorer than expected outcomes. We will use the data collected in different communities over time to create temporally dynamic map products that chart environmental correlates in relation to shifting maternal morbidity and mortality.

Geospatial analysis will be conducted in each country by an individual from the PRE-EMPT Vancouver team with help from local GIS experts. This analysis will entail using the GPS tagged survey record to chart trends in maternal mortality and morbidity while cross referencing these outcomes to aspects of the built environment like transport and access to health care. Prior to this analysis, all personal identifiers would have been removed from the data. The data will be aggregated to describe frequencies for each of the captured variables at village level. This second set of aggregate data will be then be further analysed at UBC.

### ***Qualitative analyses***

We will use survey tools, FGDs and IDIs to explore feasibility and acceptability of use of the blood pressure device in CLIP in collaboration with the CRADLE study team. Full details of this plan are provided in Appendix E. In addition, a cross-sectional survey of cHCPs and physicians along with interviews of randomly selected women enrolled in the CLIP study and their families will be completed to understand the impact of the CLIP intervention package on cHCP decision making confidence.

A similar mixed methods approach will be utilized to evaluate the usability and acceptability of the PIERS on the Move tool and to explore the impact of use of the mobile tool on health worker knowledge, self-efficacy and role within the health system, from their perspectives.

Furthermore, to enhance the understanding of the health policy environment, we aim to undertake a policy analysis to evaluate whether the national policies in the state of Ogun, Nigeria respond to the needs of postpartum women i.e. how they address any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman’s wellbeing following childbirth. Further details about this policy analyses can be seen in Appendix G.

## **2.16 FREQUENCY OF ANALYSES**

An interim analysis is planned for each of the three countries once complete data (until 42 days postpartum) has been received for women making up half of the planned sample size for that country. In the event that the site is unable to reach planned sample size, due to logistical and pragmatic challenges, then the interim analysis will be conducted once complete pregnancies (until 42 days postpartum) are expected for women making up half of the projected sample size for that country.

The stopping rule for both benefit and harm will require an observed difference between groups associated with an alpha <0.001 (power: 80%). Reporting and handling of adverse events will be in accordance with Good Clinical Practice (GCP) guidelines.

A single economic analysis will be performed.

## **2.17 SUBGROUP ANALYSES**

We will analyse the interventions and outcomes by country and locality (i.e., Ogun State, Maputo and Gaza Provinces, Sindh Province, and Karnataka State).

## SECTION 3 TRIAL MANAGEMENT

### 3.1 PRE-RECRUITMENT PHASE

Currently, we are conducting the CLIP Feasibility Study in the relevant Nigerian, Mozambican, Pakistani, and Indian sites. We will finalize a tailored intervention that will be culturally sensitive, effective at reducing barriers, and increase enthusiasm for the CLIP package amongst decision makers through respectful dialogue with professional associations and government decision makers.

An educational package will be developed, and the cHCPs, midwives and physicians working in the intervention clusters will be trained.

Having spent the first 30 months of the PRE-EMPT grant completing the PIERS modelling, trial design and registration, feasibility and barriers assessment, cHCP, nurse, midwife and physician training, and ethics and contracts processes, we will commence recruiting to the trial after July 2013.

### 3.2 DATA SAFETY AND MONITORING BOARD

The *DSMB* will be created, including methodological and content expertise.

The role of DSMB will be to deal with any ethical issues that may arise while the trial is in progress and to decide either benefit or harm at the planned interim analyses. SAEs will be reported to the DSMB as outlined below. SAEs should be: **(i) serious, (ii) unexpected (in nature, severity, or frequency), and (iii) thought to be related to the study intervention.** This plan reflects the expected nature of the other AE, which are events of note but that do not necessitate stoppage of the trial due to safety concerns prior to the interim analysis.

#### **SAE reporting**

When all required information has been gathered in the reporting field site, the field site supervisor will forward 'blocked' copies (without patient, site or allocated intervention group identifiers) of all documentation and an updated 'Serious Adverse Event Form' to the National CLIP Trial Co-ordinating Centre. That centre will assess whether or not: (i) additional information is required, and (ii) the National Principal Investigator and Co-ordinator should be informed immediately, or at the next scheduled meeting. *The documents to be reviewed are: (i) all data forms (including those derived from the POM tool) for each woman with a reported primary outcome (for mother or baby), masked to the cluster allocation, and (ii) copies of the relevant facility documents (if applicable) that serve as the 'source documents' and detail the outcome for the woman/baby. If the outcome were reported in the community with no associated facility admission, then the data forms should be reviewed for consistency and to ensure that the woman's story make sense from a clinical perspective.*

After review (and collection of additional information, as applicable) of a reported SAE by the relevant National CLIP PI and National CLIP Trial Co-ordinating Centre, the 'blocked' documentation (including the SAE Form and summary of the case) **should be reviewed by the in-country National Outcomes Adjudication Committee. That Committee will decide whether or not the reported SAE is a true SAE or a pre-specified Trial outcome. Then,** the 'blocked' documentation (including the SAE Form and summary of the case) and the Committee's opinion should be sent to the UBC Trial Co-ordinating Centre (TCC) for review by the UBC Outcomes Adjudication Committee; if UBC agrees that the reported SAE is a true SAE, UBC will send the report to the DSMB for urgent review. However, if UBC agrees that the reported SAE is a pre-specified Trial outcome, then the report will be sent to the DSMB at the time of the next analysis.

The UBC Outcomes Adjudication Committee decision will be reviewed by the CLIP Trial Steering Committee (SC) at the next scheduled quarterly teleconference, or earlier if the UBC Outcomes Adjudication Committee feels that this is appropriate. Possible reasons for urgent review by the SC are

because the reported SAE (i) is not a pre-specified trial outcome (i.e. it is deemed to be a true SAE), or because (ii) is a pre-specified trial outcome but the UBC Outcomes Adjudication Committee has further concerns. After review of the SAE by these groups, the UBC TCC will generate and distribute a summary report of the Serious Unexpected Event(s) to be reported and reviewed by the DSMB at the time of the interim analyses, or earlier if either the UBC Outcomes Adjudication Committee and/or SC have additional concerns.

The summary report should include the ‘Serious Unexpected Event Form’ received from the site, and a typed summary of all accumulated supporting documentation for each reported event. Ensure all patient, site or allocated intervention group identifiers have been removed. The DSMB can then request further information if they wish to take a closer look at any particular event.

For reported events ruled by the Outcomes Adjudication Committee to be pre-specified trial outcomes (and NOT true SAEs), the UBC TCC will: (i) communicate with the reporting site to let them know about the outcome of the evaluation of their reported Serious Unexpected Event by the UBC Outcomes Adjudication Committee; (ii) inform them that the reported event will also be reviewed by the SC and included in a summary report made to the DSMB at the time of the next scheduled analysis (after DSMB review, a written summary of all reported Serious Unexpected Events, and the DSMB’s ultimate assessment of these events, will be distributed to their site (and all sites)); and (iii) invite the site to inform the TCC if they have any concerns.

For reported events ruled by the UBC Outcomes Adjudication Committee and SC to be true SAEs, UBC TCC will: (i) communicate with the reporting site to let them know about the outcome of the evaluation of their reported Serious Unexpected Event by the UBC Outcomes Adjudication Committee and Steering Committee; (ii) inform them that the reported event will also be included in a summary report made to the DSMB (either immediately or at the time of the next scheduled analysis, as decided by the Steering Committee) (after DSMB review, a written summary of all reported Serious Unexpected Events, and the DSMB’s ultimate assessment of these events, will be distributed to their site (and all sites)); and (iii) invite the site to inform the UBC TCC if they have any concerns.

For all reported events, following review by the DSMB, the Principal Investigator will prepare a written summary of the reported Serious Unexpected Event(s), and the DSMB’s assessment of these event(s). If the event(s) is (are) deemed to be a true SAE, the anonymised SAE Report Form(s) will also be attached. This report will be submitted to: (i) UBC REB. As the Clinical and Data Co-ordinating Centre, UBC will inform the UBC REB of all reported Serious Unexpected Events; (ii) the study sponsor, BMGF, will be informed through the routine monthly/alternate monthly dialogue; and (iii) all Site Investigators, including the reporting Investigator. Each Site Investigator will be responsible for reviewing this Serious Unexpected Event summary report and forwarding it to their local REB. It will be recommended that each Site Investigator check with their local REB for other local reporting requirements.

Membership of the DSMB is:

- **Professor Eileen Hutton (Chair)**

Associate Professor, Department of Obstetrics and Gynaecology, Assistant Dean, Faculty Health Sciences, and Director, Midwifery Education Program, McMaster University, Hamilton, ON, Canada

[http://fhs.mcmaster.ca/ceb/faculty\\_member\\_hutton.htm](http://fhs.mcmaster.ca/ceb/faculty_member_hutton.htm).

- **Lehana Thabane**

Professor and Associate Chair, Department of Clinical Epidemiology & Biostatistics, Director, Biostatistics Unit, Centre for Evaluation of Medicine, and Senior Scientist, Population Health Research Institute (PHRI), Hamilton Health Sciences, McMaster University  
([http://fhs.mcmaster.ca/ceb/faculty\\_member\\_thabane.htm](http://fhs.mcmaster.ca/ceb/faculty_member_thabane.htm)).

- **Romano Byaruhanga**

Consultant Obstetrician, Nsambya, Uganda and President of the Association of Obstetricians and Gynaecologists of Uganda.  
(<http://www.sogc.org/aogu/index.aspx?contentID=41>).

- **Mario Merialdi**

Senior Director, Maternal and Newborn Health, Global Health, Becton, Dickinson and Company

- **Brian A. Darlow**

CureKids Professor of Paediatric Research, University of Otago Christchurch, PO Box 4345 Christchurch 8140, New Zealand  
(<http://www.otago.ac.nz/healthsciences/expertise/profile/index.html?id=229>)

### 3.3 OUTCOME ADJUDICATION COMMITTEE

Each country will perform a masked review of all occurrences of the primary outcome that is embedded in the data collection process; the national team will review outcomes where there is uncertainty. *The National Outcomes Adjudication Committee will consist of an uneven number of members of the national CLIP Team, including but not limited to one obstetrician, one paediatrician, and one methodologist/trialist.* The UBC management team will provide final arbitration if required.

### 3.4 TRIAL REGISTRATION

The CLIP Trial has been registered with [clinicaltrials.gov](http://clinicaltrials.gov) (ID NCT01911494).

### 3.5 GENERAL ASSUMPTIONS

We assume that the results of the CLIP Feasibility Studies being conducted in Nigeria, Mozambique, Pakistan, and India will inform some of the details of the CLIP trial, including costs. Therefore, each Pilot CLIP Trial will not be started until the relevant CLIP Feasibility Study is completed.

We have assumed that the clinical and data co-ordinating centre will be located at UBC, Vancouver, where the statistical analyses will also be performed. We do not anticipate any delays related to gaining IRB approval for this intervention.

For the CLIP Feasibility Studies, we have received firm stakeholder support and involvement at the ministerial level of health care in the identified countries. We assume that each of the three stages of the relevant CLIP Feasibility Study will be completed according to the specified timelines and budget. In addition, we have assumed the established pattern of community level cRCTs in Nigeria, Mozambique, Pakistan, and India will support the CLIP Trial, including cHCP-based BP control.

It is our intention that the results of the household surveys and registries will provide a replete community-



level dataset for each participating centre. These datasets will span not only HDP-related deaths and morbidities, but also the other leading causes of maternal mortality (obstetric haemorrhage, obstructed labour, and puerperal sepsis), and will be invaluable resources for local communities, local investigators, demographers, and scientists. Whatever the results of the CLIP Trial, the data will be novel and important and we anticipate the acceptance of resulting paper(s) for publication. We have assumed that no natural or human-caused disaster will occur to curtail our work.

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**Table 4** CLIP interventions

Level of care/foci	Care component
<b>cHCPs</b>	
<b>Triage</b>	<ul style="list-style-type: none"> <li>◇ Community education: symptoms, signs, &amp; consequences of pre-eclampsia</li> <li>◇ Community engagement &amp; mobilization: transport funds; prior permissions from proxy decision-makers; health system managers &amp; funders</li> <li>◇ Menstrual calendars to be held by married women of reproductive age (South Asia) or all women of reproductive age (Africa)</li> <li>◇ Urine dipstick at first antenatal encounter</li> <li>◇ Symphysis-fundal height at first antenatal encounter <math>\geq 24^{+0}</math> weeks to assess GA if unknown</li> <li>◇ Ongoing antenatal surveillance (BP [&amp; urine dipsticks, if indicated] as described in the protocol)</li> <li>◇ Opportunistic screening &amp; triage of symptomatic women</li> <li>◇ Diagnostic &amp; triage tool (miniPIERS)</li> <li>◇ PIERS on the Move decision aid Android application</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>◇ 750mg <math>\alpha</math>-methyl dopa p.o. for severe hypertension (sBP <math>\geq 160</math>mmHg); single dose only)</li> <li>◇ 10g MgSO<sub>4</sub> IM loading dose (single dose only) for women with stroke, eclampsia (single or recurrent seizures), vaginal bleeding (presumed severe pre-eclampsia), severe hypertension (presumed severe pre-eclampsia), or a miniPIERS probability <math>\geq 25\%</math></li> </ul>
<b>Transport</b>	<ul style="list-style-type: none"> <li>◇ Arrangements made for patient transfer to nearest referral centre               <ul style="list-style-type: none"> <li>○ High risk: within 4h</li> <li>○ Low risk: within 24h</li> </ul> </li> <li>◇ Discussion with referral centre</li> <li>◇ Patient transferred</li> </ul>
<b>Primary health centre</b>	
<b>Triage</b>	<ul style="list-style-type: none"> <li>◇ Menstrual calendars to be held by married women of reproductive age (South Asia) or all women of reproductive age (Africa)</li> <li>◇ Symphysis-fundal height at first antenatal encounter <math>\geq 24^{+0}</math> weeks to assess GA</li> <li>◇ Ongoing antenatal surveillance (BP and urine dipsticks every 4 weeks)</li> <li>◇ Opportunistic screening &amp; triage of symptomatic women</li> <li>◇ Diagnostic &amp; triage tool (miniPIERS)</li> <li>◇ PIERS on the Move decision aid Android application</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>◇ 750mg <math>\alpha</math>-methyl dopa p.o. for severe hypertension (sBP <math>\geq 160</math>mmHg); single dose only (not repeated if already administered by cHCP in community)</li> <li>◇ 10g MgSO<sub>4</sub> IM loading dose (single dose ONLY if not already administered by cHCP; no repeat dosing) for women with stroke, eclampsia (single or recurrent seizures), vaginal bleeding (presumed severe pre-eclampsia), severe hypertension (presumed severe pre-eclampsia), or a miniPIERS probability <math>\geq 25\%</math></li> </ul>
<b>Transport</b>	<ul style="list-style-type: none"> <li>◇ Arrangements made for patient transfer to nearest EmOC facility</li> <li>◇ Patient transferred</li> </ul>
<b>Hospital providing CEEmOC– unfunded by CLIP but expected standard of care (supported by planned facility enhancement)</b>	
<b>Triage</b>	<ul style="list-style-type: none"> <li>◇ Triage tool (miniPIERS and/or fullPIERS)</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>◇ 200mg labetalol p.o. or 10mg nifedipine p.o. or hydralazine 5mg IV for severe hypertension (sBP <math>\geq 160</math>mmHg); maintenance therapy titrated against response; parenteral antihypertensives as required</li> <li>◇ MgSO<sub>4</sub> loading dose (IV/IM if not already administered in the community or 10g IM MgSO<sub>4</sub> was administered more than 4 hr prior to facility admission) for women with severe hypertension or vaginal bleeding (as indicators of severe pre-eclampsia) or eclampsia (single); MgSO<sub>4</sub> dose of 2g IV for women who had a seizure after the 10g IM MgSO<sub>4</sub> was administered in the community. Then, maintenance therapy (usually 1g/h) until 24 hours postpartum.</li> <li>◇ Arrangements made for definitive therapy               <ul style="list-style-type: none"> <li>◇ If &gt;local threshold for viability (e.g., 28 weeks' by best clinical estimate), &lt;34+0 weeks', and PIERS probability &lt;25%: administer 12mg dexamethasone i.m. x 2 12h apart, wait 48h and deliver (transfer to regional centre, if relevant)</li> <li>◇ If &lt;viability, <math>\geq 34+0</math> weeks', or PIERS probability <math>\geq 25\%</math>: deliver</li> </ul> </li> </ul>
<b>Transport (as required)</b>	<ul style="list-style-type: none"> <li>◇ Arrangements made for patient transfer to regional (e.g., Hyderabad DHQ) or supraregional (e.g., AKU Medical Centre/JPMC) referral centres, if indicated</li> <li>◇ Patient transferred</li> </ul>

AKU Aga Khan University; BP blood pressure; CPD continuing professional development; DHQ district headquarter hospital; CEEmOC emergency obstetric care; GA gestational age; i.m. intramuscularly; JPMC Jinnah Postgraduate Medical College; p.o. orally; sBP systolic blood pressure



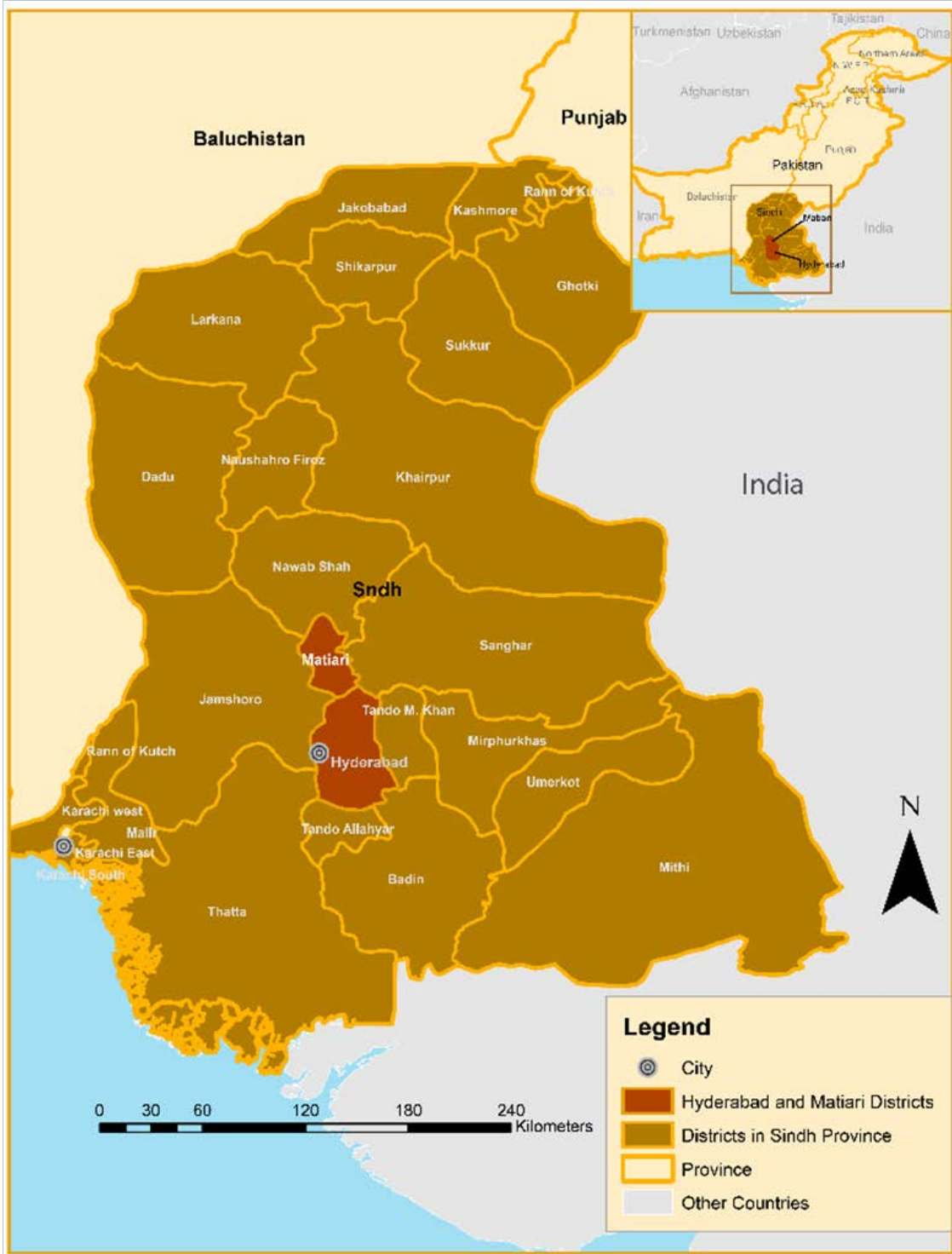
**FIGURE 11. Ogun State, Nigeria**

Putting the physical location of the CLIP Trial into context



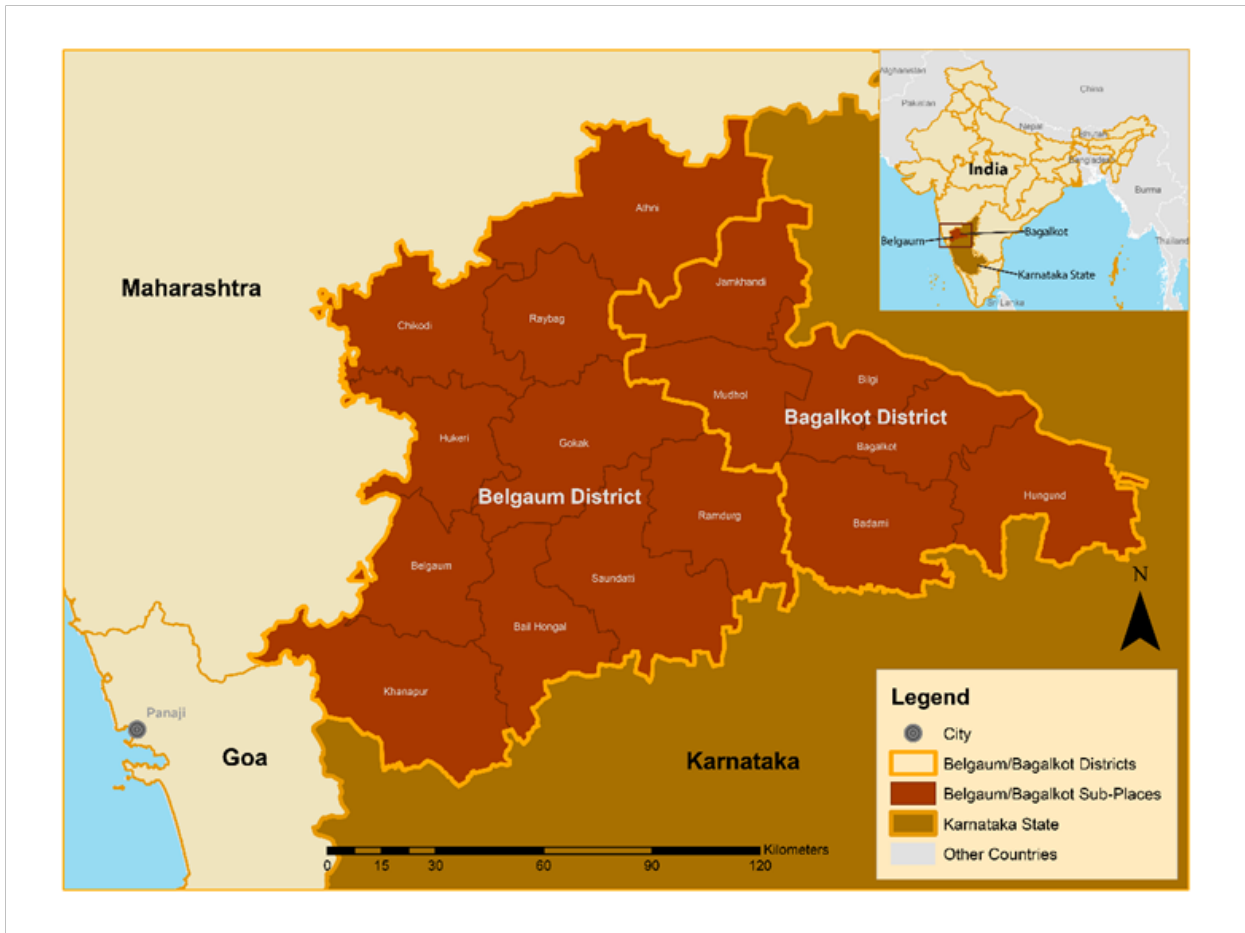


**Figure 12** Maputo Province, Mozambique  
 Putting the physical location of the CLIP Trial into context



**Figure 13. Hyderabad and Matiari Districts, Sindh Province, Pakistan**

Putting the physical location of the CLIP Trial into context



**Figure 14. Belgaum and Bagalkot Districts, Karnataka State, India**

Putting the physical location of the CLIP Trial into context

## **Appendix A – Summary of site visit and initial Feasibility Study findings**

### ***Partnerships***

The following stakeholders have been engaged and have provided support for the trial:

#### ***Nigeria – Academic***

Centre for Research in Reproductive Health, Sagamu, Ogun State, Nigeria.

#### ***Nigeria - Regional & national***

Commissioner of Health, Ogun State; Ogun State Ministry of Health; Olabisi Onabanjo University Teaching Hospital; Medical Officers of Health, Ogun State LGAs; Society of Gynaecology and Obstetrics of Nigeria (SOGON); Association of Maternal and Fetal Medicine Specialists of Nigeria; Yewa South Local Government (Ilaro State Hospital, Leysley PHC, Igbo-gidi PHC); Remo North Local Government (General Hospital, Isara, Ode-Remo PHC, Ipara PHC, Idi-Aba Health Post; Sagamu Local Government (Ogijo PHC, Sagamu LGA) and Imeko Local Government (General Hospital, Imeko, Imeko PHC).

#### ***Mozambique - Academic***

Manhiça Health Research Centre, Maputo, Mozambique

Eduardo Mondlane University, Maputo, Mozambique

#### ***Mozambique - Regional & National***

Mozambique Ministry of Health; Maputo Municipal Council (responsible for health); Mozambique Association of Obstetricians and Gynecologists (AMOG); Eduardo Mondlane University, Maputo; Maputo Central Hospital; Clinton Foundation.

#### ***Pakistan - Academic***

Aga Khan University and Jinnah Postgraduate Medical College, Karachi, Pakistan

#### ***Pakistan - Regional & national***

Sindh Ministry of Health; National Lady Health Worker Programme; Society of Obstetricians and Gynaecologists of Pakistan; Isra University Hospital; Liaquat University Medical Health Sciences Hospital; Aga Khan Maternal & Child Care Centre, Hyderabad; Taluka Headquarter Hospital; Aga Khan University Hospital, Karachi; Jinnah Postgraduate Medical College Hospital, Karachi.

#### ***India - Academic***

Jawaharlal Nehru Medical College, Karnataka Lingayat Education University, Belgaum, India.

#### ***India - Regional & national***

District Health Officers, Belgaum and Bagalkot; Chief Executive Officer, Zilla Panchayat (local self government), Belgaum and Bagalkot; Programme Director, RCH, Ministry of Health and Family Welfare, Government of Karnataka, Bangalore; Reproductive Health and Nutrition Division, Indian Council of Medical Research, New Delhi; Representatives of Federation of Obstetric and Gynaecological Societies of India (FOGSI) and Indian Academy of Paediatrics (IAP).

#### ***World Health Organization Department of Maternal, Newborn, Child and Adolescent Health (MNCAH)***

The chair of the PRE-EMPT objective 5 (knowledge translation) group is Dr Matthews Mathai, from this WHO department. The MNCAH group was instrumental in co-ordinating the development of the 2011 WHO pre-eclampsia guidelines, and will be instrumental in updating the guideline to reflect the findings of

the CLIP trial, and in promulgating the results of the CLIP trial to key decision makers in LMICs. Dr Lale Say is a member of the advisory group advising on maternal mortality and morbidity methods for CLIP.

### ***UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (RHR)***

The WHO RHR group have been important partners in the PIERS research agenda (Mario Merialdi and Mariana Widmer), as well as for objectives 1 (Ana Pilar Bertràn) and 5 (Metin Gülmezoglu) of the PRE-EMPT project.

### ***Royal College of Obstetricians and Gynaecologists (RCOG)***

We have developed a partnership with the RCOG (London) International Office (Senior Vice-President Professor James Walker). An element of the RCOG's international mandate is to strengthen the capacity of inpatient facilities in LMICs in terms of the use of evidence-based care. We will co-ordinate our activities in Nigeria, Mozambique, Pakistan, and India so that the RCOG will support public and private facility capacity building in the referral centres in Nigeria (Sagamu), Mozambique (Manihça and Maputo), Pakistan (Matiari, Hyderabad and Karachi), and India (Belgaum and Bagalkot). This commitment of time, energy and expertise will ensure that women in the study clusters will receive timely and effective care in the centres to which they are referred.

### ***Society of Obstetricians and Gynaecologists of Canada (SOGC)***

We have developed a partnership with the SOGC International ALARM Course team. An element of the SOGC's international mandate is to strengthen the capacity of inpatient facilities in LMICs in terms of the use of evidence-based care. We will co-ordinate our activities in Nigeria, Mozambique, Pakistan, and India so that the SOGC will support public and private facility capacity building in the referral centres in Nigeria (Sagamu), Mozambique (Manihça and Maputo), Pakistan (Matiari, Hyderabad and Karachi), and India (Belgaum and Bagalkot). This commitment of time, energy and expertise will ensure that women in the study clusters will receive timely and effective care in the centres to which they are referred.

### ***USAID/MCHIP (Maternal & Child Health Integrated Program)***

We have developed a partnership with MCHIP, particularly through Jeffrey Smith (PRE-EMPT TAG member). MCHIP is the USAID Bureau for Global Health's flagship programme focussed on maternal, neonatal and child mortality reduction and acceleration of progress towards MDGs 4 and 5. An element of MCHIP's mandate is to strengthen the capacity of inpatient facilities in LMICs in terms of the use of evidence-based care. We will co-ordinate our activities in Nigeria, Mozambique, Pakistan, and India so that the MCHIP will support public and private facility capacity building in the referral centres in Nigeria (Sagamu), Mozambique (Manihça and Maputo), Pakistan (Matiari, Hyderabad and Karachi), and India (Belgaum and Bagalkot). This commitment of time, energy and expertise will ensure that women in the study clusters will receive timely and effective care in the centres to which they are referred.

### ***Current practice - the provision of maternity care and pre-eclampsia interventions***

#### ***Nigeria***

Antenatal care is delivered at the primary health centre level. Most women attend antenatal care every 3-4 weeks up to 28 weeks gestation, every 2 weeks till 36weeks gestation and weekly thereafter. A typical antenatal visit does include blood pressure measurement and proteinuria testing by indication. Few clinics have a laboratory or ultrasound capacity. Much of obstetric services are paid out of pocket. Few PHCs have ambulance services for referral of complex cases.

Care is accessed through both public and private facilities throughout OGUN State with an estimated 40% of women accessing care through private institutions and 60% attending public facilities.

### ***Community Health Extension Worker (CHEW) training & current scope of practice***

Community Health Extension Workers (CHEW) are responsible for delivery of primary health care services in Nigeria. They work both in the community and clinic settings; however due to workload restraints CHEWs often remain stationed predominantly at the PHC. The training and regulation of practice is under the jurisdiction of Community Health Practitioners' Registration Board of Nigeria. The CHEW program includes certification in community health, practical exercises and examinations, supervised clinical experience and supervised community experience. The areas of focus for CHEW training relevant to CLIP are: English training, computer education, medical sociology, reproductive health, clinical skills, and referral system and outreach services. The current CHEW curriculum does not include specific training for management or diagnosis of pre-eclampsia/eclampsia or any other pregnancy complication.

### ***Health Assistants (HA's) training & current scope of practice***

The HA's are admitted into the health assistant training program with a secondary school certificate (high school qualification) either at registered private or government training institutions. They work almost entirely in private institutions after completion of their training. They undergo training for three years at these training institutions and assist the trained nurse midwife with care of patients and pregnant women in the community. They are trained to take vital signs, collect preliminary clinical history of symptoms and signs from patient and take pregnant history from patronizing pregnant women at private clinics, where they exist. At the private institutions, Health Attendants are trained to give intramuscular drugs/injections, take normal deliveries and they do give injections when prescribed by doctors in the private clinics.

### ***Mozambique***

The Mozambique health system is largely supported by foreign aid<sup>56</sup>. There are significant human resource shortages which require task shifting for obstetric care services. Countrywide, there is a low number of available skilled birth attendants. Access to primary health care facilities, where antenatal care is delivered, is also low<sup>56</sup>. The first antenatal visit is typically delayed until the 2<sup>nd</sup> or 3<sup>rd</sup> trimester, with 84% coverage for at least one antenatal visit during pregnancy<sup>57</sup>. As a result of these constraints the majority of births are rural many without skilled attendants.

Magnesium sulphate has long been used in Mozambique for the management of pre-eclampsia and eclampsia, however, its use has been primarily at central hospitals and alternative anti-seizure medications have been used in the periphery<sup>58</sup>.

### ***Agente Comunitarios de Saude (ACS) training & current scope of practice***

Agente Comunitarios de Saude (or basic multi-task health care helpers) help to promote health in their communities; constituting the link between them and the national health system. ACSs are recruited from within the community and receive six months' training to provide basic preventive (community health education) and curative community based-care for diarrhoea, pneumonia and malaria, focussing on the widespread use of diagnostics and appropriate treatment. The ACSs allow isolated populations to have access to basic health care and essential drugs for high burden diseases like malaria, and act as an entry point for referral to higher level health services, providing basic first aid before transfer where needed.

### ***India***

The Government of India has recently committed to the National Rural Health Mission. This initiative aims to obtain universal skilled birth attendance across the country. The National Rural Health Mission highlights the role of ANMs in providing antenatal care, timely referrals, and provision of treatment in emergency obstetric cases. Health care workers providing obstetric care at the community level are ANMs,

ASHAs and Anganwadi Workers. Each antenatal visit should include: a medical history, physical exam, abdominal exam, laboratory investigations, clinical interventions (IFA supplement, TT injection, malaria), and health promotion counselling. A minimum of four antenatal visits for all pregnancies is encouraged: before 12 weeks, 12-26 weeks, 28-34 weeks and 36 weeks-term.

Facilities are generally equipped to manage cases of pre-eclampsia and eclampsia. Due to concerns regarding safety and availability diazepam is frequently used in place of MgSO<sub>4</sub>.

### ***Auxiliary Nurse Midwife (ANM) training & current scope of practice***

Training for Assistant Nurse Midwives includes a wide range of health competencies: understanding of holistic health/social determinants of health, ability to mobilize communities, provide emergency care, treatment of minor ailments, midwifery services and referral, basic neonatal care and referral, child services, guide and train TBAs and AWWs, health counselling, participate in National programmes, collaborate with community organizations, manage health care settings. Their midwifery services include care during pregnancy, intrapartum and postpartum.

They are expected to measure blood pressure at every visit and test for albumin in the cases of high blood pressure. If a woman is identified with high blood pressure the ANM is responsible to referral to a 24 hour PHC to initiate antihypertensive therapy. ANMs also follow-up and advise of the warning symptoms. In cases of eclampsia the ANM should ensure safety, give MgSO<sub>4</sub> (10g i.m.) and refer to a facility within two hours.

### ***Accredited Social Health Activist (ASHA) training & current scope of practice***

ASHAs are local women trained to act as health educators and promoters in their communities. They receive a total period of 28 days' training in five episodes. However, this core training is supplemented by ongoing CPD activity in parallel with the development of necessary skills and expertise through on the job training. After a period of 6 months of functioning in her village, she is then sensitised to issues related to HIV, AIDS, and STIs (prevention and referral), as well as trained on newborn care.

Their tasks include motivating women to have a facility birth, bringing children to immunisation clinics, encouraging family planning, treating basic illness and injury with first aid, keeping demographic records, and improving village sanitation. In addition, ASHAs are central to communication between the health care system and rural populations.

### ***Pakistan***

Pakistan's public health system is centralized under the Federal Government and provincial Health Ministries. The public health sector employs LHWs and Lady Health Visitors (LHV) in rural sectors and nurses and doctors in health facilities and hospitals.<sup>1</sup> According to the 2008 Demographic and Health Survey: Pakistan, less than 30% of women receive four antenatal visits during pregnancy. In many rural settings, staffing levels are inadequate and referral systems function poorly. Almost 70% of births take place at home, usually attended by a Dai (traditional birth attendant [TBA])<sup>59</sup>. Rural and urban public facilities provide free consultation for obstetric care, whereas consultation charges in private facilities range from \$0.5-3USD in rural areas and \$4-16USD in urban areas. Some public and private facilities provide ambulance services, additional ambulance services are provided by non-profit organizations in some regions. The majority of health facilities in Hyderabad and Matiari do not have protocols/guidelines for managing pre-eclampsia and eclampsia. There is awareness of MgSO<sub>4</sub> for the management of pre-eclampsia and eclampsia however, many continue to use diazepam.

### ***Lady Health Worker (LHW) training & current scope of practice***

The Lady Health Worker Programme commenced in 1994 and currently employs 96000 LHWs as part of the federal healthcare system. Each LHW has to cover a population of around 1000-1500 individuals. This

existing number of LHWs is insufficient as WHO suggests the requirement of 150,000 LHW's to cater to the country's healthcare needs.<sup>9</sup> The Government of Pakistan is the major contributor to the funds for this program, external sources only contribute around 11% of the total amount.<sup>9</sup> The role of LHWs is pivotal in Pakistan's healthcare system. They have 15 months of training in MCH<sup>2</sup>. The LHW role in antenatal care includes: health promotion, hospital referrals, and basic neonatal care. Currently LHW is not responsible for immediate management of eclampsia /pre-eclampsia and refers such patients. LHW don't carry any antihypertensive medicine for pregnant woman, and don't have BP apparatus, their role was found to be limited 'to advice to seek care from nearest referral facility' in case if a pregnant woman complained about severe headache with dizziness. An external evaluation of the LHW programme concluded that it was effective in delivering family planning services and immunization services, in the management of diarrhoea, and, most recently through a cRCT, reducing the burden of stillbirth in Sindh Province<sup>9;12</sup>.



## Appendix B – relevant systematic reviews

### ***Antihypertensives for severe hypertension in pre-eclampsia and the other HDP***

Short-acting parenteral agents, such as i.v. hydralazine and labetalol, have been most widely studied in RCTs, although systematic reviews have failed to reveal clear differences between agents<sup>60,61</sup>. We undertook a comprehensive search for RCTs of oral antihypertensive therapy to assess the effectiveness for treatment of severe pregnancy/postpartum hypertension. Also, we reviewed additional relevant RCTs of oral antihypertensive therapy for severe hypertension outside pregnancy to supplement effectiveness data in pregnancy (Firoz, submitted).

In pregnancy and postpartum, we identified 15 trials in pregnancy (914 women), one of which was a postpartum trial (38 women). Trials were generally small with a median of 50 women (range 20 to 150) and fair in quality. There was a wide range in the type of HDP at inclusion and gestational age at enrolment. When specified, the BP treatment goal was usually a  $\text{dBP} < 100\text{-}110\text{mmHg}$  and the success of treatment was evaluated over a short time frame ranging from 20-120 min. Here we summarise the analyses that are relevant to CLIP.

#### ***Nifedipine***

Twelve RCTs in pregnancy compared oral/SL nifedipine capsules (8-10mg, 12 trials, 724 women) with another agent. Most compared nifedipine with i.v. hydralazine (5-20mg, 7 trials, 350 women) or i.v. labetalol (20mg, 2 trials, 100 women). Other trials compared short-acting nifedipine to oral nifedipine 10mg PA tablets (1 trial), oral prazosin 1mg (1 trial), or i.v./i.m. chlorpromazine 12.5mg (1 trial). The postpartum RCT (38 women) compared SL nifedipine with i.v. hydralazine.

When short acting nifedipine was compared with i.v. hydralazine in pregnancy, there was no difference in effectiveness as seen by achievement of target BP [84% (nifedipine) vs. 79% hydralazine; RR 1.07 95% CI 0.98, 1.17; 5 trials, 273 women] or time taken to achieve it [WMD -1.36 hours, 95% CI -6.64, 4.14], and the number of doses needed [51% vs. 55%; RR 0.97 95% CI 0.50, 1.88; 4 trials, 246 women]. There was also no difference in maternal mortality [as no studies reported maternal deaths RD 0.00 95% CI -0.03, 0.03; 3 trials, 96 women] or maternal hypotension [1.6% vs. 0%; RD 0.00 95% -0.02, 0.03; 4 trials, 246 women]. There were no differences in perinatal outcomes including adverse fetal heart rate effects, stillbirth and perinatal/neonatal death.

When short-acting nifedipine was compared with i.v. labetalol (N=2 trials), results were similar and there was no difference seen in achievement of target blood pressure, number of doses needed or the requirement for additional antihypertensive therapy. There was no difference in maternal hypotension, maternal mortality and other adverse effects. Similarly, there were no differences in perinatal outcomes including caesarean section [RR 1.13 95% CI 0.76, 1.96; 1 trial, 50 women], stillbirth, and perinatal death [WMD 0.00 95% CI -0.07, 0.07; 1 trial, 50 women].

Nifedipine capsules (10mg orally), compared with nifedipine PA tablets (10mg orally), were associated with more maternal hypotension at 90 minutes [35% vs. 9%; RD 0.26, 95% CI 0.07, 0.46, 1 trial, 64 women]. The absolute rate of hypotension with nifedipine capsules in this trial (35%) was higher than that seen in other nifedipine capsule trials of similar dosage (8-10mg) where the rate of maternal hypotension was 0.8%.

#### ***Labetalol and methyldopa***

There was a single trial (74 women) that compared oral labetalol 100 QID with oral methyldopa 250 mg QID. There was no difference in achieving target BP [47% vs. 56%; RR 0.85 95% CI 0.54, 1.33], Caesarean section [50% vs. 59%; RR 0.85, 95% CI 0.56, 1.30], or perinatal death [5% vs. 0%; RD 0.05

95% CI -0.03, 0.14]. A three-arm trial compared oral methyldopa with either atenolol (50-200mg) or oral ketanserin (80-120 mg). This trial did not report on effectiveness in lowering BP. Perinatal outcomes did not differ between the groups including perinatal death [WMD -0.04 95% CI -0.10, 0.03; 2 trials, 192 women] and stillbirth [WMD 0.01 95% CI -0.03, 0.05; 2 trials, 192 women]

### ***Other antihypertensive agents***

One small trial (36 women) compared SL isosorbide with parenteral magnesium sulphate and found no difference between the groups with respect to additional antihypertensive therapy required but there was a significant difference in the rate of Caesarean section between the two groups [16% vs. 89%; RR 0.19, 95%CI 0.07, 0.53].

In summary, our results are similar to that of previous systematic reviews. The analysis of the evidence is complicated by the small numbers of patients, rare events as outcomes and variations in the drug administration regimens among other factors. We found that oral antihypertensive agents, particularly short-acting nifedipine, are a suitable option for treatment of severe hypertension in pregnancy/postpartum.

### ***Oral antihypertensives in SEVERE NON-pregnancy hypertension***

Thirty-four studies (1843 patients) met inclusion criteria. Generally, trials were small with a median of 36 patients (range 7 to 374). The dBP for inclusion in most studies was between 110-120 mmHg. When specified, the BP treatment goal was usually a dBP<100-110mmHg and the success of treatment was evaluated over a short time frame with between-trial variability in the time to reach the target BP ranging from 30 minutes to 24 hours. The quality of included studies was poor as there was an unclear risk of bias for sequence generation, allocation concealment, blinding, selective outcome reporting and incomplete outcome data.

### ***Nifedipine***

Eighteen trials (describing 21 comparisons) compared oral/SL (short-acting) nifedipine with either another antihypertensive or other doses/formulations of nifedipine. Compared with captopril, oral/SL nifedipine was associated with similar effectiveness in lowering BP: achievement of target BP at 60 minutes [88% (nifedipine) vs. 76% captopril; RR 1.09 95% CI 0.87, 1.37; N=4 trials, 174 patients], number of doses of antihypertensive required [56% vs. 64%; RR 0.88 95% CI 0.56, 1.38; N=1 trial, 50 patients], or the need for additional antihypertensive therapy [50% vs. 70%; RR 0.71 95%CI 0.34, 1.50; N=1 trials, 20 patients]. The absolute rates of effectiveness were similar to that in pregnancy, but there was significant heterogeneity for achievement of blood pressure.

Only one trial evaluated hypotension and found that there were no episodes in either group. Also, there were no differences seen for other adverse effects including headache [4% vs. 10%; RR 0.86, 95% CI 0.16, 4.71; 4 trials, 145 patients] and cardiac arrhythmia [13% vs. 0%; RR 8.73, 95% CI 0.49, 155.62; 1 trial, 63 patients]. Nifedipine appeared to be associated with more flushing [13% vs. 0%; RR 6.75, 95% CI 1.26, 36.10; 3 trials, 133 patients].

In all other subgroups, nifedipine po/SL was compared with another drug or another dose/formulation of nifedipine in only one or two small trials that enrolled a median of 40 patients. No between-group differences in outcomes were seen.

### ***Labetalol***

Four trials (5 comparisons, 568 patients) compared oral labetalol to either: two other doses of oral labetalol (i.e., 100 mg vs. 200 mg vs. 300 mg/d)(66), either amlodipine or perindopril, clonidine, or nifedipine (as discussed above). There were no between-group differences in achievement of target BP or hypotension in any of these comparisons. There was no difference in achievement of BP when 200 mg of oral labetalol was

compared to 100 mg [58% vs. 75%; RR 0.78 95% CI 0.44, 1.39; 1 trial, 24 patients] and 300 mg [58% vs. 67%; RR 0.78 95% CI 0.44, 1.63; 1 trial, 24 patients] with no hypotension observed at either 100 mg, 200 mg and 300 mg doses.

### **Methyldopa**

One trial (3 comparisons) compared oral methyldopa 500 mg with either oral captopril 50 mg, indapamide 2.5 mg, or placebo. Pre-treatment MAP in the methyldopa arm was  $127.7 \pm 6$  mmHg and two hours after treatment, the MAP reduced to  $119 \pm 4$  mmHg. This was comparable to the post-treatment MAP seen in the captopril ( $125.2 \pm 13$  mmHg), indapamide ( $119.3 \pm 11$  mmHg) and placebo ( $122.9 \pm 12$  mmHg) groups.

### **Other antihypertensive agents**

There were one or two trials each of other comparisons including captopril versus placebo or other agents (methyldopa, indapamide, quinapril, telmisartan, nifedipine, urapidil), oral vs. aerosol isosorbide dinitrate, different doses of isradipine and ketanserin versus placebo or agents. These trials did not report on outcomes related to effectiveness but reported on adverse effects.

Our results are similar to that found in the 2009 systematic review by Souza *et al* with similar challenges included poor quality, small trials and few trials reporting outcomes of interest<sup>62</sup>.

### **Summary**

Based on RCTs in pregnancy/postpartum, oral nifedipine (10mg) is a suitable oral agent for treatment of severe hypertension in pregnancy/postpartum, with treatment success rates of at least 84%, low rates of maternal hypotension (upper 95% CI 3%), and similar maternal and perinatal outcomes compared with parenteral hydralazine or labetalol. Although it should be noted that the one 10mg nifedipine capsule vs. 10mg PA tablet trial that did report more hypotension with the capsule formulation found much higher rates of hypotension in *both* arms of the trial (35% in the capsule arm and 9% in the 10mg tablet arm) compared with the six other nifedipine capsule trials of similar dosage (<1%)<sup>63</sup>; also, that hypotension was not necessarily associated with adverse clinical effects.

The few, small comparative trials of other antihypertensive agents in pregnancy/postpartum preclude any firm conclusions. However, the limited data suggest that oral labetalol and methyldopa may be effective in approximately 50% of pregnant women, and each may be a reasonable alternative to nifedipine. Caution should be exercised if considering use of oral prazosin given its association with more Caesarean deliveries and, possibly, stillbirth.

The data from trials outside pregnancy lend further support to the effectiveness of short-acting nifedipine for treatment of severe hypertension (at least 88% success) without significant hypotension. Similar rates of success were also seen with SL captopril (76% success) with which nifedipine was most frequently compared. These data would suggest that oral captopril, which is acceptable for use in breastfeeding, should be considered for use postpartum in the absence of renal impairment.

To our knowledge, this is the first systematic review to specifically examine oral antihypertensive therapy for severe hypertension in pregnancy and postpartum. However, there are other meta-analyses of trials of short-acting parenteral agent or oral nifedipine in pregnancy/postpartum, and the results of the oral nifedipine vs. parenteral hydralazine subgroup are consistent with our analysis.

In the systematic review of oral antihypertensive therapy for severe hypertension outside pregnancy, captopril was associated with fewer minor side-effects than nifedipine [i.e., flushing (RR 0.22 95% CI 0.02, 0.72) and headache (RR 0.34 95% CI 0.13, 0.92)]; the difference in results may be explained by Souza *et al.*'s inclusion of several Spanish-language papers as well as a study (that we excluded) of several patients with pheochromocytoma.

Our review presents reasonable options for oral antihypertensive therapy. Options are key as there may be contraindications to use of a given drug (or women may already be on high doses of an oral agent when they present with severe hypertension). For example, there are published concerns about heightened cardiovascular morbidity/mortality associated with use of short-acting nifedipine outside pregnancy, and neuromuscular blockade with contemporaneous use of magnesium sulphate and nifedipine in pregnancy (although the risk was estimated to be <1% in a controlled study that incorporated data from RCTs<sup>32</sup>). The usefulness of beta-blockers may be limited in areas where reactive airways disease is prevalent and air quality is poor (such as in Pakistan).

## ***MgSO<sub>4</sub> for the prevention and treatment of eclampsia***

### ***Prevention of eclampsia***

A Cochrane systematic review of 15 RCTs investigated the relative effects of MgSO<sub>4</sub> and other anticonvulsants when used for prevention of eclampsia<sup>3</sup>. Notable comparisons in this review were between MgSO<sub>4</sub> and placebo or no anticonvulsants (six trials, 11,444 women); phenytoin (four trials, 2345 women); diazepam (two trials, 66 women); and nimodipine (one trial, 1750 women). One small trial (36 women) compared MgSO<sub>4</sub> with isosorbide and another trial (33 women) compared magnesium chloride with methyldopa.

**MgSO<sub>4</sub> versus placebo or no anticonvulsant** Six RCTs (11,444 women) including the large multicentre RCT<sup>64</sup> that involved 10,141 participants provided the evidence related to this comparison. About half of the women recruited into the Magpie trial had the maintenance regimen for MgSO<sub>4</sub> through the intravenous route (1g/hr) and the other half through the intramuscular route. Maintenance was strictly by intravenous route for four trials and intramuscular for one trial. For most trials, clinical monitoring for potential adverse effects were reported and none of the six trials reported using serum monitoring of MgSO<sub>4</sub>.

When compared with placebo or no anticonvulsant, MgSO<sub>4</sub> was associated with statistically and clinically significant reduction in the risk of eclampsia by almost 60% (six trials, 11,444 women; RR 0.41 [0.29, 0.58]). This effect was consistent for women who were antepartum at trial entry (six trials, 10,109 women; RR 0.40 [0.27, 0.57]) but non significant for those who were postpartum at trial entry (one trial, 1335, RR 0.54 [0.16, 1.80]). The effect was also consistent and more pronounced among women who were ≥34 weeks' pregnant (two trials, 6498 women; RR 0.37 [0.24, 0.59]) and those who had received no anticonvulsants prior to trial entry (three trials, 10,086 women; RR 0.33 [0.22, 0.48]). It was consistent regardless of the route of administration for MgSO<sub>4</sub> maintenance.

No statistically significant differences were observed between MgSO<sub>4</sub> and placebo regarding the risks of maternal death, any serious maternal morbidity, respiratory arrest and toxicity as shown by respiratory depression and absent tendon reflexes and calcium gluconate administration. Any reported side effects were significantly more common among women treated with MgSO<sub>4</sub> rather than placebo (one trial, 9992 women; RR 5.26 [4.59, 6.03]). For the baby, no clear difference were observed in the risks of stillbirth or neonatal death, admission to NICU and Apgar score <7 at 5min.

**MgSO<sub>4</sub> versus phenytoin** MgSO<sub>4</sub> was compared with phenytoin for prevention of eclampsia in four RCTs (2343 women). Compared with phenytoin, MgSO<sub>4</sub> significantly reduced the risk of eclampsia (three trials, 2291 women; RR 0.08 [0.01, 0.60]). No statistical differences were observed between the two groups in terms of stillbirth, neonatal death, Apgar score <7 at 5min and admission to NICU.

**MgSO<sub>4</sub> versus diazepam** A small trial involving 66 women compared MgSO<sub>4</sub> and diazepam for prevention of eclampsia. The sample size and the events recorded were too small for any reliable conclusions.

**MgSO<sub>4</sub> versus nimodipine** In the one trial comparing MgSO<sub>4</sub> with nimodipine (1650 women), there were fewer cases of eclampsia among women allocated MgSO<sub>4</sub> (RR 0.33 [0.14, 0.77]).

### **Treatment of eclampsia**

**MgSO<sub>4</sub> versus diazepam for women with eclampsia** A Cochrane systematic review of seven RCTs, involving 1396 women, provided the evidence on the differential effects of MgSO<sub>4</sub> when compared with diazepam for the care of women with eclampsia<sup>4</sup>. Most women in the trials had eclampsia either before or after delivery and about half of them received an anticonvulsant before trial entry. All regimens used in the trials for both MgSO<sub>4</sub> and diazepam included loading and maintenance dose. MgSO<sub>4</sub> fared better than diazepam regarding primary maternal outcomes of death (seven trials; 1396 women; RR 0.59 [0.38, 0.92]) and recurrence of convulsions (seven trials; 1390 women; RR 0.43 [0.33, 0.55]). There were no statistical differences between the two drugs for any serious maternal morbidity or any of its proxies addressed in this comparison. Regarding fetal outcomes, no clear difference was demonstrated between the comparison groups for perinatal death and admission to NICU. MgSO<sub>4</sub> was associated with fewer cases of babies born with Apgar scores <7 at 5min (three trials, 643 infants; RR 0.70 [0.54, 0.90]).

Comparison of the two treatment groups according to route of administration of MgSO<sub>4</sub> maintenance showed that intramuscular maintenance significantly reduced the risks of maternal respiratory depression (two trials, 120 women; RR 0.30 [0.10, 0.13]) and maternal ventilation (two trials, 120 women; RR 0.20 [0.05, 0.88]) but no statistical difference for maternal cardiac arrest. The two contributing trials had moderate risk of bias, small sample size and few events and resultant imprecise observations.

**MgSO<sub>4</sub> versus phenytoin for women with eclampsia** Evidence related to the effects of MgSO<sub>4</sub> compared with phenytoin for care of women with eclampsia came from a Cochrane systematic review of six RCTs, involving a total of 972 women<sup>5</sup>. Most of the women had eclampsia before delivery and had received anticonvulsants prior to trial entry.

Compared with those treated with phenytoin, women treated with MgSO<sub>4</sub> were at reduced risk of recurrence of convulsions (six trials, 972 women; RR 0.34 [0.24, 0.49]), admission to intensive care (one trial, 775 women; RR 0.67 [0.50, 0.89]) and need for ventilatory support (two trials, 825 women; RR 0.68 [0.50, 0.91]). There were no statistically significant differences between the two treatment groups for maternal death, any serious maternal morbidity and the reported proxy outcomes for severe maternal morbidity. Babies born to women treated with MgSO<sub>4</sub>, rather than phenytoin, were less likely to be admitted for NICU (one trial, 518 infants, RR 0.73 [0.58, 0.91]) but no clear differences was observed between the two treatment groups in the risks of perinatal death and Apgar score <7 at 5min.

**MgSO<sub>4</sub> versus lytic cocktail for women with eclampsia** The evidence on the differential effects of MgSO<sub>4</sub> compared with 'lytic cocktail' (usually a combination of chlorpromazine, promethazine and pethidine/meperidine) was derived from a Cochrane systematic review of three small trials involving a total of 397 women<sup>6</sup>. Compared with lytic cocktail, MgSO<sub>4</sub> was associated with significantly fewer cases of maternal death (three trials, 397 women; RR 0.14 [0.03, 0.59]), recurrent convulsions (three trials, 397 women; RR 0.06 [0.03, 0.12]), coma for >24h (one trial, 108 women; RR 0.04 [0.00, 0.74]) and respiratory depression (two trials, 198 women; RR 0.12 [0.02, 0.91]). No clear

differences were observed for any other proxy outcome for severe maternal morbidity. The risks of stillbirth and neonatal mortality were also similar between the two treatment groups.

**Alternative regimens of MgSO<sub>4</sub> for treatment of pre-eclampsia and eclampsia** Evidence related to the comparative effects of alternative MgSO<sub>4</sub> regimens for treatment of preeclampsia and eclampsia came from a Cochrane systematic review of six RCTs involving 866 women<sup>49</sup>. Two of the trials (451 women) compared regimens for eclampsia while the other four (415 women) compared regimens for pre-eclampsia. None of the trials used dosages shown to be effective in large RCTs demonstrating effectiveness of MgSO<sub>4</sub>.

When loading dose alone was compared with loading dose plus maintenance regimen for women with eclampsia, one trial (401 women) showed no statistical differences in the critical outcomes of recurrent convulsions and maternal death and the proxy outcome for perinatal death, stillbirth. The loading dose employed in this trial was 4g intravenous (i.v.) plus 6g intramuscular (i.m.), while the maintenance was 2.5 g i.m. every 4h for 24h. The trial had very serious limitations in its quality and the observations were generally imprecise. A small trial (50 women) compared low dose (similar to the regimen above) with 'standard' regimen (4 g i.v. + 8 g i.m. as loading dose, then 4 g IM every 4 hours for 24 hours) for women with eclampsia). The only case of recurrent convulsion in the trial was reported among women treated with the low dose regimen thus generating highly imprecise and unreliable data for this critical outcome. No statistically significant difference was observed between the two treatment groups for admission to NICU and proxy outcomes of oliguria and any baby death. One small trial (17 women) compared i.v. (2g hourly for 24 hours) and i.m. (5g. 4-hourly for 24 hours) maintenance regimens for women with pre-eclampsia. There was no case of eclampsia in either arm of the trials. The trial was too small to yield any reliable conclusions regarding other priority and proxy outcomes reported [MgSO<sub>4</sub> toxicity; renal failure; and stillbirth.

Three trials involving 398 women evaluated short versus 24h postpartum regimens for women with mild and severe pre-eclampsia or imminent eclampsia. Two of these trials, accounting for approximately two-thirds of the participants, were at low or no risk of bias while one was at moderate risk of bias. None of the women in both arms of these trials developed any of the critical outcomes addressed: eclampsia (two trials, 394 women); MgSO<sub>4</sub> toxicity (one trial, 196 women).

### ***Summary of the trial evidence:***

Therefore, we have identified that MgSO<sub>4</sub> is the agent of choice for the prevention and treatment of eclampsia – however, it has never been examined as a community-level intervention (either in isolation or as a package of care). In addition, we have identified that there is no clear choice of oral antihypertensive for the management of severe pregnancy hypertension – however, we are completing the relevant trial as part of the PRE-EMPT project in preparation for CLIP.

## Appendix C – Community Engagement Mapping

Intervention Cluster (name/identifier)			
Activities related to:	Do current activities exist targeting this objective? Y/N If yes, please describe current activities (what types of activities, for whom, how often, where, and who leads them)	Contact person	Source of information
Pregnancy-related complications			
General Maternal Health			
Household decision-making around pregnancy and childbirth (eg. husband's and mother in-law's permission to go to hospital when necessary)			
Transportation initiatives			
Fundraising, insurance schemes or other initiatives related to reducing the barrier of cost of transport and treatment			
Other activities at the individual, household or community level related to maternal health			

## Appendix D – cHCP Working Protocol

### THE CLIP (COMMUNITY LEVEL INTERVENTIONS FOR PRE-ECLAMPSIA) CLUSTER RANDOMIZED CONTROLLED TRIAL – CHCP WORKING PROTOCOL

#### SECTION 1: BACKGROUND

##### 1.1 WHAT IS THE PROBLEM TO BE ADDRESSED?

The hypertensive disorders of pregnancy (HDP) are defined by high blood pressure in pregnancy. Globally, the HDP are the second leading direct cause of maternal death; every year the HDP are responsible for the death of an estimated 75,000 women and over 500,000 babies. Almost all of these deaths occur in Africa and South Asia and are preventable. Maternal deaths relate primarily to delays in triage (ability of care provider and women to identify who is severely ill and requires urgent care), transport (ability to get women to appropriate care when needed) and treatment (ability to provide appropriate treatment when care accessed).

The CLIP trial approach to reducing these delays involves task-shifting the monitoring for complications related to the HDP to community health care providers (cHCPs); a cadre of health workers that is currently available in low-resourced settings. The health workforce shortage is a significant global problem that is preventing many countries from reducing child and maternal mortality associated with HDP. Care of these pregnancy disorders previously relied on doctors and midwives in facilities. Treatment for HDP in facilities involves costly medication for reducing blood pressure and, because delivery is the only way to stop the disorder, it often requires emergency Caesarean section when the severity of the disorder is identified too late. By identifying those women and babies at highest risk of complications through community-level screening and monitoring, transportation and treatment can be targeted to those most in need and timed to allow induction of labour instead of Caesarean delivery. There are two key benefits for poor and vulnerable populations: first, at the individual level women are not suffering the cost and time away from their families for unnecessary referrals or interventions when safe, increased community surveillance would be appropriate; second, at the health systems level, moving monitoring from the facility to the community increases the potential for broad population based screening, and more efficient use of already burdened acute care facilities.

##### 1.2 CLIP TRIAL HYPOTHESIS AND OBJECTIVES

###### Hypothesis

That implementing community-level evidence-based care will reduce pre-eclampsia-related maternal mortality and major morbidity.

###### Objectives

To reduce pre-eclampsia-related, and all-cause, maternal and perinatal mortality and major morbidity by 20% in intervention clusters in Ogun (Nigeria), Maputo and Gaza Provinces (Mozambique), Sindh (Pakistan) and in Karnataka (India).

##### 1.3 DOCUMENT PURPOSE AND SCOPE

###### Purpose

This document provides full descriptions of daily CLIP activities to be performed by cHCPs in all intervention clusters.

###### Scope



This document covers the following cHCP activities:

- Collecting demographic information on new patients
- Measuring blood pressure
- Measuring SpO<sub>2</sub> (Mozambique and Pakistan only)
- Estimating gestational age using symphysis-fundal height measurement
- Measuring proteinuria
- Assessing symptoms of pre-eclampsia
- Administering treatment for severe hypertension (oral methyldopa)
- Administering treatment to prevent seizures (intramuscular MgSO<sub>4</sub>)
- Providing recommendations for transport to hospital

## **SECTION 2: CHCP ANTENATAL VISIT PROTOCOL**

The cHCPs will be encouraged to identify pregnant women in their area, will have pregnant women referred to them when identified by the surveillance team during regular surveillance cycles, and will provide CLIP assessment during regular antenatal visits that place women in one of three care trajectories: 1) usual antenatal care 2) non-urgent referral, or 3) urgent referral. The regular CLIP visits will occur: 4-weekly during pregnancy until 28 weeks, fortnightly from 28-35 weeks and weekly thereafter, within 24 hours of birth, and on approximately days 3, 7, and 14 after delivery.

This section provides a description of each component of a CLIP assessment. These steps are meant to be performed in addition to any regular antenatal or postnatal care processes routinely performed by the cHCPs.

**NOTE:** CLIP visits should only occur after the woman being assessed has registered for the trial and provided informed consent for her participation.

Figure 9 provides a flow-chart outlining the assessment protocol and decision points used to generate recommendations for care.

## 2. FIRST VISIT PROTOCOL

### Overview

Each CLIP assessment visit will first involve an assessment of obvious signs of maternal risk including significant vaginal bleeding, stroke, lack of consciousness and seizures. All visits will also include a component of education by the cHCP regarding warning signs and symptoms of pregnancy.

On the first CLIP visit all women will have their blood pressure and proteinuria measured and, if antenatal, will have an assessment of gestational age performed based on last menstrual period dates and symphysis-fundal height measurement. If the woman is found to be hypertensive (systolic BP  $\geq$  140 mmHg) she will also be asked targeted questions about symptoms as described below.

#### 2.1.1 Step 1: Observe for overt signs of maternal compromise

- **signs of unconsciousness**

cHCP will observe to determine if the woman is unconscious at the time of the visit. If a woman is found to be unconscious her family members should be asked to determine if she had been observed to show signs of seizure or stroke prior to losing consciousness.

PLEASE NOTE: Any woman found unconscious at the time of the cHCP visit will not be evaluated as described in the remaining protocol. The immediate concern when a cHCP encounters an unconscious woman will be to position the woman on her left side by placing a rolled blanket or hard pillow under her right hip and lumbar area. Once the woman is positioned this way the cHCP should attempt to measure the unconscious woman's blood pressure (see 2.3.5) and treat with MgSO<sub>4</sub> if sBP  $\geq$  160mmHg before urgently referring for follow-up at a CEmOC facility. While transport is being arranged the cHCP should ensure the woman is placed in the recovery position on her left side and have nothing placed in the woman's mouth.

- **signs of stroke**

cHCP will visually assess for obvious signs of stroke at the beginning of the visit. Signs of stroke include either paralysis of one side of the body or a report of recent sudden loss of vision.

- **signs of eclampsia**

cHCP will visually assess for obvious signs of eclampsia at the beginning of the visit. Signs of eclampsia are defined as a sudden, violent, uncontrollable contraction of a group of muscles or a subtler sign as a brief loss of consciousness.

- **signs of vaginal bleeding**

The cHCP will visually assess for obvious signs of significant vaginal bleeding at the beginning of the visit defined as antepartum vaginal bleeding with pain before the onset of labour or rupture of membranes

#### 2.1.2 Step 2: Introduction and greeting

The cHCP should introduce her/himself and provide an acceptable introduction to the purpose of the visit, as defined by local ethics board. At this stage the cHCP will use the warning signs and symptoms of pregnancy pictorial aide to describe the intervention and provide information to the woman and her family about signs and symptoms to watch out for. The woman should be encouraged to seek care from the C-HCP or at a primary health centre should they note any of the warning signs or symptoms during the pregnancy.

#### 2.1.3 Step 3: Wash hands

The cHCP should wash their hands before performing any assessments on the woman.

#### 2.1.4 Step 4: Record demographic data

Demographic data will be collected at the first visit only. If the woman has already been registered for the study by the surveillance team, the first step will be to locate this woman based on her surveillance ID in the CLIP-POM tool database. This will ensure new evaluations of the woman being evaluated are added to any existing data collected through CLIP trial activities. If the surveillance ID is unknown or the woman cannot be found, this information along with all demographic data can be manually entered.

- 1 Name
- 2 Age of pregnant woman
- 3 Phone number of pregnant woman or head of household
- 4 History of previous deliveries

#### 2.1.5 Step 5: Assess maternal status

Determine if the woman is antepartum (has not delivered yet) or postpartum (has delivered a baby recently).

PLEASE NOTE: Women who are visited for the first time postpartum are ineligible for inclusion in the trial and should be provided with routine postpartum care according to local protocols.

#### 2.1.6 Step 6: Assess fetal status

cHCP asks:

- “Have you noticed fetal movements in the last 12 hours?”

#### 2.1.7 Step 7: Measure proteinuria

1. Provide woman with small cup/bottle for urine sample collection
2. Pregnant woman urinates into a small cup provided, all samples should be “clean catch” and collected in a clean container
3. Immerse the dipstick completely in fresh urine and withdraw immediately, drawing edge along rim of container to remove excess
4. Hold dipstick horizontally before reading

\*cHCPs should wear clean gloves when measuring proteinuria; gloves to be discarded when measurement complete

#### 2.1.8 Step 8: Take blood pressure

\* Let the woman rest (seated, no talking) for at least 5min before taking the first measurement.

1. Place cuff on either arm supported at heart level – on a table (or arm rest of the chair) with woman sitting with back against a chair, no tight clothing around upper arm, both feet on the floor, cuff 1-2cm above elbow.

\*\*Women must remain still (i.e. no movement or talking) while the measurement is being taken for an accurate reading.

2. Turn on machine and inflate cuff by hand, the cuff will then deflate automatically. If the cuff has not been inflated to the correct pressure, the device will indicate this with a 'beeping' sound - inflate the cuff to 30mmHg higher than the previous inflation pressure. Try to keep the device as still as possible during cuff deflation or alternatively let it rest on the table during deflation.
3. Note measurement

4. Wait 1 minute (during which the woman should remain still i.e. no movement or talking) and repeat - all women will receive two blood pressure measurements; an average of the two readings will be taken.
5. If the second measurement differs significantly (>10mmHg) from the first, a third measurement is required. In this case the second and third measurements will be averaged to determine blood pressure.

\*\*\*If the result is an error readout, repeat the above process

### 2.1.9 Step 9: Determine estimated date of delivery

1. Determine if ultrasound is available, if this information is available record it in the space provided.
2. Estimate LMP, if available record.
3. Measure symphysis-fundal height (SFH)
  1. Lie semi-recumbent on a firm surface
  2. Place tape at base of pubic bone
  3. Measure from pubic bone up to the top of the fundus and note measurement

To be taken at every visit until 24 weeks gestation is identified. This measurement will be taken in all women hypertensive and non-hypertensive.

The SFH will be used to estimate gestational age if an ultrasound is unavailable.

\*\*This will only be done at the first antepartum visits

### 2.1.10 Step 10: Assess warning symptoms of pre-eclampsia (if systolic blood pressure found to be $\geq 140$ mmHg)

cHCP asks specifically about each warning symptom for pre-eclampsia:

“Are you experiencing the following?”

- a. Headache: the patient has experienced any headache, as specifically stated to the community health care provider
- b. Visual disturbances: the patient has experienced visual disturbances (blind spots, blurry vision, scintillations/flashing lights, transient blindness), as specifically stated to the cHCP
- c. Chest pain: the patient has experienced chest pain or tightness, as specifically stated to the cHCP
- d. Dyspnoea: the patient has experienced dyspnoea (difficult, laboured breathing or shortness of breath), as specifically stated to the cHCP
- e. Abdominal pain: the patient has experienced abdominal pain (not described as right upper quadrant/epigastric pain), as specifically stated to the cHCP

### 2.1.11 Step 11: Measuring Blood Oxygen saturation using the pulse oximeter (Mozambique and Pakistan only)

As with measurement of blood pressure, while measuring the SpO<sub>2</sub>, women should be seated comfortably and asked to stay still while the device is in use. Movement can impact the validity of the measured result.

To measure SpO<sub>2</sub> the following steps should be followed:

- 
1. Ensure that the sensor is plugged into the mobile phone correctly and the light within the sensor is on
  2. Position the sensor on the woman’s finger so that the light and the detector are directly opposite each other with the light passing through the middle of the finger
  3. The sensor should fit snugly around the woman’s finger so that it does not move around but not too snugly that it is impacting the blood flow through the finger
-

4. Wait until the waveform on the phone's display becomes consistent in shape and the background colour on the screen turns green, as this indicates good signal quality from the sensor – then press start to begin the measurement.
  5. The measurement will take 60 seconds. Progress of the measurement will be indicated by a progress bar on the top part of the mobile phone screen. The progress bar will change between green and red depending on the quality of the signal coming from the finger sensor. If the majority of the measurement had poor signal quality (indicated by red background colour) the CHCP is required to repeat the measurement.
  6. Once the measurement is complete at sufficient quality, the result will be displayed as a percentage.
  7. Remove the sensor from the woman's finger once the measurement has been completed.
  8. Clean the sensor by wiping all surfaces with a 70% isopropyl alcohol wipe.
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#### **NOTES**

\*\* all recording should take place in the cell phone as well as the woman's personal antenatal card and the CHCP log book

\*\* this visit does not REPLACE an existing protocol for antenatal assessment but should be purely in addition to.

## 2.2 SUBSEQUENT VISIT PROTOCOL

### Overview

Each CLIP assessment visit will first involve an assessment of obvious signs of maternal risk including significant vaginal bleeding, stroke, lack of consciousness and seizures. In addition, all visits will include a component of education by the cHCP regarding warning signs and symptoms of pregnancy.

On all subsequent CLIP visits (after the first visit) all women will have their blood pressure measured. If the woman is found to be hypertensive (systolic BP  $\geq$  140 mmHg) she will also have her proteinuria measured and will be asked targeted questions about symptoms as described below.

### 2.2.1 Step 1: Observe for overt signs of maternal compromise

- **signs of unconsciousness**

cHCP will observe to determine if the woman is unconscious at the time of the visit. If a woman is found to be unconscious her family members should be asked to determine if she had been observed to show signs of seizure or stroke prior to losing consciousness.

PLEASE NOTE: Any woman found unconscious at the time of the cHCP visit will not be evaluated as described in the remaining protocol. The immediate concern when a cHCP encounters an unconscious woman will be to position the woman on her left side by placing a rolled blanket or hard pillow under her right hip and lumbar area. Once the woman is positioned this way the cHCP should attempt to measure the unconscious woman's blood pressure (see 2.3.5) and treat with MgSO<sub>4</sub> if sBP  $\geq$  160mmHg before urgently referring for follow-up at a CEmOC facility. While transport is being arranged the cHCP should ensure the woman is placed in the recovery position on her left side and ensure nothing is placed in the woman's mouth.

- **signs of stroke**

cHCP will visually assess for obvious signs of stroke at the beginning of the visit. Signs of stroke include either paralysis of one side of the body or a report of recent sudden loss of vision.

- **signs of eclampsia**

cHCP will visually assess for obvious signs of eclampsia at the beginning of the visit. Signs of eclampsia are defined as a sudden, violent, uncontrollable contraction of a group of muscles or a subtler sign as a brief loss of consciousness.

- **signs of vaginal bleeding**

cHCP will visually assess for obvious signs of significant vaginal bleeding at the beginning of the visit defined as antepartum vaginal bleeding with pain before the onset of labour or rupture of membranes

### 2.2.2 Step 2: Introduction and greeting

The ccHCPc should introduce her/himself and provide an acceptable introduction to the purpose of the visit, as defined by local ethics board. At this stage the ccHCPc will use the warning signs and symptoms of pregnancy pictorial aide to describe the intervention and provide information to the woman and her family about signs and symptoms to watch out for. The woman should be encouraged to seek care from the cHCP or at a primary health centre should they note any of the warning signs or symptoms during the pregnancy.

### 2.2.3 Step 3: Wash hands

The cHCP should wash their hands before performing any assessments on the woman.

#### 2.2.4 Step 4: Assess maternal status

Determine if the woman is antepartum (has not delivered yet) or postpartum (has delivered a baby recently).

#### 2.2.5 Step 5: Assess fetal status (if antenatal)

cHCP asks:

- “Have you noticed fetal movements in the last 12 hours?”

#### 2.2.6 Step 6: Take blood pressure

\* Let the woman rest (seated, no talking) for at least 5min before taking the first measurement.

1. Place cuff on either arm supported at heart level – on a table (or arm rest of the chair) with woman sitting with back against a chair, no tight clothing around upper arm, both feet on the floor, cuff 1-2cm above elbow.

\*\*Women must remain still (i.e. no movement or talking) while the measurement is being taken for an accurate reading.

2. Turn on machine and inflate cuff by hand, the cuff will then deflate automatically. If the cuff has not been inflated to the correct pressure, the device will indicate this with a 'beeping' sound - inflate the cuff to 30mmHg higher than the previous inflation pressure. Try to keep the device as still as possible during cuff deflation or alternatively let it rest on the table during deflation.
3. Note measurement
4. Wait 1 minute (during which the woman should remain still i.e. no movement or talking) and repeat - all women will receive two blood pressure measurements; an average of the two readings will be taken.
5. If second measurement differs significantly ( $>10\text{mmHg}$ ) from the first a third measurement is required. In this case the second and third measurements will be averaged to determine blood pressure.

\*\*\*If the result is error readout, repeat the above process

**PLEASE NOTE: If the woman has a systolic blood pressure  $<140\text{ mmHg}$  the visit is complete at this stage and no other CLIP assessments should be performed.**

#### 2.2.7 Step 7: Measure proteinuria (if systolic blood pressure found to be $\geq 140\text{ mmHg}$ )

1. Provide woman with small cup/bottle for urine sample collection
2. Pregnant woman urinates into a small cup provided, all samples should be clear catch and collected in a clean container
3. Immerse the dipstick completely in fresh urine and withdraw immediately, drawing edge along rim of container to remove excess
4. Hold dipstick horizontally before reading

\*cHCPs should wear clean gloves when measuring proteinuria, to be discarded

#### 2.2.8 Step 8: Assess warning symptoms of pre-eclampsia (if systolic blood pressure found to be $\geq 140\text{ mmHg}$ )

1. cHCP asks specifically about each warning symptom:  
“Are you experiencing the following?”



- a. Headache: the patient has experienced any headache, as specifically stated to the community health care provider
- b. Visual disturbances: the patient has experienced visual disturbances (blind spots, blurry vision, scintillations/flashing lights, transient blindness), as specifically stated to the community health care provider
- c. Chest pain: the patient has experienced chest pain or tightness, as specifically stated to the community health care provider
- d. Dyspnoea: the patient has experienced dyspnoea (difficult, laboured breathing or shortness of breath), as specifically stated to the community health care provider
- e. Abdominal pain: the patient has experienced abdominal pain (not described as right upper quadrant/epigastric pain), as specifically stated to the community health care provider

2.2.9 Step 9: Measuring Blood Oxygen saturation using the pulse oximeter (Mozambique and Pakistan only)

As with measurement of blood pressure, while measuring the SpO<sub>2</sub>, women should be seated comfortably and asked to stay still while the device is in use. Movement can impact the validity of the measured result. To measure SpO<sub>2</sub> the following steps should be followed:

- 
1. Ensure that the sensor is plugged into the mobile phone correctly and the light within the sensor is on
  2. Position the sensor on the woman's finger so that the light and the detector are directly opposite each other with the light passing through the middle of the finger
  3. The sensor should fit snugly around the woman's finger so that it does not move around but not too snugly that it is impacting the blood flow through the finger
  4. Wait until the waveform on the phone's display becomes consistent in shape and the background colour on the screen turns green as this indicates good signal quality from the sensor then press start to begin the measurement.
  5. The measurement will take 60 seconds. Progress of the measurement will be indicated by a progress bar on the top part of the mobile phone screen. The progress bar will change between green and red depending on the quality of the signal coming from the finger sensor. If the majority of the measurement had poor signal quality (indicated by red background colour) the CHCP is required to repeat the measurement.
  6. Once the measurement is complete at sufficient quality, the result will be displayed as a percentage.
  7. Remove the sensor from the woman's finger once the measurement has been completed.
  8. Clean the sensor by wiping all surfaces with a 70% isopropyl alcohol wipe.
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**NOTES**

\*\* all recording should take place in the cell phone as well as the woman's personal antenatal card and the CHCP log book, if these final two documents are in common use

\*\* this visit does not REPLACE an existing protocol for antenatal assessment but should be purely in addition to.

## SECTION 3: CHCP PROTOCOL FOR TREATMENT

As outlined in the CLIP visit flow-chart, several clinical measures will trigger recommendations for treatment and transport to be performed by the cHCP. This section provides instruction on how to administer the oral antihypertensive treatment (methyldopa), intramuscular magnesium sulphate, how to give advice on recommendations for referral to a facility and how to follow-up once these treatment or transport recommendations have been provided.

### 3.1 METHYLDOPA ADMINISTRATION INSTRUCTIONS

In the CLIP trial, any woman found to have a systolic blood pressure reading of  $\geq 160$  mmHg (or diastolic blood pressure  $\geq 110$  mmHg in Nigeria only) will be recommended to receive 750 mg of the oral antihypertensive, methyldopa. The following instructions outline how to provide this medication to an eligible woman:

1. Open the oral antihypertensive medication container contained in the CLIP intervention box
2. Check for expiry date and any changes in colour, consistency etc. of the medication.
3. Read the label
4. Explain to the woman the purpose of administration is to reduce her blood pressure, which was found to be very high and puts her and her baby at risk of severe complications in her pregnancy
5. Allow woman to ask any question about drugs.
6. Offer water or juice to help swallow medication.
7. Provide woman with 3 methyldopa tablets of 250mg each
8. Stay with the woman to arrange transport to a recommended facility, if possible .
9. Complete the referral card by selecting all conditions experienced by the woman and medications given. This card should be given to the woman or her accompanying family to be brought to the facility with her.
10. Save the tablet strip in the same box with woman's name, date of administration and the other details

\*\*\*Pregnant women should not receive oral medication if unconscious

### 3.2 MAGNESIUM SULPHATE ADMINISTRATION INSTRUCTIONS

In the CLIP trial, all woman who are found to be experiencing signs of recent seizure or stroke, who have a systolic BP  $\geq 160$  mmHg (or diastolic blood pressure  $\geq 110$  mmHg in Nigeria only) or a miniPIERS predicted probability  $\geq 25\%$  will be recommended to receive two, 5g intramuscular injections of magnesium sulphate, one in each buttocks. The following instructions outline how to administer this drug to an eligible woman:

1. Explain the reason and procedure briefly to the woman or attendant (as appropriate)
2. Wash hands
3. Put on gloves
4. Take the pre-prepared syringe from the medicine box
5. Check for expiry date and any change in colour, consistency etc
6. Attach needle to syringe and ensure needle is securely attached x2
7. Fill syringe with vial contents x2
8. Clean the injection site
9. Inspect skin surface for bruises, oedema or inflammation
10. Have patient assume a position appropriate for the site selected
11. Administer intra-muscularly in upper and outer quadrant of buttock x2

12. Discard needle and syringe in the designated disposal container
13. Apply pressure to the injection site for 2 minutes
14. Store the used syringe in the box with the name of the woman and reason for administration
15. Stay with the woman as long as possible to help arrange transport, accompany the woman if possible.
16. Complete the referral card by selecting all conditions experienced by the woman and medications given. This card should be given to the woman or her accompanying family to be brought to the facility with her.

\*\*Normotensive women with vaginal bleeding should not be given MgSO<sub>4</sub>

### **3.3 FACILITY REFERRAL INSTRUCTIONS**

Women in the CLIP trial will be recommended to go to a facility within 4 hours of a visit for follow-up care if they meet any treatment criteria outlined in sections 3.1 and 3.2 above or if there have been no fetal movements felt within the last 12 hours. In addition, any woman who has a systolic blood pressure measured  $\geq 140$  mmHg but who does not qualify for referral within 4 hours will be recommended to go to a facility for follow-up care within 24 hours of the visit. The process of recommending referral should include the following steps:

- 1 Refer to health facility
- 2 Assist the woman and family to identify the reason for referral by completing the referral card and providing it to them.
- 3 Have a discussion with the family in order to raise awareness of complications and danger signs and receive permission for transport from the pregnant woman and/or the family decision maker
- 4 Contact the appropriate/available mode of transport for the transfer
- 5 Carry out and report the assessment of the woman at the time of referral (blood pressure, proteinuria, seizures, and other signs and symptoms like frontal headache, visual changes, right upper quadrant pain). Enable completion of appropriate documentation and feedback to referring practitioner.
- 6 Contact referral facility to notify of transfer and current condition of pregnant woman

## Appendix E – Microlife BP 3AS1-2 and N3 BP Validation test results and Qualitative Evaluation Plans

### 1.1 Background

Accurate and regular blood pressure (BP) monitoring is a cost-effective screening tool for the early identification and management of pre-eclampsia in pregnancy. In low- and middle-income countries (LMICS), pre-eclampsia is frequently under-detected not only because attendance to antenatal care is often low, but due to inadequate training in how to take accurate blood pressure measurements, and insufficient, poorly functioning equipment. Firstly, training in the use of a cheap yet technically challenging method, the traditional sphygmomanometer is often lacking amongst health care workers staffing antenatal clinics. Secondly, there is concern over the robustness and safety of these traditional devices (those containing mercury), while the next generation aneroid instruments ideally require six-monthly re-calibration to maintain accuracy. Thirdly, the use of 'manual' BP devices such as these which require manual inflation, auscultatory skills and the observer recording the BP from a calibrated scale is associated with user-bias resulting in inaccurate measurement. This has been attributed to terminal digit preference, wrong Korotkoff sound interpretation, threshold avoidance, and incorrect deflation speeds. Third generation BP devices which automatically inflate the cuff and provide a digital reading, whilst circumventing some of these issues, also have problems since they depend on a reliable power supply or source of batteries and have poor resistance to shock and fluctuations in temperature. In addition, for all devices, staff may not always be trained in the interpretation of the BP readings, especially in those settings where it is seldom taken due to lack of equipment.

### 1.2 The Microlife 3AS 1-2 Model

The Microlife 3As 1-2 semi-automatic handheld blood pressure device will be used to measure all blood pressures for participants enrolled in the CLIP cluster randomized control trial. It has been designed and validated specifically for use in developing countries by the CRADLE (Community Blood Pressure Measurement in Rural Africa: Detection of Underlying Pre-Eclampsia, Kings College London, PI: Professor Andrew Shennan). This small handheld device can be used effectively by unskilled personnel after minimal training. We have shown it to be easy to use, reliable and accurate. It can be manufactured at low cost and the manual



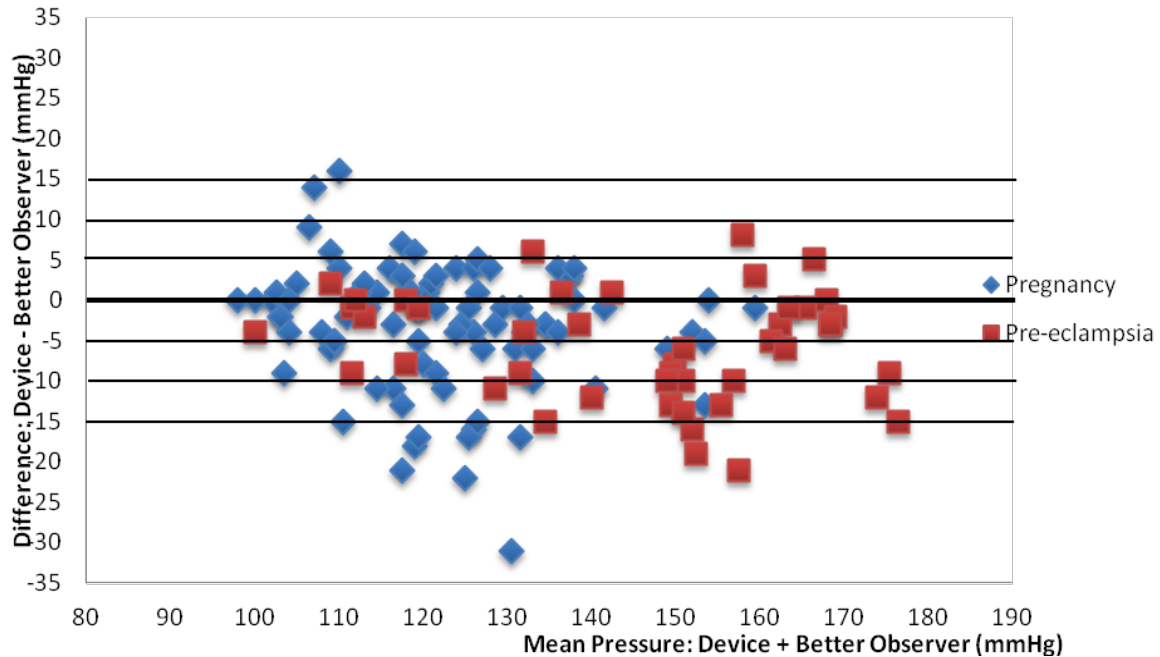
The Microlife

pump cuff inflation (rather than battery operated) means that battery supply (2 AA alkaline batteries) is only used to power the liquid crystal display showing the BP reading, allowing it to generate 1000-1500 readings on one battery set, with a lifetime use of >20,000 cycles i.e. > decade with daily use (x5). This device was uniformly acceptable to clinic health-care workers in Tanzania (formative research, CRADLE project) and functional after 3 years of extensive use in harsh environments.

#### 1.2.1 Validation of the device

Whilst many BP monitors are validated for general adult populations, few are validated in pregnancy. Common electronic BP monitors have significant difficulties in measuring during pregnancy, and are thought to significantly underestimate pressure by up to 50 mm HG. This means that even when measurements are taken with these devices, it may not be accurate in a pregnant population. The CRADLE research group, in collaboration with the Kimberly Hospital Complex, South Africa, validated the Microlife 3AS1-2 for use in a pregnant population according to the requirements of the British Hypertension Society

(BHS) protocol in a South African population. A total of 45 pregnant women were recruited. The first 30 women to fulfil the BHS Protocol criteria were selected for the analysis of systolic and diastolic pressures respectively. The Microlife 3AS1-2 device achieved an overall B/A grade in the analysis of 45 pregnant women (Table 4). Overall, the device achieved the AAMI standard for mean difference and standard deviation ( $<5\pm 8$  mmHg) in pregnancy. Mean-against-difference plots are used to illustrate the data graphically for systolic (Figure 1) and diastolic pressures (Figure 2). The poorer performance in the higher blood pressures is consistent with all BP devices and does not preclude its recommendation for use in pre-eclampsia



**Figure 1. Mean-against-difference plot of the *systolic pressures* of the better observer and the device plotted against their difference in pregnancy and preeclampsia (n=135)**

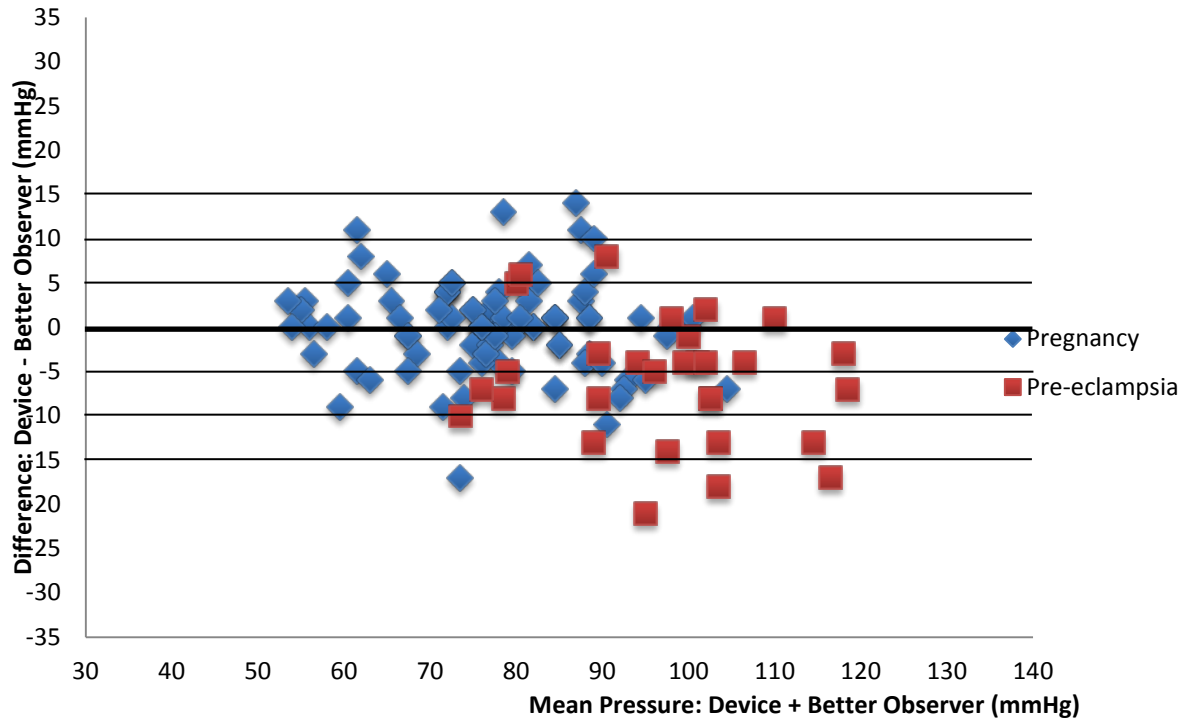


Figure 2. Mean-against-difference plot of the *diastolic pressures* of the better observer and the device plotted against their difference in pregnancy and preeclampsia (N-135)

### 1.2.2 Microlife N3 BP device

CLIP and CRADLE research groups have completed work with our partners at Microlife to adapt the 3AS1-2 device to further suit the environment. The new device (Microsoft CRADLE Vital Signs Alert) will be used in Nigeria only during the definitive trial (Figure 2). The current handheld device has been equipped with a micro-USB adapter (generic) to allow the device to be charged with generic mobile phone charging technology. Rechargeable batteries have been sealed in the device to prevent theft or loss. We have adapted the monitor to include a 'traffic light' approach to BP readings whereby readings above particular thresholds are highlighted with red or amber LED displays to alert a provider to act on the result. A traffic light approach will greatly simplify the decision making process for community health care providers regardless of literacy or dialect spoken.

The new Microsoft CRADLE Vital Signs Alert device includes the following indicators for a warning light:

- If the  $(HR/SYS) \geq 1.7$ , the **RED LED** will flash (1Hz) and show the arrow down ↓ flashing (1Hz) => severe shock (index > 1.7)
- If  $SYS \geq 160$  and  $(HR/SYS) < 1.7$ , the **RED LED** will flash (1Hz) and show the arrow up ↑ constantly (no flashing) => no severe shock, but severe hypertension or PE
- If  $DIA \geq 110$  and  $(HR/SYS) < 1.7$ , the **RED LED** will flash (1Hz) and show the arrow up ↑ constantly (no flashing) => no severe shock, but severe hypertension or PE
- If  $SYS \leq 159$  and  $(HR/SYS) \geq 0.9$  &  $< 1.7$ , the **YELLOW LED** will flash (1Hz) and show the arrow down ↓ flashing (1Hz) => high BP, shock (index < 1.7)
- If  $SYS \geq 140$  &  $\leq 159$  and  $(HR/SYS) < 0.9$ , the **YELLOW LED** will flash (1Hz) and show arrow up ↑ constantly => high BP, no shock

- If DIA  $\geq 90$  &  $\leq 109$  and (HR/SYS) < 0.9, the **YELLOW LED** will flash (1Hz) and show arrow up  $\uparrow$  constantly => high BP, no shock
- If SYS < 140 and DIA < 90 and (HR/SYS) < 0.9, the **GREEN LED** will light constantly and don't show any arrow.

In the CLIP trial, only indicators for a red light will be included as triggers for immediate treatment or referral. This device is currently being validated for use in pregnancy.

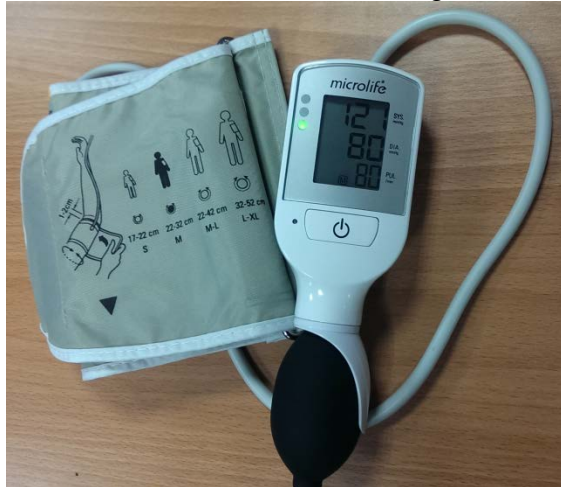


Figure 2: N3 BP device showing a normal (green light) blood pressure and heart rate reading.

### **CRADLE Qualitative Evaluation during CLIP Study**

Community Blood Pressure Monitoring in Rural Africa and Asia: Detection of Underlying Pre-Eclampsia and Shock

#### **Aim of Qualitative Evaluation**

To assess the acceptability, usability, feasibility and fidelity of the Microlife 3AS1-2 blood pressure device to community health care providers (cHCPs) in a low-resource setting and the acceptability of the device to women and other community members.

The CRADLE team would like to explore the following:

- 1. Do the cHCPs consistently use the device?**  
If not, are there particular reasons why?
- 2. Do the cHCPs consistently act on the traffic light early warning system within the device?**  
If not, are there particular circumstances when/reasons why they do not?
- 3. How easy is it to use the device?**  
Areas to explore: measuring blood pressure, reading the display, understanding traffic light early warning system, charging the device.
- 4. What impact has the device had on the workload of the cHCP and referring HCPs?**  
Areas to explore: traffic light early warning system, referral pathway, impact of false positives/negatives
- 5. What are the opinions of the women, family members, village elders, higher-level HCPs and stakeholders?**

#### **Methods of Data Collection**

**One cluster site from each country** (India, Pakistan, Mozambique, Nigeria) will be selected. From each cluster site, eight cHCPs will be selected to participate in the evaluation. Sites used in the pilot trial will be excluded, ensuring the cHCPs have not used the pilot BP device. The selection of cluster sites will be based on convenience and feedback from the site leads. The selection of cHCPs will be based on advice from the site leads.

Data collection will take place at 3 months (after initial training and sufficient practice with device) and 12 months (once users have become experienced with using the device) from the start of the definitive CLIP trial. At both time-points, data will be collected from observation, focus groups and semi-structured face-to-face interviews, over a one-week period.

**Observation** of cHCPs using the device in a clinic setting (lowest level healthcare facility) will occur at each of the selected cluster sites over a one-day period by a site researcher. **One focus groups discussion** will be run at each of the selected cluster sites and will comprise of eight cHCPs. The focus groups will be led by the site researchers in collaboration with CRADLE.

Per cluster site focus group discussion, four of the eight cHCPs will be selected to participate in **semi-structured face-to-face audio-recorded interviews**. The interviews will be led by the site researcher.

**Respondent-driven (snowball) sampling** may also take place, depending on feedback from cHCPs. Barriers to appropriate use of the device may exist at levels other than cHCP level. Therefore it may be necessary to perform interviews with women and families, members of the community, key policy-leaders and opinion leaders, and members of the referral unit, to explore these issues.

All participants will be asked to give written informed consent. Incentives, such as transport costs and refreshments, will be provided by CRADLE for all participants.



## **Appendix F – ECONOMIC EVALUATION ALONGSIDE THE CLIP TRIAL**

### **1. BACKGROUND:**

Pre-eclampsia / eclampsia imposes tremendous financial burden on the health care system and the family of the pregnant woman. Economic studies have determined that PE/E are the major reasons for antenatal admission to hospital (20%), and obstetric admissions to intensive care units (25%). Other studies determined that the hospitalization costs for the management of pre-eclampsia and associated complications were on average US\$11,208 per woman. Financial costs to the health system aside, studies elsewhere found that the death or serious illness of a mother leads to reduced household income and increased risk of dying for children under 10 years of age.

Economic evaluation in health care can play a pivotal role in informing health decision / policy makers about maximizing health benefit given the set of resource constraints. Cost-effectiveness analysis, in particular, compares the costs (in monetary units) and benefits (in natural units, for example health effects) of interventions to inform whether a particular intervention is worth implementing at a health system or population level. Literature reveals that cost-effectiveness studies have focused only on the diagnostic and clinical management of Pre-eclampsia/eclampsia (PE/E), and less on the community based interventions in the context of high burden countries. This is mainly because of the knowledge gap in the area of comprehensive community based interventions for PE/E, as large scale research trials do not exist. Therefore, we propose to undertake an economic evaluation of the CLIP Trial to determine the cost-effectiveness of the intervention in reducing maternal and perinatal mortality and severe morbidity in the selected countries.

The primary research objectives are to:

- a) Determine the costs and benefits of the CLIP Trial interventions to design the cost-effectiveness model;
- b) Estimate the incremental cost-effectiveness ratio of the CLIP Trial interventions compared with standard care for reducing maternal and perinatal mortality and major morbidity.

The secondary research objectives are to:

- a) Qualitatively identify the resources needed (cost drivers) during the trial implementation to inform design of the model;
- b) Explore perceptions of community, health care providers, and policy makers related to the implementation challenges during the trial, and perceived cost-benefits of interventions;
- c) Inform health decision / policy makers about the cost-effectiveness of the CLIP Trial for post-trial programmatic scale-up, and sustainability into existing maternal health policies in the CLIP countries.

### **2. METHODS AND RESEARCH PLAN (PAKISTAN AND MOZAMBIQUE)**

#### **2.1 Research design:**

We propose to use cost-effectiveness analysis (CEA), in conjunction with qualitative analysis, alongside the trial to prospectively evaluate the economic impact of the CLIP Trial. Cost-effectiveness remains the design of choice in economic evaluations when any particular experimental intervention (non-standard) is proposed to have similar or better clinical outcomes at decreased or equal costs compared with the standard intervention. Specifically,

our CEA will be based on a societal perspective, accounting for both costs to families and the health care system. The CLIP Trial is being conducted in four countries, which have different health care delivery systems, healthcare financing, resource allocation interests, diversity of community beliefs surrounding PE/E, care seeking behaviours and treatment preferences. Therefore, the combined approach (CEA and qualitative) will help in designing the cost modeling, and will support interpretation of economic analysis for decision makers who are considering evidence of economic value along with the effectiveness of interventions.

## **2.2 Research setting:**

The primary CLIP Trial is recruiting in four countries in two regions i.e., South Asian countries (Pakistan and India); and African countries (Nigeria and Mozambique). Given the budgetary limitations, the economic evaluation of the CLIP Trial will take place in two countries (i.e., Pakistan, and Mozambique) representing each of the two regions in the CLIP Trial. These sites are selected in consultation with lead organizations in each country, as well as through existing academic relationships. The experience of community-based maternal or perinatal health research and research infrastructure in the country was also taken into account when selecting study sites for the economic analysis of the CLIP Trial.

## **2.3 Research duration:**

The pilot phase of the CLIP Trial began in January-February 2014 and will be followed by two years of the Definitive CLIP Trial across multiple sites. The cost estimation and modelling will be developed alongside the definitive CLIP Trial, and the country specific cost-effectiveness analysis will be completed within 5 months of the trial end date. The total duration of the proposed research will be 2.5 years (December 2014 – July 2017).

## **2.4 Description of variables for designing the cost model**

### **2.4.1 Costs to health care system:**

The intention is to provide as complete a picture as possible with respect to resource utilization in the health care system. The costs to the health system will comprise the cost of the CLIP Trial interventions including mHealth technology and infrastructure, blood pressure devices, urine dipsticks, community engagement sessions, and trainings of healthcare providers at community and health facility. In addition, the cost of follow-up household visits and time spent on blood pressure monitoring/ urine dipstick by cHCP in each of the selected sites, such as Agente Polivalente Elementar (community health agents, APE) in Mozambique, and Lady Health Workers (LHW) in Pakistan. Also, the cost of cHCP's additional time and transport costs, when accompanying any identified HDP woman to a referral health facility will be calculated. Health system costs including cost of managing triage, in-patient / out-patient services, diagnostics or drugs for the treatment of HDPs provided by hospital for will also be captured. Moreover, the cost of maternal health programmes (obstetrics clinics/hospitals and outreach services) for obstetric emergencies particularly HDPs, run by NGOs or charity-based organizations working on sites will also be included.

**2.4.2 Cost to family of pregnant women:** All relevant out of pocket expenses for ambulance, hospitalization (physician fees, bed charges, nursing services), drugs and diagnostic workup related to the care for HDPs from the referral health facility. Also, the cost for informal care (care provided by family/friend-who lost wages, or paid help) will be captured, as well as, cost of lost productivity resulting from morbidity or mortality of patients with or without paid jobs. The value of the lost wages will be estimated by using a mean wage rate to missed work time, obtained from country-specific standards.

**2.4.3 Societal costs:** The total societal costs (i.e., combining of costs to the health care system and cost to the family) will be calculated for the intervention and control groups respectively.

**2.5 Methods for collecting resource utilization and unit costs data**

The information about resources utilization and costs will be collected from primary and secondary data sources in the intervention and control clusters. The consistent approach will be followed to collect these data in the intervention and control clusters. (See Table 1)

Table 1: Methods of collecting resource utilization and cost estimations in the intervention and control clusters

Types of data	Intervention Clusters	Control Clusters
<b>Resource utilization</b>	The quarterly surveillance tools, as follows: A. Pregnancy registration (Form 1) B. Regular community surveillance (Form 2) C. Health facility patient admission chart review (Form 3)	
<b>Unit cost-estimation</b>	Review of hospital budget for maternal health services (costing for bed charges, consultant fees, diagnostic services, nursing services etc.)	
	Review of district level cHCP program budget (costing for cHCP Salaries)	
	Review of site specific CLIP Trial budget (costing for intervention package)	

**2.5.1 The quarterly surveillance tools:** The structured questionnaires will be administered during the quarterly CLIP Trial surveillance in all intervention and control clusters. These questionnaires will be translated into local language, and to be pilot tested before the start of definitive CLIP Trial, are as follows:

- Pregnancy registration questionnaire (Form 1 attached): will focus on resource utilization data, which will be useful to establish baseline resource utilization in the intervention and control clusters.
- Regular community surveillance questionnaire (Form 2 attached): will focus on hospitalization of mother for pregnancy related illnesses, delivery and or newborn (after delivery) over the last 3 months. This information will be useful to quantify resource utilization (frequency of hospital visits, type of health facility), level of health facility, in-patient / out-patient care for delivery or pregnancy complications, length of stay, diagnostic tests, and therapeutic management. Also, information will be collected about mode of transport used, number of accompanying family members, days of missed wages, and information about negative externalities resulting in family-borne costs. Moreover, we will ask the respondents about out-of-pocket cost of illness for each health

resource utilized in the current pregnancy to determine unit cost estimation in the intervention and control clusters.

- Health facility patient admission chart review (Form 3 attached): will focus on the diagnostic and therapeutic interventions utilized by mother or newborn, which will be useful to quantify hospital resources utilization in the intervention and control clusters.

**2.5.2 *Review of hospital budget for health services:*** The unit cost of hospital services (diagnostics and maternal and newborn intervention) at the referral health centre will be obtained in the intervention and control clusters. The referral health facilities include both public and private health facilities, where the current CLIP Trial participants are being referred. The cost variables will focus laboratory investigations, maternal and newborn interventions as outlined in the form 3).

**2.5.3 *Review of district level cHCP program budget:*** The salaries of cHCP who are currently involved in the CLIP Trial will be determined through review of district level program budget. In addition, the transport expenses will be calculated for the extra visits of cHCP.

**2.5.4 *Review of site specific CLIP Trial budget:*** The unit cost estimates for CLIP Trial intervention package include the cost of blood pressure device, urine dipstick, oxygen saturation prop, cost of community engagement sessions, cost of training doctors, nurses, midwives, and community health workers will be determined from the trial budget for each site in the CLIP Trial.

## **2.6 *Qualitative methods of data collection to inform design of cost modeling***

Focus group (FG) is commonly used method for data collection in qualitative research to gather group opinions. Specifically, the FGs in this study are aimed to better understand the contextual variations of intervention compliance, explore any additional resources utilized, and perceptions of benefits from community perspectives. The community perspectives will be obtained from women identified as hypertensive disorders of pregnancy, husbands / father-in-law of women identified at risk of HDP, cHCP, doctors at referral health facilities, and district health decision/policy makers. (Table 2)

The semi-structured guides have been developed for each focus group (see attached) to explore the community perspectives on the following priori themes:

- Theme I: Costs drivers and health resource utilization as result of the CLIP package of care.
- Theme II: Perceived benefits of the CLIP package of care and task-shifting to community health care providers.
- Theme III: Implementation challenges for the CLIP package of care.
- Theme IV: Strategies for knowledge translation of the CLIP package of care to the wider community.
- Theme V: Strategies for health policy advocacy and program scale-up of the CLIP package of care.

The FG guides will be translated into the local languages and will be pilot tested in a randomly selected intervention clusters before the actual data collection. The digital voice recorders and hand written notes will be used to record the participants' responses during

all FGs. The FG data will be transcribed into the local language, followed by translation into English. All the translations will be confirmed by researchers with back-translation of randomly selected data segments for quality control. We anticipate a total of 10 FGs inclusive of all groups at each site; however, the desired number of FGs will be determined by the data saturation.

Table 2: Number and distribution of FGs

Number of Focus Groups with target population at each site					Total
Women identified as HDP	Husbands / father –in-law of women identified as HDP	Community health care providers	Doctors at the referral health facilities	District health decision / policy makers	
2	2	2	2	2	10

### **2.7 Participants' eligibility (Inclusion and exclusion criteria):**

The pregnant women aged 15 – 49 years recruited in the CLIP Trial in both intervention and control clusters will be eligible to take part in the economic data collection (i.e., Form 1, Form 2 and Form 3) during the quarterly surveillance rounds. For qualitative assessments, only women who were identified at risk to a HDP in the pilot phase of the CLIP Trial, those willing to participate in 45-60 session will be eligible for participating in FGs. Likewise, husbands/father-in-law of those women (identified at risk to a HDP), those willing to participate in 45-60 session will be eligible for FGs. The cHCP handling the CLIP Trial package of intervention, the medical doctors at the referral health facilities where CLIP Trial participants are referred, and district health decision makers those willing to participate in 45-60 session will be eligible to participate in the FGs. Participants will be excluded, those who are not recruited in the primary CLIP Trial and or refuse to take part in the economics data collection procedures. The participants for qualitative assessments will be selected with the help of project staff, who are making home and health facility visits for CLIP Trial surveillance.

### **2.8 Plan of data analysis:**

The total cost (quantities of resource utilized multiplied by their unit costs) will be calculated to estimate the cost on health system and family, and it will be denoted as an annual equivalent cost in US dollars rate of 2015. The incremental cost-effectiveness ratio (ICERs) will be calculated for maternal deaths/adverse pregnancy outcomes to compare the CLIP package of interventions and standard care from the societal perspective. The ICER represents additional cost of a more expensive but more effective intervention above that of the less expensive but less effective intervention divided by the difference in effectiveness. This estimate will allow us to compare the cost per unit maternal deaths/adverse pregnancy outcomes averted when switching from standard care to the CLIP package of interventions. Given the uncertainties involved in calculating the costs and trial outcomes, we will use simplistic sensitivity analysis to plot cost-effectiveness ratios. A key literature recommended using simple sensitivity analysis for CEA of package of interventions, because of the complexity of inherent correlations. The confidence region surrounding the cost-effectiveness ratio will be estimated using appropriate statistical methods, including bootstrap and Monte-Carlo analyses.

The qualitative data will be analyzed using QSR NVivo v10 software, and responses will be coded to form similar categories. Data will be interpreted through close communication between site investigators to ensure accuracy. Thematic analyses will be performed to

underscore additional cost drivers for cost modeling, implementation challenges, and perceptions of cost-benefits.

### **3. METHODS AND RESEARCH PLAN (INDIA)**

#### **Background and need for additional data collection in India**

The CLIP India Trial recruitment was completed as of October 2016; and data on health resource use was captured as part of Maternal and Newborn Health (MNH) data collection during the trial period. In addition, we have collected a wide range of maternal and newborn health services costs at 60 private health facilities; and six public health facilities. However, the data on patient level costs (i.e., out-of-pocket costs) are merely limited to health facility utilization.

*Study objective:* We aim to estimate societal costs, inclusive of opportunity costs as a result of HDPs- and other pregnancy- related illnesses and/or hospitalizations in order to complete CEA for the India CLIP trial in line with analysis completed in Pakistan and Mozambique, as described above.

*Design/settings:* A two-stage cluster rapid survey technique will be undertaken, using a population proportion to size sample in the study settings for definitive CLIP India Trial. This survey design has been widely used in expanded program on immunization (EPI) and endorsed by World Health Organization as 30X7 technique (i.e., 30 clusters; and 7 randomly selected households per cluster).

*Data collection:* A short-structured questionnaire will be administered to study eligible participants. The woman will be considered eligible, if she delivered (that resulted into a live and/or still birth(s)) during August to October 2016. Key variables will include, missed wage(s) by immediate care provider, missed wages by pregnant women; hired caretaker to do household chores; costs for meal procured during hospitalization, costs of anti-hypertensive medications at home, and transport cost (to and from health facility) related to HDPs and other pregnancy related illnesses-(other than HDPs). (Please refer to survey questionnaire)

A list of eligible households (i.e., pregnancies identified as HDP, and no-HDP in the intervention and control clusters) will be generated from MN-02 database for women who delivered during August to October 2016; and further stratified into women identified with HDPs and without HPDs. Later, we will group these eligible IDs into second-stage cluster(s) in respect to the geographical boundaries (i.e. distance of 1-2 kilometres between second-stage clusters); and randomly draw potential households for survey. A research assistant will administer the survey questionnaire. The total duration of face-to-face interview will be 15-20minutes/household.

Sample size: The CLIP cluster(s) serve as the primary-stage clusters, and Probability Proportion to Size (PPS) technique is applied to calculate number of second-stage clusters. Each cluster represents 7 households; and altogether 210 households will be needed to meet the desired sample size for this survey. Having added ~15% non-response rate to the sample size per cluster, we will have a total of 240 households (average 8 households per cluster). Out of 8 households in a given second-stage cluster, we will have a representative sample of 25% (~2 households/cluster) with HDPs; and 75% (~6 households/cluster) with no-HDPs. (Table 1)

Table 1: Desired sample size for household survey

Cluster #	# of preg. Recruited	# of clusters (PPS)	# of households (8 HH/Cluster)	HDP HH	No HDP HH
3	987	2	16	4	12
6	1291	3	21	5	16
5	1371	3	22	6	17
8	1111	2	18	5	14
1	1266	3	21	5	15
12	918	2	15	4	11
2	1065	2	17	4	13
4	1627	3	26	7	20
7	1045	2	17	4	13
10	1390	3	23	6	17
9	1678	3	27	7	20
11	1029	2	17	4	13
<b>Total</b>	<b>14778</b>	<b>30</b>	<b>240</b>	<b>60</b>	<b>180</b>

Ethics: Informed consent will be taken from participant(s) prior to administering survey questionnaire.

Data analysis:

Data analysis for the Indian CLIP trial CEA will be completed as described for both Mozambique and Pakistan in Section 2.8 above.

## **APPENDIX G: A policy analysis of postpartum maternal health policies in Ogun State, Nigeria**

### **1. Background**

The WHO defines postpartum period as beginning immediately after childbirth and lasting a period of six weeks<sup>1</sup>. This period is considered to be most critical for newborn and mothers, marking the most deaths for mothers and babies. However, this is the most neglected period for provision of critical care<sup>1</sup>. In low income countries, an estimated 70% of women do not receive postpartum care<sup>2</sup>. Further it is estimated that an estimated 15% develop potentially life-threatening problems<sup>2</sup>. It is equally important to note that for every maternal death there are a large number of women who suffer illness and suffer long-term consequences of obstetric morbidity. From a purely clinical perspective, postpartum morbid consequences include problems such as postpartum infection, anaemia, perineal tears, urinary tract infection, and depression; others defined in the literature as long-term morbidities/disabilities include incontinence, fistula, pelvic inflammatory disease, genital prolapse, hypertension, haemorrhoids, nerve damage, pituitary failure, anaemia, and infertility<sup>3,4</sup>.

Most of these deaths and morbidities are preventable, and a consequence of the poor health and nutritional status of the mother coupled with inadequate care before, during, and after delivery.

In a 2013 WHO systematic analysis of the causes of maternal deaths (in the years 2003–09), 480,000 or 19.7% maternal deaths worldwide occurred postpartum. In sub Saharan Africa alone, 15.2% maternal deaths occurred in the postpartum period, i.e. 42 days following delivery.<sup>4</sup>

The WHO guidelines on the postnatal care for the mother and the newborn<sup>1</sup> (2013) provide clinical recommendations for the care of the mother and baby upto six weeks after birth. Recommendations beyond the 24 hour period after birth include that the health care provider enquire about the general well-being and assess the woman's micturition and urinary incontinence, bowel function, healing of any perineal wound, headache, fatigue, back pain, perineal pain and perineal hygiene, breast pain, uterine tenderness and lochia. Further, the guidelines strongly suggest that women should be asked about emotional well-being as part of an assessment of overall well-being two to six weeks after birth.<sup>1</sup>

Nigeria's maternal mortality contributes to 10% of the world's maternal death<sup>4</sup>,. However, data from the 2005 National HIV/AIDS and Reproductive Health Survey indicates that only 41.2% of the women receive postnatal care<sup>4</sup> and data from 2008 Nigeria Demographic and Health Survey in 2008 shows that only 32% of women received postnatal care within 42 days of delivery<sup>5</sup>.

### **2. Main aim**

The main aim of the project is to perform policy analysis to evaluate whether the national policies in the state of Ogun, Nigeria respond to the needs of postpartum women i.e. how they address any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing following childbirth.

### **3. Objectives**

The policy analysis has the following objectives:



1. Review and compare the existing guidelines on postnatal care produced by Nigeria and International knowledge professional organizations-WHO (World Health Organisation), and national organisations such as the SOGON (Society of Obstetricians and Gynecologists of Nigeria)
2. Determine the current/recent postpartum needs in Nigeria by:
3. undertaking a literature review using papers published over the last five years (2009-2015) and using the data from the Demographic Health Survey (DHS) Nigeria to determine “needs” using the following proxies:
  - The burden of ill health postpartum in women in Nigeria by examining the prevalence and mortality rates in the postpartum period using the DHS (Demographic Health Survey) data
  - The service utilisation of postnatal care services in Nigeria
  - The service provision of postnatal care services in Nigeria
4. Identify gaps in national and local policies to address women’s needs for optimum postpartum care.
5. Interview stakeholders to triangulate findings from the literature and see what steps would be needed to address these gaps
6. Develop a set of evidence based policy recommendations for postpartum care for women in Ogun, Nigeria.

#### **4. Methods**

##### Review of guidelines

Buse Mays and Walt (2005) define ‘policy’ as a “broad statement of goals, objectives and means that create the framework for activity”.<sup>6</sup> According to the WHO, ‘guidelines’ are systematically developed evidence-based statements which assist providers, recipients and other stakeholders to make informed decisions about appropriate health interventions (defined broadly to include not only clinical procedures but also public health actions).<sup>7</sup>

In this project, both international guidelines and national policies to be analysed will be sought via literature reviews, agencies such public health institutions, professional societies, and via in-depth interviews and surveys with expert personnel, policy makers, health practitioners and patient-group representatives. The guidelines included would provide some recommendations to address postpartum maternal health.

##### Identification of policies and guidelines

To identify policies, a comprehensive search for documents (2010-present) will be done via the following sources:

- 1) peer-reviewed publications by searching the following databases: PUBMED, MEDLINE, EMBASE, CINAHL

2) grey literature search using Google to identify technical meeting reports, workshop reports, and evaluations produced by interest groups including academic institutions, governmental and intergovernmental (eg WHO, UNFPA, SOGON ) organisations

3) Policy actors will be identified from the relevant documents, and from the contacts gained via the CLIP Trial and via snowballing. Stakeholders will also be asked to share, where possible, relevant organization/office documental sources of additional information, This information will be added to secondary data sources review.

#### Determining postpartum needs using DHS data<sup>10</sup>:

Asadi-Lari et al (2003) define “needs” as “the requirement of individuals to enable them to achieve, maintain or restore an acceptable level of social independence or quality of life, as defined by a particular care agency or authority”

In the context of postpartum women this can be considered as what the women need/desire from health care services to improve overall health.

On a macro level, proxies to measure this need can be mortality rates, prevalence rates, socio economic status and service utilisation. Hence the postpartum needs would be determined via:

- The burden of ill health postpartum in women in Nigeria by examining the prevalence and mortality rates in the postpartum period using the DHS (Demographic Health Survey) data
- The service utilisation of postnatal care services in Nigeria
- The service provision of postnatal care services in Nigeria

## **5. Interviews and online questionnaires**

Stakeholders will be asked to share information about any existing sub-national, institutional or national policies that has not been found prior to the interview/online survey.

### *Definition of Stakeholders*

Stakeholders are defined as actors (individuals and organizations) involved in the development, adoption and/or implementation of policy related to postpartum health in Nigeria. These actors may be directly involved in work related to postpartum health or working in an area of global maternal health where they have had influence over the postpartum health policy in these countries. Stakeholders may be operating internationally or at the level of the country. Stakeholders’ institutional affiliations will be categorized (categories listed below). There is an understanding that some stakeholders may belong to more than one category; the stakeholders will be asked to self-identify with one of the categories below:

- global institution: Intergovernmental organisations who undertake activities to address global health issues
- academic institution: An educational institution dedicated to education and research with the ability to grant educational degrees

- government organization: An institution that is organisationally and financially not dependent on governments (non-state), non-profit orientation (non-market) and has a public benefit motive. These institutions deliver health interventions or lobby for change in policy to tackle health problems.
- non-governmental organisation/civil society organization: Associations of citizens (outside their families, friends and business) entered voluntarily to advance their interests, ideas and ideologies.
- Public health specialist institution: A public health agency or institution dedicated to specialised health issues
- professional organization: A public health agency or institution dedicated to specialised health issues (no reference)

## **6. Identification of Stakeholders**

The identification of diverse and appropriate stakeholders will be imperative to the analysis of the data. I plan to identify the stakeholders by literature searches, and by personal contacts gained in the PRE-EMPT CLIP (Community Level Interventions for Pre-eclampsia) Study, and further via "snowballing". I plan to invite 40 stakeholders (knowing that some non-responses are expected) to complete in-depth interview in person in Lagos, via Skype or via the online questionnaire.

A sample size of 20 stakeholders (either via online questionnaires or interviews) would be large enough to give a broad range of perspectives on this topic and can be expanded if it feels necessary to explore in further details the issues being raised in earlier interviews.

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## **7. Ethical considerations**

Ethics approval from the University of British Columbia (UBC) and Children's and Women's Hospital and the local ethics board in Nigeria has been obtained for the CLIP Trial. To conduct interviews, an amendment to the CLIP Trial Protocol will be submitted to the UBC ethics board and to the local ethics board in Nigeria. I anticipate this will take one or two months for approval as this is an amendment.

The LSHTM Care Ethics application will be submitted along with this process; ethics approval from the ethics board at Olabisi Onabanjo Teaching Hospital, Nigeria has been obtained for stakeholder analysis, and for the amendment.

For the analysis of publically available policy documents, ethics approval is not required.

The online survey and in-depth interviews of stakeholders will be anonymised and will include the following statement about consent: "By completing this survey/questionnaire, you are giving consent to use the information for analysis and publication." Further,

participants will be advised that their individual comments will not be linked to their institutional affiliation, just the category. Other ethical considerations are listed below.

**Online survey:** No names or e-mail addresses will be collected for the online survey. The survey will be administered using a secure portal and survey responses will be downloaded and saved on a password-protect laptop. The responses will be deleted after completion of the study

**Questionnaires:** Names and e-mail addresses will be collected to contact the participants. The participant name will be anonymised, and individual comments would not indicate their institutional affiliation, rather just the category (as listed above). The questionnaires will be stored on a password-protected computer, and all files will be deleted after conclusion of the study.

**In-depth interviews:** Names and e-mail addresses will be collected to contact the stakeholder. The participant name will be anonymised, and individual comments would not indicate their institutional affiliation, rather just the category (as listed above). Interview data will be recorded and saved for transcription. This will be stored on a password-protected computer, and all files will be deleted after conclusion of the study.

## **8. How will the data be analyzed?**

The qualitative data will be analysed using NVIVO. The framework for analysis will be decided after data collection has begun. A representative sample of the data set will be used to develop a thematic framework, and identify the major themes that emerge from the data. This thematic framework will be then developed into an index and applied to the full data set. Following this, the process of charting will be done to compare themes across cases. The data, and the charts will be reviewed to look for patterns across data and associations within the data.

To improve the quality of the qualitative analysis, the thoroughness of the analysis will be checked by comparison between cases, and within cases and also by being critical and testing of the emerging hypotheses.

The stakeholder interview will be used to triangulate findings from the literature review and the guidelines. The method of 'process tracing'<sup>8</sup> will be used to perform a within-case analysis to evaluate causal processes of decision making, and to enhance the comparative policy analysis.

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**The Community-Level Interventions for Pre-eclampsia (CLIP)  
cluster randomised trials in Mozambique, Pakistan, and India:  
an individual participant data meta-analysis – Appendix**

**CLIP Trial Protocol – Summary of Changes**

## Community-Level Interventions for Pre-eclampsia (CLIP) Trial Protocol – Summary of changes

This supplement contains the following items:

- A summary of changes between the original protocol (dated 18 February 2013) and final protocol (dated 15 July 2017). There are nine different versions of the protocol with minor changes between each; these changes have been outlined below and are highlighted in red.

### Version 1.3 (18 February 2013) to Version 1.5 (27 June 2013)

Subheading, page	Change(s)	V1.5
Objective, <b>Pg. 2</b>	Addition of Gaza throughout the document	Maputo and <b>Gaza</b> Province (Mozambique)
Pre-requisite knowledge: CLIP Feasibility Study <b>Pg. 3</b>	From D Sawchuck to P von Dadelszen throughout the document	(co-PIs: <b>P von Dadelszen</b> & R Qureshi)
The miniPIERS model (Figures 4 & 5) <b>Pg. 4</b>		The components of the miniPIERS model are: <b>parity (multiparity vs. Nuliparity)</b> gestational age <b>at identification</b> ; symptoms (Y/N) of headache/ visual disturbances, chest pain/ dyspnoea, or abdominal pain with vaginal bleeding; systolic blood pressure (sBP); and dipstick proteinuria. The AUC ROC is <b>0.8788</b> [95% CI <b>0.4744</b> , 0.80], decreasing to 73 on internal validation.
Figures 4 & 5 <b>Pg.5</b>		miniPIERS model ROC <b>curve and calibration curve</b>
<b>Pg. 10</b>		The trial will be phased from the Pilot CLIP trial to Definitive CLIP trial on the basis of a satisfactory rate of use ( $\geq 50\%$ ) of the CLIP ‘package of care’ in appropriate women <b>n all countries but Mozambique. Mozambique will be unique in that they will rely on an extended period of feasibility to pilot test all Trial systems and tools before directly beginning a definitive trial. Foregoing the Pilot in Mozambique was felt to be appropriate based on their experience with community-based surveillance and will ensure timelines of the trial are met within a manageable budget.</b>  <b>For all other countries, use of the package in the Pilot phase</b>

<b>Pg. 10</b>	Replacing HA with CHEWs	In Nigeria, these are Community Health Extension Workers (CHEWs)
Component 2a: cHCP training in home-based maternity surveillance <b>Pg. 14</b>		b. Determination of gestational age (GA) by <b>either ultrasound fetal biometry</b> , last menstrual period dates, or measurement of symphysis-fundal height.
<b>Pg. 15</b>		We anticipate that CLIP training will take an initial 2-3 days and add an extra day <b>for refresher training as needed or at a maximum</b> of every 3 months, making a total of 8-9 extra days <b>at most in each country</b> .
<b>Pg. 15</b>	New paragraph added	<b>These visits are not meant to supplement regular ANC clinical visits, but will be performed in coordination with those existing programs to achieve the frequency as previously described.</b>
2b: Diagnosis & triage – miniPIERS & CLIP POM <b>Pg. 15 and 16</b>	Removed “When the final model was applied to the validation dataset, the discrimination ability was similar to that found in the development dataset, with an AUC ROC of 0.702 (0.643 – 0.761). The model retained good calibration ability. Validation did show some reduction in model performance based on the likelihood ratio (LR) associated with using 25% as a cut-off for a positive test (LR+ 4.98 [95% CI 3.35 – 7.42]) but this was not significant. The upper limit of the confidence interval for the positive LR remains > 5 showing the”	Added: The final miniPIERS cohort used for analysis included 2081 women. The worst clinical values within the first 24hr after admission were used to develop the model. Variables included in the final miniPIERS model are parity ( <b>multiparity vs. nulliparity</b> ), gestational age on admission (or delivery if assessing a postpartum woman), the symptoms of chest pain and/or dyspnoea, headache and/or visual disturbances, vaginal bleeding with abdominal pain, and right upper quadrant pain; sBP; and dipstick proteinuria. The AUC ROC for this model was <b>0.6876868</b> (95% CI <b>0.37353 – 0.18011</b> ) which demonstrates a great ability to discriminate between women with and without adverse maternal outcomes  The stratification capacity of the model is good. Using a predicted probability cut-off of 25% resulted in a positive likelihood ratio of <b>5.09 [4.12, 6.29]</b> and classified women with <b>85.000%</b> accuracy, suggesting moderate utility of the model as a rule-in test for adverse maternal outcomes
2c: Lowering severe hypertension – oral methyldopa <b>Pg. 18</b>	Remove:  •There are signs of recent stroke	



	•miniPIERS probability is $\geq$ 25%.	
Clusters Pg. 21		There will be no Pilot phase in Mozambique. definitive phase, we will will will include 12 (6 intervention and 6 control) clusters in the trial with a public and private sector referral facility in the provinces of and Gaza Maputo and Gaza.
Pg 22	2-3 paragraphs added	We will be using only one continuous will be maternal maternal mortality and for the remaining three countries this will be Population size. The randomization algorithm ensures adequate balance on the stratification variable over the Intervention arm and the Control arm. Allocations that fail any of the balance criteria will be excluded, and only allocations that meet all criteria are eligible for consideration. The final allocation scheme is a random selection from the list of eligible allocations. The current algorithm is implemented using R Programming and can consider the following balance criteria: 1. Means ratios: the mean value over intervention clusters and the mean value over control clusters have a ratio no less than 0.9 and no greater than 1.1 (10%). 2. Mean relative to overall mean: the overall mean is the mean over all clusters; mean value in each arm is within 10% of overall mean. 3. Absolute difference in sums: the absolute difference between sums in the two arms is within 10,000. 4. Wilcoxin rank sum: Allocations where the Wilcoxin rank sum test have p-value
Pg.22		At the stage of analysis other cluster level factors identified as having an impact on the outcome will be adjusted for, including those used for stratification, such as (i) cHCP density by cluster, (ii) population density, (iii) distance to referral facilities (public or private)
Specifying and selecting study clusters Pg. 23	Removed: “The intervention and control clusters will be non-adjacent to reduce the risk of contamination.”	

Maternal death <b>Pg. 24</b>		(defined as the number of deaths during pregnancy or within 42 days of pregnancy (or last contact day if contact not maintained to 42 days) / 1,000 identified pregnancies), <b>termed Maternal Death Rate.</b>
<u>Serious end-organ complications of pre-eclampsia:</u>  <b>Pg.25</b>	Remove “intravenous/ injection sites”	Disseminated intravascular coagulation (DIC): abnormal bleeding from mucosa(mouth and/or ears)
A baseline household and facility survey <b>Pg. 26</b>	New paragraph added	In all countries except India this will be performed based on retrospective information on pregnancies occurring in the previous year. In India, the baseline data will draw from the existing prospective Maternal and Neonatal Health Registry (MNH Registry).
Cross-sectional surveys of all households <b>Pg. 27</b>		quarterly (Nigeria and Pakistan), 6-monthly (Mozambique) <b>while in India, household surveys will continue prospectively using the MNH Registry</b>
Facility-based chart audit <b>Pg. 27</b>		throughout the Trial <b>will occur in all but India where the MNH registry system already incorporates a facility chart review for each registered woman.</b>
Geo-temporal analyses <b>Pg. 32</b>	New paragraph added	Geospatial analysis will be conducted in each country by an individual from the PRE-EMPT Vancouver team with help from local GIS experts. This analysis will entail using the GPS tagged survey record to chart trends in maternal mortality and morbidity while cross referencing these outcomes to aspects of the built environment like transport and access to health care. Prior to this analysis, all personal identifiers would have been removed from the data. The data will be aggregated to describe frequencies for each of the captured variables at village level. This second set of aggregate data will be then be further analysed at UBC
Membership of the DSMB is  <b>Pg. 35</b>	Removal of: •Mike English (TBC) Reader, Department of Paediatrics, University of Oxford, Oxford, Oxon, UK and Honorary Lecturer, University of Nairobi, Nairobi, Kenya	

	<p>(<a href="http://www.kemri-wellcome.org/people/researchers/mike-english">http://www.kemri-wellcome.org/people/researchers/mike-english</a>).</p> <ul style="list-style-type: none"> <li>•Md Abdul Quaiyum (TBC) Associate Scientist, Quality and Impact of Maternal Newborn Health Service Delivery Department, International centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh.</li> </ul> <p>(<a href="http://www.icddr.org/media-centre/news/2190-icddr-scientist-receives-grant-from-the-bill-and-melinda-gates-foundation-to-support-innovative-study-on-early-management-of-post-partum-haemorrhage">http://www.icddr.org/media-centre/news/2190-icddr-scientist-receives-grant-from-the-bill-and-melinda-gates-foundation-to-support-innovative-study-on-early-management-of-post-partum-haemorrhage</a>).</p>	
3.4 TRIAL REGISTRATION <b>Pg. 36</b>	The CLIP Trial will be registered with <del>both ISRCTN and</del> clinicaltrials.gov.	The CLIP Trial will be registered with clinicaltrials.gov.
<b>Pg. 56</b>	Removed section on Health Assistant (HA) Training and current scope of practice	
<b>Pg. 66</b>		NOTE: CLIP visits should only occur after the woman being assessed has registered for the trial and provided informed consent for her participation.
2.1.4 Step 4: Record demographic data <b>Pg. 68</b>		Now will be collecting info about directins to household, age, phone number, history of previous deliveries.
Signs of unconsciousness <b>Pg. 67</b>		While transport is being arranged the cHCP should ensure the woman is placed in the recovery position on her left side <b>and ensure nothing is placed in the woman's mouth.</b>
METHYLDOPA ADMINISTRATION INSTRUCTIONS <b>Pg. 73</b>	Changes:	8. Stay with the woman to arrange transport to a recommended facility, if possible . 9. Complete the referral card by selecting all conditions experienced by the woman and medications given. This card should be given to the woman or her accompanying family to be brought to the facility with her.

		10. Save the tablet strip in the same box with woman's name, date of administration and the other details
MAGNESIUM SULPHATE ADMINISTRATION INSTRUCTIONS		15. Stay with the woman as long as possible to help arrange transport, accompany the woman if possible. 16. Complete the referral card by selecting all conditions experienced by the woman and medications given. This card should be given to the woman or her accompanying family to be brought to the facility with her
3.3 FACILITY REFERRAL INSTRUCTIONS		2 Assist the woman and family to identify the reason for referral <b>by completing the referral card and providing it to them.</b>

**Version 1.5 (27 June 2013) to Version 1.6 (09 December 2013)**

<b>Subheading, page</b>	<b>Change(s)</b>	<b>V1.6</b>
Table 2 - CLIP-related maternity care service provision <b>Pg. 7</b>	Multiple changes made within the table	
<b>Pg. 10</b>		In India, the Pilot phase will be shorter due to the difference in surveillance process as described later in this protocol.
<b>Pg. 11</b>		cHCPs will assess pregnant women with a target frequency of every 4 weeks <b>at a minimum</b> , and according to protocol (Appendix C: CLIP cHCP Working Protocol). <b>These visits can occur in the home or PHC as both are considered part of the community for the purpose of the CLIP Trial.</b>
Component 1: Community engagement <b>Pg. 14</b>	More details added to The CLIP community engagement activities	
Component 2a: cHCP training in home-based maternity surveillance <b>Pg. 15</b>	Education module for LHW was removed	
<b>Pg. 16</b>		4-weekly visits over the course of a pregnancy in women enrolled in the

		study will be considered a minimum standard for exposure to this aspect of the intervention; anything less than 4-weekly will be recorded as non-compliance with the intervention.
<b>Pg. 16</b>	Addition of Pakistan's enhanced education module	
<b>Pg. 18</b>		In Nigeria and Pakistan, women, their families and communities will be responsible for identifying and paying for transport to the CEmOC facility <b>unless the woman is found in critical condition. In these cases an emergency transport fund will be made available to ensure no undue harm comes to women found in critical condition during a CLIP visit.</b> The related fundraising activity will be a focus of the community engagement, particularly in these two countries <b>to ensure in non-urgent situations women can get to care.</b>
2d: Preventing & treating eclampsia – intramuscular MgSO4 <b>Pg. 19</b>	Addition to the optimal treatment protocol for CLIP	Through CPD activities, we will suggest optimal treatment protocols for CLIP; women referred to facilities. Following administration 10g i.m of MgSO4 in the community.
<b>Pg. 21</b>	Change from local council to PHC	In India, the unit of randomisation will be the PHC.local councils. All villages and PHCs within the PHC catchment
<b>Pg. 25</b>	Removed: "We will identify the strata in which all study clusters fall in relation to population density and randomly select 2 clusters in each group (above and below the population median) to participate in the Pilot Trial phase, within each strata the clusters will then be randomly allocated to either intervention or control using a computer-generated random number."	
Inclusion/exclusion criteria <b>Pg. 26</b>		Participants will be all consenting pregnant women aged <b>15-49 (except in Mozambique where reproductive age begins at 12)</b>

Pilot CLIP Trials <b>pg. 27</b>	With the exception of India were assessment will occur at 6 months	To justify continuing on with the Definitive CLIP Trial, by 8 months into the 12 month Pilot ( <b>with the exception of India were assessment will occur at 6 months</b> ), at least 50% of eligible women (i.e., with a trigger) should have received the package of care.
Other outcomes <b>Pg. 29</b>	More details added on functional disability	Functional disability for any reason: Inability to perform usual daily duties at specific points in time during the postpartum period that would be acceptable and expected culturally (we are determining these normal limits through local focus group discussions; these will be defined for each country prior to the commencement of each Pilot CLIP Trial)
MEASURING THE OUTCOME MEASURES AT FOLLOW UP <b>Pg. 29 and 30</b>	More details about Nigeria added to baseline household and facility survey and cross sectional survey sections	
Data collection using mHealth technology <b>Pg. 30</b>	Removed paragraph on CLIP POM data and referral centers	Added: "The first will be used in all countries and the second and third will be used in Nigeria, Mozambique and Pakistan during the definitive trial phase"
OUTCOME ADJUDICATION COMMITTEE <b>Pg. 39</b>		<b>The National Outcomes Adjudication Committee will consist of an uneven number of members of the national CLIP Team, including but not limited to one obstetrician, one paediatrician, and one methodologist/trialist.</b> The UBC management team will provide final arbitration if required.
Mozambique <b>Pg. 52</b>	Agentes Polivalentes Elementares	Agente Comunitarios de Saude

Version 1.6 (09 December 2013) to Version 1.7 ( 06 August 2014)

Subheading, page	Change(s)	V1.7
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The miniPIERS model (Figures 4 & 5)  <b>Pg. 5</b>	New paragraph added	In <b>Mozambique</b> and <b>Pakistan</b> an additional component to the miniPIERS mobile phone application will be the use of a low-cost mobile phone adapted pulse oximetry sensor to measure blood oxygen saturation (SpO2) in the pregnant population under study.
Tools & pre-requisite knowledge: Blood pressure monitoring in LMICs  <b>Pg. 5</b>	Change from Appendix D to E	See <b>Appendix E</b> for details on the validation study for the Microlife BP 3AS-2.
<b>Pg. 5</b>	New paragraph added	<b>We will undertake qualitative analysis</b> relating to the use of this tool in CLIP. Qualitative analysis plans are outlined in <b>Appendix E</b> of this protocol.
2.1 THE CLIP TRIAL DESIGN  <b>Pg. 9</b>	New sentence	The trial will be phased from the Pilot CLIP trial to Definitive CLIP trial on the basis of a satisfactory rate of use ( $\geq 50\%$ ) of the CLIP ‘package of care’ in appropriate women in all countries but Mozambique ( <b>see section 2.2 intervention for details on the ‘package of care’</b> ).
<b>Pg. 9</b>	New sentence	Monitoring during the Pilot phase of the trial to determine rate of use of the CLIP package of care will be performed by the cHCPs <b>using the POM mobile application</b> in an ongoing manner after the Pilot trial begins.
<b>Pg. 9</b>	Minor changes throughout the document	BMGF changed to <b>Bill and Melinda Gates Foundation (sponsor)</b> and DSMB changed to <b>Data Safety Monitoring Board (DSMB)</b> throughout the document.
Component 1: Community engagement  <b>Pg. 12</b>	5. Transport and treatment funds  (minor changes within the first bullet point)	<ul style="list-style-type: none"> <li>Recognise the need to develop plans for financial resources when required in emergency conditions associated with pre-eclampsia/eclampsia. Funds may be personal or from the community. <b>The community engager</b></li> </ul>

		should facilitate the individual communities to form a plan for transport and treatment funds.
<b>Pg. 14</b>	Addition of a new bullet point	iv. SpO2 measurement using the LGT Medical audio oximeter connected to the mobile phone (Mozambique and Pakistan only)
<b>Pg. 15</b>		Removed this paragraph: The CLIP POM data and clinical decisions will be transmitted to the referral CEmOC facilities so that those centres can both: (i) provide support, advice, and feedback to chCPS, and (ii) anticipate and prepare for the arrival of women who are referred with severe disease through automatic notification by SMS texting.
<b>Pg. 15</b>		Added this paragraph:  In Mozambique and Pakistan additional CLIP triggers based on use of the audio oximeter will also be included in the POM decision aid. As with the original miniPIERS model, the enhanced model including SpO2 uses a risk threshold of $\geq 25\%$ predicted probability to identify high-risk cases. Recommendations based on the updated miniPIERS model will include treatment with MgSO4 and urgent referral. An additional independent trigger of SpO2<93% will also be used in Mozambique and Pakistan to indicate urgent referral.
Lowering severe hypertension – oral methyldopa <b>Pg. 16</b>	New paragraph added	Women will be given methyldopa if identified as having severe hypertension as defined above regardless of current medication use.
<b>Component 3: Facility enhancement</b>  <b>Pg. 18</b>	Minor changes within the sentence	In India and Pakistan, EmOC facilities may be shared by intervention and control clusters, whereas they are distinct in Nigeria and Mozambique.
<b>2.4 Method of Randomisation</b>  <b>Clusters</b>  <b>Pg. 19</b>	Minor changes within the sentence	There will be no Pilot phase in Mozambique. For definitive phase, we will include 12 (6 intervention and 6 control) clusters in the trial with a public and private sector referral facility in the provinces of Maputo (3 de Fevereiro, Maluana/Maciana, Ilha Josina/Calanga, Magude) and Gaza (Xilembene, Chicumbane, Nhancutse, Chibuto, Macia, Chissano, Mazivila, Messano).
2.6 INCLUSION / EXCLUSION CRITERIA	Minor changes within the sentence	In India and Mozambique, consent will be written



Pg. 22																		
Pg. 28	<p>Mozambique column has some changes</p> <p>Before:</p> <table border="1" data-bbox="474 464 643 848"> <tr><td>24,000</td></tr> <tr><td>n/a</td></tr> <tr><td>4244,000</td></tr> <tr><td>100 [81, 119]</td></tr> <tr><td>50</td></tr> <tr><td>44</td></tr> <tr><td>10</td></tr> <tr><td>TBD</td></tr> </table>	24,000	n/a	4244,000	100 [81, 119]	50	44	10	TBD	<p>After:</p> <table border="1" data-bbox="844 451 1013 835"> <tr><td>24,405</td></tr> <tr><td>n/a</td></tr> <tr><td>24,405</td></tr> <tr><td>100 [81, 119]</td></tr> <tr><td>50</td></tr> <tr><td>44</td></tr> <tr><td>10</td></tr> <tr><td>170</td></tr> </table>	24,405	n/a	24,405	100 [81, 119]	50	44	10	170
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170																		
Economic analyses Pg. 31	Some more paragraphs added in this section	An <b>economic evaluation of the intervention and its impact will be performed</b> alongside the trial from a societal perspective (accounting for both costs to health care system and families) to guide health services decision-making for post-trial programme scale-up in the selected countries. (Full details of this plan are provided in Appendix F).																
Qualitative analysis Pg. 32	A new section added	We will use <b>survey tools, FGDs and IDIs to explore feasibility and acceptability of use of the blood pressure device</b> in CLIP in collaboration with the CRADLE study team. Full details of this plan are provided in Appendix E. In addition, <b>a cross-sectional survey of cHCPs and physicians along with interviews of randomly selected women enrolled in the CLIP study and their families will be completed</b> to understand the impact of the CLIP intervention package on cHCP decision making confidence.																
Membership of the DSMB is: Pg. 34	A few more names added	<b>Mario Merialdi</b> Senior Director, Maternal and Newborn Health, Global Health, Becton, Dickinson and Company email: <a href="mailto:mario_merialdi@europe.bd.com">mario_merialdi@europe.bd.com</a>																

		<p><b>Brian A. Darlow</b>  CureKids Professor of Paediatric Research, University of Otago Christchurch, PO Box 4345 Christchurch 8140, New Zealand  <a href="http://www.otago.ac.nz/healthsciences/expertise/profile/index.html?id=229">http://www.otago.ac.nz/healthsciences/expertise/profile/index.html?id=229</a></p>
Appendix A <b>Pg. 47</b>	New sentence under <b>Mozambique - Academic</b>	Manhiça Health Research Centre, Maputo, Mozambique
1.3 Document purpose and scope <b>Pg. 59</b>	New bullet point added	<ul style="list-style-type: none"> <li>• Measuring SpO2 (Mozambique and Pakistan only)</li> </ul>
<b>Pg. 64</b> <b>Pg. 68</b>	Adding section 2.11 and 2.29 on how to measure Blood Oxygen Saturation	Measuring Blood Oxygen saturation using the pulse oximeter (Mozambique and Pakistan only)
Appendix E <b>Pg. 71</b>	Change in the title	Appendix E – Microlife BP 3AS2 Validation test results and <b>Qualitative Evaluation Plans</b>
<b>Pg. 73</b>	Addition of a whole new section	CRADLE Qualitative Evaluation during CLIP Study
<b>Pg. 76</b>	Addition of a new appendix	Appendix F

**Version 1.6 (06 August 2014) to Version 1.8 (08 June 2014)**

<b>Subheading</b>	<b>Change(s)</b>	<b>V 1.8</b>
Current practice - the provision of maternity care and pre-eclampsia interventions Nigeria <b>Pg. 48</b>		Care is accessed through both public and private facilities throughout OGUN State with an estimated 40% of women accessing care through private institutions and 60% attending public facilities.

<b>Pg. 49</b>	Addition of Health Assistant section	Health Assistants (HA's) training & current scope of practice
3.2 MAGNESIUM SULPHATE ADMINISTRATION INSTRUCTIONS <b>Pg. 71</b>		mmHg (or diastolic blood pressure $\geq 110$ mmHg in Nigeria only)

**Version 1.8 (08 June 2014) to Version 1.9 (16 December 2014)**

<b>Subheading</b>	<b>Change(s)</b>	<b>V 1.9</b>
Figure 8: CLIP intervention diagram <b>Pg. 11</b>	Additional triggers for Nigeria, Mozambique and Pakistan	In green (for Nigeria), there are <b>additional triggers for severe diastolic hypertension and shock</b> . In red (Mozambique and Pakistan), <b>there is an additional trigger for SpO<sub>2</sub> <math>\leq 93\%</math></b> .
Tools & pre-requisite knowledge: Blood pressure monitoring in LMICs <b>Pg. 6</b>	Minor changes to the sentence	Addition of <b>Microlife CRADLE VSA</b> , throughout the document.
2b: Diagnosis & triage – miniPIERS & CLIP POM <b>Pg. 16</b>	Adding no.8 to the list	<b>8. Shock index <math>\geq 1.7</math> in Nigeria only</b>
	Additional triggers added for Nigeria	<b>In Nigeria, additional triggers will be included for severe diastolic blood pressure or severe shock index to coincide with the traffic light warning signs included in this device (see Appendix E).</b>
2c: Lowering severe hypertension – oral methyldopa <b>Pg. 17</b>	Addition of dBP	<b>sBP is <math>\geq 160</math> mmHg, or dBP <math>\geq 110</math> mmHg (in Nigeria only)</b>
Neonatal morbidity <b>Pg. 24</b>	Minor changes and additions within the section	
Qualitative analyses <b>Pg. 33</b>	Plan to undertake a policy analysis for Nigeria	We aim to undertake a <b>policy analysis to evaluate whether the national policies in the state of Ogun, Nigeria</b> respond to the needs of postpartum women.

<b>Pg. 10</b> <b>Pg. 14</b>	Addition of Health Assistants for Nigeria throughout the document	In Nigeria, there are CHEWs and Health Assistants (Has);
Appendix A <b>Pg. 50</b>	More information on access to care in Nigeria	<b>40% of women accessing care through private institutions and 60% attending public facilities.</b>
<b>Pg. 32</b>		Furthermore, to enhance the understanding of the health policy environment, we aim to undertake a policy analysis to evaluate whether the national policies in the state of Ogun, Nigeria respond to the needs of postpartum women i.e. how they address any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing following childbirth. Further details about this policy analyses can be seen in Appendix G.
<b>Pg. 83</b>	Addition of Appendix G	<b>Appendix G</b>

**Version 1.9 (16 December 2014) to Version 2.0 (07 July 2015)**

<b>Subheading</b>	<b>Change(s)</b>	<b>V 2.0</b>
<b>2b: Diagnosis &amp; triage – miniPIERS &amp; CLIP POM</b>  <b>Pg.15</b>	GA>20 weeks was added to the treatment criteria	<ol style="list-style-type: none"> <li>1. Unconsciousness (MgSO<sub>4</sub> if sBP <math>\geq</math> 160 mmHg and <b>gestational age is equal to or greater than 20 weeks (GA <math>\geq</math> 20 weeks)</b> [to be reasonably sure that the unconsciousness is associated with severe pre-eclampsia and not due to obstetric sepsis], urgent transport)</li> <li>2. Signs of recent stroke or seizure (methyldopa if sBP <math>\geq</math> 160 mmHg [to ensure BP is not lowered too much], MgSO<sub>4</sub> (if <b>GA <math>\geq</math> 20 weeks</b>) urgent transport)</li> <li>3. Significant vaginal bleeding (MgSO<sub>4</sub> if sBP <math>\geq</math> 140 mmHg and <b>GA <math>\geq</math> 20 weeks</b> [presumed abruption associated with severe pre-eclampsia] , urgent transport).</li> <li>4. No fetal movements felt in the previous 12 hrs (urgent transport [a threshold for identifying at risk fetuses</li> </ol>

		<p>that are alive at the time of screening] 39)</p> <p>5. sBP <math>\geq</math>160 mmHg (or dBP <math>\geq</math> 110 mmHg in Nigeria only) (methyldopa, MgSO4 (if GA <math>\geq</math>20 weeks) urgent transport [consistent with severe pre-eclampsia])</p> <p>6. Heavy proteinuria (<math>\geq</math>4+ by dipstick – predictive of stillbirth in miniPIERS cohort, urgent transport)</p> <p>7. miniPIERS predicted probability <math>\geq</math>25% (MgSO4 (if GA <math>\geq</math>20 weeks)urgent transport)</p> <p>8. Shock index <math>\geq</math> 1.7 in Nigeria only (the Shock index is a ratio of pulse/sBP; high shock index is an indication of poor prognosis in women with postpartum haemorrhage)</p>
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**Version 2.0 (07 July 2015) to Version 2.1 (10 March 2016)**

<b>Subheading</b>	<b>Change(s)</b>	<b>V 2.1</b>
<p><b>Figure 1</b></p> <p><b>Pg.1</b></p>	<p>Deleted the description under the figure:</p> <p>The origins and consequences of pre-eclampsia            ARDS acute respiratory distress syndrome; ARF acute renal failure; ATN acute tubular necrosis; CVA cerebrovascular accident; DbM diabetes mellitus; DIC disseminated intravascular coagulation; EVT extravillous trophoblast; IUGR intrauterine growth restriction; LV left ventricular; PRES posterior reservible leukoencephalopathy syndrome; RIND reversible ischaemic neurological deficit; SNPs single nucleotide polymorphisms; TIA transient ischaemic attack</p>	

1.3 RELEVANT CONVERGENT ACTIVITIES  <b><i>Pre-requisite knowledge: CLIP Feasibility Study</i></b>  <b>Pg. 3</b>	New sentence added:	A <b>process evaluation may be conducted in all the sites</b> to provide information on mechanisms of impact
2.16 Frequency of analyses <b>Pg. 33</b>	Interim analysis added	In the event that the site is unable to reach planned sample size, due to logistical and pragmatic challenges, then the interim analysis will be conducted once complete pregnancies (until 42 days postpartum) are expected for women making up half of the projected sample size for that country
The miniPIERS model  <b>Pg. 5</b>	New paragraph added after:	<b>Raw photoplethysmogram (PPG) will be recorded</b> to facilitate the optimal estimation of hearth rate, heart rate variability, pulse pressure variation, oxygen saturation and other parameters
	New paragraph added	<b>Raw pressure waveforms will be recorded</b> during the measurement of blood pressure
2.6 INCLUSION / EXCLUSION CRITERIA <b>Pg. 23</b>	written consent and verbal concent added	written consent <b>for surveillance (head of household/women of reproductive age) and verbal consent for the secondary visits</b> for the entire CLIP trial
2.15 TYPES OF ANALYSES/STATISTICAL PLAN  <b>Pg. 31</b>	New sentence	<b>A detail of analysis plan is included in the CLIP cRCT Statistical Analysis Plan.</b>

Version 2.1 (10 March 2016) to Version 2.2 (15 July 2017)

Subheading, pg. no	Change(s)		V 2.2	
Table 2 CLIP-related maternity care service provision (see table inserted below): <b>Pg. 7</b>				
	<b>Nigeria</b>	<b>Mozambique</b>	<b>Pakistan</b>	<b>India</b>
<b>Community-based care</b>				
<b>HOME-BASED CARE</b>				
<b>cHCPs</b>	<b>Community Health Extension Workers (CHEWs; cover 2500 population each)</b> <b>Health Assistants (Has)</b>	<b>Agente Comunitarios de Saude (APEs; cover 500-2000 population each)</b>	<b>Lady Health Workers (LHWs; cover 1000 population each)</b>	<b>Auxiliary Nurse Midwives (ANMs; cover 3000-5000 population each)</b> <b>Accredited Social Health Activists (ASHAs; cover 1000 population each)</b>
<b>Delivery in the home</b>	<b>70% births at home</b>	<b>30% births at home</b>	<b>40% births at home</b>	<b>5-10% births at home</b>
<b>PHC-based care</b>				
<b>Medical officers</b>	<b>Sometimes</b>	<b>No</b>	<b>Yes</b>	<b>Yes</b>
<b>Nurses</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>cHCPs</b>	<b>CHEWs, Health Assistants (HA)</b>	<b>ACSS</b>	<b>LHWs</b>	<b>ANMs, Lady Health Visitors (LHV)</b>
<b>BP device</b>	<b>Yes (93%)</b>	<b>Yes</b>	<b>Yes (100%)</b>	<b>Yes (100%)</b>
<b>Urine dipsticks</b>	<b>Sometimes (20%)</b>	<b>Yes</b>	<b>Few (37%)</b>	<b>Yes (90%)</b>
<b>Laboratory testing</b>	<b>Sometimes (11%)</b>	<b>Some</b>	<b>Yes (100%)</b>	<b>No</b>
<b>Ultrasound</b>	<b>Sometimes (5%)</b>	<b>No</b>	<b>Sometimes</b>	<b>No</b>
<b>Methyldopa</b>	<b>Yes (purchased by patient at pharmacy)</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>MgSO4</b>	<b>Availability of some anticonvulsant</b>	<b>Yes</b>	<b>Sometimes (38%)</b>	<b>Sometimes (56%)</b>

	(82%)			
Attend deliveries	Yes	Yes	Yes	Yes
BEmOC	Varies	No	Yes	No
Hours of available care	Information pending	Information pending	Day time only	Some services are 24/7
Facility-based care				
Number of facilities serving CLIP clusters	936 (32 public, 904 private)	56	12 (3 public, 9 private)	96
BEmOC in CLIP clusters	Information pending	10	17 (14 public, 3 private)	Information pending
CEmOC in CLIP clusters		1	12	Majority
General practitioners/ medical officers	Yes	Yes	Yes	Yes
Specialists	Rarely	Rarely	At some highest level facilities	Yes
Nurses	Yes	Yes	Yes	Yes
cHCPs	Yes	Yes	No	ANMs
BP device	Yes	Yes	Yes (100%)	Yes (100%)
Urine dipsticks	Yes	Yes	Sometimes	Yes
Laboratory testing	Yes	Yes	Yes (100%)	Yes
Ultrasound	Yes	Yes	Yes	Yes
Fetal heart assessment	Pinard; US	Pinard, Doppler, US	Pinard, CTG, US	Pinard, Doppler, CTG, US
Methyldopa	Sometimes (30%)	Yes	Yes	Yes
Other antihypertensives	Sometimes (7%)	Yes	Yes	Yes
MgSO4	Sometimes (20% stock outs)	Yes	Some	Yes
3.2 Data Safety and Monitoring Board	The DSMB will be created, including methodological and content expertise and will be comprised mainly of investigators from LMICs.		The DSMB will be created, including methodological and content expertise.	
Appendix E	Addition of N3 BP validation test		Appendix E – Microlife BP 3AS1-2 and N3 BP Validation test results and Qualitative Evaluation Plans	
	1.2.2 Planned modifications to the device		1.2.2 Microlife N3 BP device	



	Changes from future tense to past tense	CLIP and CRADLE research groups have completed work with our partners at Microlife to adapt the 3AS1-2 device to further suit the environment.
	New addition of CRADLE device indicators for warning lights	The new Microsoft CRADLE Vital Signs Alert device includes the following indicators for a warning light:
	New addition	In the CLIP trial, only indicators for a red light will be included as triggers for immediate treatment or referral. This device is currently being validated for use in pregnancy.  Insert picture  Figure 2: N3 BP device showing a normal (green light) blood pressure and heart rate reading.
Appendix F Pg. 83	Addition of:  METHODS AND RESEARCH PLAN (INDIA)	

**The Community-Level Interventions for Pre-eclampsia (CLIP)  
cluster randomised trials in Mozambique, Pakistan, and India:  
an individual participant data meta-analysis – Appendix**

**CLIP Trial Statistical Analysis Plan**

Document Title: **Statistical analysis plan for CLIP Pilot and Definitive Trials**

Version: 1.7

Date: Drafted 16 October 2015, amended last March 1, 2017

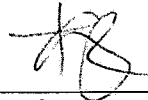
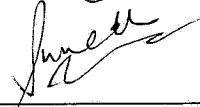
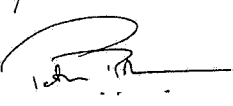
Authors: Peter von Dadelszen, Tang Lee, Joel Singer, Hubert Wong, Sumedha Sharma, Beth Payne, Marianne Vidler, Zulfiqar Bhutta, Laura A Magee

Protocol Number: ClinicalTrials.gov identifier NCT01911494

Study Title: Community level interventions for pre-eclampsia (CLIP) Trials

Principal Investigator: Peter von Dadelszen

This document has been reviewed and approved by:

Statistician <i>Tang Lee</i>		March 1, 2017
Program co-ordinator Sumedha Sharma		March 1, 2017
Principal Investigator Peter von Dadelszen		March 1, 2017

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Appended in the ‘SAP Tables’ document are the following

Table 1 Design of the Pilot Trial

Table 2 Design of the Definitive Trial

Table 3 Data fields used in the analysis of baseline and demographic variables

Table 4 Baseline outcome variables collected, by country

Table 5 Decision rule for POM acceptance of referral

Table 6 Data fields used in the analysis of POM acceptance of referral

Table 7 Data fields used in the analysis of primary outcome

Table 8 Data fields used in the analysis of secondary outcomes

Table 9 Data fields used in the analysis of other outcomes

Table 10 Data fields used in the analysis of adverse events

## 1. Introduction

### 1.1 Study Description

A cluster randomised trial designed to evaluate the implementation of community-level evidence-based care aimed at reducing pre-eclampsia-related maternal and perinatal mortality and major morbidity.

The CLIP intervention consists of the following three components:

- (i) **Community engagement** including community leaders, the women of the communities themselves, and their mothers, husbands, and mothers-in-law, regarding pre-eclampsia, its origins, symptoms, signs, and potential consequences, pre-permissions for maternal transport, and microfinancing activities around transport and treatment costs;
- (ii) Provision of hypertensive disorders of pregnancy (HDP) oriented antenatal care through **CLIP visits** and use of CLIP PIERS On the Move (POM) tool for risk stratification. Community-based health care providers (cHCPs) will assess pregnant women with a target frequency of every 4 weeks at a minimum, and according to protocol. These visits can occur in the home or primary health centre (PHC) as both are considered part of the community for the purpose of the CLIP Trial. They will be trained to enquire about women's symptoms (using country-specific pictograms), take women's blood pressure (BP) (using systolic blood pressure (sBP), check urine for protein using dipstick and measure SpO<sub>2</sub> (in Pakistan and Mozambique) on the first visit or on any subsequent visits for sBP  $\geq$ 140 mmHg. This will inform the diagnosis and risk assessment of women with pre-eclampsia.
- (iii) Use of the **CLIP 'package of care' for women with a CLIP 'trigger'** as indicated on the POM tool (i.e., oral antihypertensive therapy when indicated, intramuscular (i.m.) MgSO<sub>4</sub> when indicated; and appropriate referral to a comprehensive emergency obstetric care (CEmOC) facility when indicated).

Facility enhancement and health worker training will be conducted in both intervention and control clusters. This activity is designed to enhance skills and promote evidence-based pre-eclampsia identification and management so that women sent to facility receive quality care.

The trial was designed to occur in two phases - a Pilot phase and a Definitive phase. The Pilot phase was designed to show that the intervention was feasible, and the data for the pilot phase form part of the definitive phase analysis. As shown in Tables 1 and 2, the Pilot trial involved four clusters per country, and the number of clusters was expanded in the Definitive phase. Surveillance data from the Pilot Trial was not analysed or reviewed and no outcomes were reviewed until after the end of the Definitive Trial. The trial protocol has been registered on [clinicaltrials.gov](https://clinicaltrials.gov) with trial identifier NCT01911494.

#### 1.1.1 Update to CLIP Nigeria

The CLIP Nigeria trial was originally designed to be undertaken in Ogun State, Nigeria as a pilot and then definitive cRCT, as in the three other CLIP countries. However, challenges with data collection and data entry prompted the decision to change the research design in Nigeria to one of process evaluation. To complement the effectiveness trials in Mozambique, India, and Pakistan, the process evaluation in Nigeria will serve to assure policy makers in Nigeria that the CLIP intervention can be undertaken successfully and is supported by both the community at large and health workers at various levels. The process evaluation in Nigeria will involve data collected electronically on the POM mobile health device. Excluded from analysis will be data that were initially collected on paper and then entered electronically,

as data entry was unreliable; these data involve the baseline household survey (feasibility study pre-pilot trial) and both pregnancy registration and trial surveillance (as part of the pilot and definitive trials).

## 1.2 Trial Objectives

### Primary Objectives

- Pilot Trial (for each of Nigeria, Pakistan and India)– To implement the use of the CLIP ‘package of care’ and to observe at a minimum 50% acceptance of referral [urgent or non-urgent, to a facility able to provide CEmOC (Comprehensive Emergency Obstetric Care)] in women with a CLIP trigger
- Definitive Trial (for each of Mozambique, Pakistan and India) – To reduce pre-eclampsia-related, and all-cause, maternal and perinatal mortality and major morbidity by 20% or more in intervention clusters compared with control clusters.
- IPD meta-analysis (combining results from Mozambique, Pakistan and India)-
  - Maternal mortality & morbidity (primary outcome for the IPD meta-analysis): reduction by  $\geq 20\%$
  - Maternal and fetal/neonatal mortality & morbidity: reduction by  $\geq 20\%$
  - Maternal mortality: reduction by  $\geq 30\%$

More details are in section 2.8 and power calculations for the IPD meta-analysis are in Appendix section 4.3

### Secondary Objectives

Definitive Trial – (1) To measure the impact of the CLIP intervention on birth preparedness and complication readiness, the proportion of women who present for care at a CEmOC, and the proportion of women who deliver in facility.


## 1.3 Sample size calculations

Each country is independently powered to assess the chosen primary outcome. The data upon which the estimates have been made are routinely at the conservative end of the published or available range, and were generally provided by the site investigators. Sample size calculation for the primary outcome can be seen in Appendix 4.1. However, these calculations were revisited as planned originally, after data from the CLIP Feasibility Study and CLIP Pilot maternal and perinatal morbidity and mortality data were collected.

This review conducted independently by the Statistical Team provided insight that neonatal mortality rate in baseline varied greatly across clusters. At this point, it was also suggested by the Statistical team that adding more clusters would increase statistical power- however, this was not deemed feasible. A suggestion was then made by the statistical team to add neonatal mortality rate as a cluster level adjustment factor. More details on adjustment factors are in Section 2.1.2.

## **2.0 Data summaries and analyses**

Participants will be all pregnant women who consent to CLIP data collection, are of reproductive age (i.e., 15-49 yr in Pakistan and India, and 12-49 in Mozambique), and are identified by the community health care providers (cHCPs) assigned to their community. Data will be analysed and reported separately for each country; an individual patient level (IPD) meta-analysis combining data from all countries will be conducted following completion of all individual trials (see Section 2.7). All data will be presented by intervention and control clusters unless otherwise specified, and for all countries combined. Section 2.3.2 outlines subgroup analyses that will include within-country analysis.





## 2.1 Trial information and patient disposition

### 2.1.1. Consort diagram

The following information will be presented:

- N women enrolled, as defined by consent to participate in trial surveillance.
- N women who withdrew
- N women who were lost to follow-up
- N women who were still on follow-up at the end of the trial
- N women who were followed up postpartum

These categories will be defined as follows:

- **Withdrawal** (from trial surveillance) - captured from the withdrawal log on REDCap and Monthly Reports, identifying women who have withdrawn from data surveillance. This is further described in appendix 4.3
- **Lost to follow-up** - women without trial surveillance, who were > 6 weeks postpartum more than one surveillance cycle from the end of the trial
- **Still on follow-up**
  - Antepartum women, **or**
  - Women, without postpartum trial surveillance, who were  $\leq$  6 weeks postpartum within one surveillance cycle<sup>†</sup> from the end of the trial, **or**
- **Followed-up** (i.e., have postpartum trial surveillance)<sup>†</sup>  
<sup>†</sup> *One surveillance cycle has been defined as 3 months (as in Pakistan), with 1 added to err on the side of caution.*

### 2.1.2. Baseline and demographic variables

Summary statistics (mean, median, standard deviation, minimum, maximum and inter-quartile range for continuous variables; the number and percentage of patients with various levels of categorical variables) will be calculated for each country, for:

- Each of intervention and control clusters; and
- Within each of intervention and control clusters, for women who were (i) lost to follow-up, (ii) still on follow-up at the end of the trial, and (iii) followed up. This analysis will enable us to see how women who were followed up may have differed from women who were not.

Adjustment will be undertaken to improve precision. Adjustment for individual level variables is likely to have less impact on the results. However, we will also include these variables to maintain consistency with how cluster level adjustment variables are being handled. The planned **adjustment variables** are at both individual and cluster-levels, in addition to any other characteristics that differ between groups at the individual and cluster level, as follows:

***Individual level (N=3): maternal age***(as a continuous variable), ***parity***(nulliparous/multiparous), and ***maternal basic education*** (defined in Mozambique as attainment of Grade 5 or above, and in Pakistan as completion of 5 years or more of schooling and in India as 8 years or more of schooling. There is no formal

*definition of literacy that can be applied across all settings, however, primary schooling was defined based on the country specific information provided by the site investigators).*

The following were considered by the committee and rejected for use:

- 'Distance from facility' (defined as primary health centre, PHC) - Average distance would have to be modelled 'as the crow flies' (i.e., using straight lines from home to PHC) for India and Pakistan because there, more precise travel distances based on the actual road network cannot be calculated because of the lack of accessibility of street datasets.
- Gestational age at enrolment - Women in intervention clusters were exposed to the intervention (community engagement) and may have booked earlier for antenatal care. By adjusting for gestational age at enrolment, we may adjust for treatment effect. It is also assumed that if women (in intervention clusters) enrol in the trial earlier, we may be able to capture greater number of outcomes such as miscarriages.
- Maternal past medical history of hypertension or seizures/epilepsy

***Cluster level (N=2): population density(population of cluster/unit size of cluster) and the 'baseline' neonatal mortality rate (from the baseline household survey)***

The following were considered by rejected for use:

- The poverty index as a measure of SES is no longer being considered, as BPL card in India is not considered a reliable measure of SES.
- CHCP density is no longer being considered.

Although baseline neonatal mortality rates were not considered in the design of either the original pilot or definitive trials, these rates were found to vary substantially across clusters in the analysis of the data gathered in the Feasibility Study. It was felt that their inclusion as an adjustment variable in the final analysis would substantially improve the power to detect a treatment effect. Without knowledge of the pilot trial results, the CLIP trial steering group elected to include based neonatal mortality from the pilot trial as an adjustment in the primary analysis.

## 2.2 Primary analysis

All analyses would be intention to treat. All statistical tests will be two-sided, with significance levels of  $< 0.05$  for the primary outcome, and  $< 0.01$  for secondary and other outcomes. Comparisons will be by means of risk ratios and mean differences with 95% confidence intervals for each site.

### 2.2.1 Pilot Trials

At the end of the specified Pilot period per country (with the exception of Mozambique), the Piers On the Move data from intervention clusters was analysed for completed pregnancies to calculate referral acceptance. Surveillance data was not reviewed for intervention and control clusters except by statistical teams.

Referral acceptance was determined based on confirmation at a follow-up visit that the woman received treatment and/or went to facility. The concordance between these initial and follow-up compliance responses will be used to impute compliance for women for whom there was no follow-up visit. A minimum 50% acceptance of referral [urgent or non-urgent, to a facility able to provide CEmOC (Comprehensive Emergency Obstetric Care)] in women with a CLIP trigger was used to assess the transition of the study site from the Pilot to Definitive Trial.

These process data were shared with the CLIP Steering Committee to assess the progression of country from the Pilot to Definitive Trial. No outcome data from either intervention and control arms would be reviewed until after the end of the Definitive Trial. The pregnancies included in the Pilot trial were carried over into the Definitive Trial and will be analysed for primary outcome at the end of the Definitive Trial.

### 2.2.2 Definitive Trials

All analyses will be based on intention-to-treat principles. The primary outcome is the proportion of pregnancies resulting in at least one of maternal death, stillbirth, neonatal death, or severe morbidity in the mother or child.

Multiple imputation by chained equations (MICE) will be used to fill missing values, for both explanatory and outcome variables, before regression modeling of outcomes. Imputation will be undertaken for the composite primary outcome and then for each category of the primary outcome (i.e. maternal mortality, maternal morbidity, neonatal mortality and neonatal morbidity). This assumes that missing values are missing completely at random, that is, there are no systematic differences between the missing values and the observed values. Imputation will be repeated at least ten times, and outcome rates will be modeled in each of the derived dataset.

A hierarchical logistic regression model will be used to take into account the clustering of women within the units of randomisation. The model will adjust for key determinants of outcome, pre-specified by the investigators, at both the individual and cluster level.

Imputation will be based on adjustment variables (both individual and cluster level) and will include a term to account for any potential interaction between intervention clusters and time of enrolment (i.e. recruitment within the first 12 months of the trial vs. last 12 months).

### 2.2.2.1 Definition of the primary outcome

**Maternal death** (defined as the number of deaths during pregnancy or within 42 days of delivery (or the last postpartum contact day if contact not maintained to 42 days postpartum) / 1,000 identified pregnancies)

**Maternal morbidity** (defined as the number of women with one or more life-threatening complications of pregnancy during pregnancy or within 42 days of delivery or last postpartum contact day if contact not maintained to 42 days) / 1,000 identified pregnancies). These are the serious end-organ complications of pre-eclampsia, other major causes of maternal mortality, or life-saving interventions related to one of the aforementioned:

#### Serious end-organ complication of pre-eclampsia:

- Eclampsia: occurrence of generalised convulsions during pregnancy, labour or within 42 days of delivery in the absence of epilepsy or another condition predisposing to convulsions
- Stroke: hemiparesis and/or blindness developed during pregnancy or in the 42 days postpartum lasting greater than 48 hours
- Coma: prolonged unconsciousness  $\geq 12$  hours
- Antepartum haemorrhage: vaginal bleeding  $\geq 15$  mL with or without pain before the onset of labour
- Disseminated intravascular coagulation (DIC): abnormal bleeding from mucosa (mouth and/or ears)

#### Other major causes of maternal mortality:

- Obstetric sepsis: In the community, defined as fever and one of: abdominal/uterine tenderness, foul smelling vaginal discharge/lochia, productive cough and shortness of breath, dysuria or flank pain, headache and neck stiffness. In the facility, defined as presence of fever ( $>38^{\circ}\text{C}$ ), a confirmed or suspected infection (e.g., chorioamnionitis, septic abortion, endometritis, pneumonia) and at least one of the following: heart rate  $>90/\text{min}$ , respiratory rate  $>20/\text{min}$ , leukopenia (total leukocyte count [TLC]  $<4 \times 10^9/\text{L}$ ) or leukocytosis (TLC  $>12 \times 10^9/\text{L}$ )
- Vesicovaginal or rectovaginal fistula: continuous loss of urine and/or faeces after delivery

#### Life-saving interventions:

- Cardiopulmonary resuscitation: a set of emergency procedures including chest compressions and lung ventilation applied in cardiac arrest victims
- Dialysis: haemodialysis and/or peritoneal dialysis
- Mechanical ventilation (other than for Caesarean delivery): intubation and ventilation not related to anaesthesia
- Blood transfusion:  $\geq 1$  unit of any type of blood product
- Interventions for major postpartum haemorrhage: brace sutures, external and internal uterine compression, anti-shock garment use, internal iliac artery ligation and/or hysterectomy with or without transfusion

**Perinatal & late neonatal death** (defined as stillbirth  $[\geq 20^{+0}$  weeks and/or  $\geq 500\text{g}$  in weight], early

neonatal mortality [d 0-7 of postnatal life] and late neonatal mortality [d 8-28 of postnatal life] / 1,000 identified pregnancies)

**Neonatal morbidity** (defined as occurrence of a primary neonatal morbidity during d 0-28 of postnatal life / 1,000 identified pregnancies). The following are the primary neonatal morbidities:

- Feeding difficulty: Including inability to suckle normally or latch on to the mother's breast to feed even if the mother's milk is not let down
- Breathing difficulty: Including grunting and in-drawing of the abdomen under the ribs
- Seizure: Occurrence of any seizure event (fits)
- Lethargy: Baby not appearing normally wakeful after activities such as feeding or sleeping
- Coma: Not medically induced period of unconsciousness of any length
- Hypothermia: Cold to touch
- Umbilical cord infection: Characterized by discharge from and redness around the umbilical stump
- Skin infection: Any appearance of abnormally red, black, swollen and blistered skin with pus
- Bleeding: From anywhere
- Jaundice: Yellow skin and eyes
- Central nervous system related morbidity: Abnormal amount of vomiting as defined by the parents or caregiver with bulging or sunken fontanelle

### **2.2.2.2 Calculation of the primary outcome**

All enrolled pregnancies, with the exception of those who withdrew consent from the trial, will be included in the analysis of primary outcome. For women who were 'lost to follow up' or 'still on follow up' at the end of the trial, the primary composite outcome data will be imputed using a mixed imputation based that takes into account the risk associated with each woman depending on her personal characteristics (from pregnancy registration), cluster characteristics, and time of enrollment relative to the beginning of the trial.

### **2.2.2.3 Analysis of the primary outcome**

The data fields used in the analysis of primary outcome composite is table 7, and primary outcome is calculated from the components using the following rules:

Primary outcome occurred: If ANY of the individual components were answered 'yes' (even if some components were missing answers). Define which components were missing, and the N (%) women who had one, two, three, etc, of the components missing.

Primary outcome did not occur: If none of the components were answered 'yes', and, ANY of the components was answered 'no' (even if some components were missing answers). Define which components were missing, and the N (%) women who had one, two, three, etc, of the components missing. Our assumptions can be checked by comparing patterns of responses among women who had complete and incomplete response sets.

Primary outcome is missing: If NONE of the components was completed as 'yes' or 'no' (only 'unknown' and missing were recorded). This women will be included in the imputation.

Denominator for the primary outcome rate will be all women included in the analysis (primary outcome occurred, primary outcome did not occur, and primary outcome missing).

These rules will also be used for the calculation of all other composite variables. Section 2.3.3 shows primary outcome and its components.

### **2.2.3 Sensitivity analyses**

#### **2.2.3.1 Completed pregnancies with postpartum follow-up:** *This will assess the impact of imputation.*

We will repeat the comparison between intervention and control groups using only cases with postpartum follow-up. This will involve no imputation.

#### **2.2.3.2 Complete postpartum follow-up (for all components of primary outcome):** *This will assess the impact of our assumptions about missing components of the primary outcome.*

Pregnancies for whom we have complete outcome data (i.e., all questions were answered for the primary outcome). This will involve no imputation. However, if this is significant, then we will consider repeating 2.2.3.1 with the imputation based only for women with 42 day postpartum follow-up.

#### **2.2.3.3 Women whose EDD+3 weeks falls within the trial timeline:** *This will assess the impact of the intervention independent of gestational age at birth.* This includes women for whom the primary outcome was imputed.

#### **2.2.3.4 Women whose EDD+3 weeks plus 42 day follow up period falls within the trial timeline:** *This will assess the impact of incomplete postpartum follow-up that was <42 days postpartum.* This will involve all women for whom the primary outcome was imputed.

#### **2.2.3.5 Without adjustment:** *This will assess the impact of adjustment.* Sensitivity analyses without adjustment at either the cluster or individual levels will be conducted. This will involve all women for whom the primary outcome was imputed.

#### **2.2.3.6 Inclusion of women enrolled postpartum** *This will assess the impact of postpartum enrollment of women.* Such women in the intervention arm may have been exposed to community engagement, however will not have CLIP antenatal visits guided by POM application.

Note to file: This change was made when it was recognised that women were also enrolled postpartum in Mozambique because of six-monthly surveillance cycles and cultural barriers (such as late disclosure of pregnancy).

#### **2.2.3.7 Evaluating 'on treatment' effect:** An evaluation of treatment effect will be undertaken comparing women with one or more CLIP visits in intervention arm to women in the control arm. Assessment of the effect of the penetration of the intervention in terms of intensity of community engagement and of the CLIP visits will take place in the process evaluation within the intervention clusters. We will be unable to look at the third aspect of the intervention (i.e., effect of compliance with treatment recommendations) given small numbers.

## **2.3. Application of the intervention**

### **Application of the intervention and challenges**

This analysis is justifiable because of challenges with application of the intervention. The following criteria may be used to define differing degrees of compliance:

- A. Community Engagement – There is no clear acceptable value for the measures of community engagement. As such, we will use the following measures to rate the degree of community engagement, according to ‘higher’ community engagement (i.e., median or higher event rate or value) or ‘lower’ community engagement (i.e., below median event rate or value) in intervention clusters:
- a. N (%) meetings held
  - b. N (%) meetings at which each key individual topic was covered
  - c. N attendees (i.e., large/small meetings)
  - d. N meetings that included male decision-makers
  - e. N meetings that included community leaders (male or female)
- B. CLIP Visits and POM-guided management

Analyses will be done according to:

- N (%) of women who received a CLIP POM visit(s)
- N (%) women (of all those in the clusters who received CLIP POM visits at least once every 4 weeks and once postpartum, as specified in the study protocol)
- N (%) women who accepted (as defined in Section 2.2.1) the POM-guided transport/treatment recommendation compared with those who were not, among women who were given a recommendation

Referral acceptance was determined based on confirmation at a follow-up visit that the woman received treatment and/or went to facility. The concordance between these initial and follow-up compliance responses will be used to describe compliance for women for whom there was no follow-up visit. Decision rule for POM acceptance of referral is shown in Table 5, data fields used in the analysis of POM acceptance of referral are shown in table 6.

Withdrawal from surveillance is described in Appendix 4.3.

## 2.4 Secondary Analyses

### 2.4.1 Secondary outcomes

The secondary outcomes have been defined to measure the impact of the CLIP intervention on the delays around triage and transport.

**(1) Birth preparedness and complication readiness**, will assess the success of community engagement, and be measured by any *three* of the following, measured antenatally as close to delivery as available\*:

- (1) arranged for transport;
- (2) obtained prior permission for transport should emergency arise;
- (3) saved money for obstetric care;
- (4) identified skilled birth attendant;
- (5) identified facility for delivery.

*\*Any measurements taken postpartum will be disregarded.*

**(2) Proportion of women presenting for care at a CEmOC facility and proportion of facility births:** (This number should increase if triage (using the miniPIERS risk stratification and POM) is effective, and if there is compliance with transport to CEmOC facility.)

Methods applied to the individual components of the primary outcome will be used for the individual components of the Secondary outcome. In addition, the proportion of women achieving birth preparedness and complication readiness will be compared between intervention and control clusters, as will be the proportion of women presenting for care at an CEmOC facility, and the proportion of facility births.

Table 8 shows the data fields used in the analysis of secondary outcomes.

#### 2.4.2 Other Outcomes

- Individual components of the primary outcome, including N seizures (overall and either pre-CLIP visit or post-CLIP visit , pre- or post- MgSO4 administration where applicable), maternal death or morbidity timing relative to administration of antihypertensive therapy for severe hypertension
- Adverse events (see 2.6.1 below)
- Knowledge of pre-eclampsia/eclampsia
- Total number of: antenatal care sought, N blood pressure measurements performed by health professionals, antihypertensive therapy received
- Gestational age at delivery
- Functional disability, which is defined as the inability to perform usual daily duties at specific points in time during the postpartum period. These are defined to reflect what would be acceptable and expected culturally in each country. The normative ranges will be defined by data from the control clusters (We hypothesise that a threshold of 90<sup>th</sup> centile would be reflect return to functional ability in each of the sites, however this would be determined from the data)
- Other perinatal morbidities: neonatal fever, congenital anomaly and birth injury.

#### 2.4.3 Other Planned secondary analysis

- Cost-effectiveness of the CLIP intervention (See Appendix 4.5 for details)
- Geo-temporal analysis (MOMI) (See Appendix 4.4 for details)

We will analyse the following subgroups by country and within each of the three countries, by cluster:

- Country
  - **Cultural beliefs and practices** (alternative medicine, religious beliefs, beliefs about the medical system)
- Clusters
  - **Size** (large vs. small) - The size of the clusters would be obtained from national census data
  - **Geographical/seasonal challenges** (e.g. rivers)
- Women



- **Parity** (nulliparous vs. parous) - This analysis would be ascertained by evaluating parity (defined as deliveries at  $\geq 20$  wk and/or  $\geq 500$ g)
- **Literacy** (literate vs. illiterate)
- **Distance that women live from the PHC** (close vs. far) - PHC Distance to the PHC may have to be ascertained using GIS mapping and analysis. This would limit this analysis to the time period of Definitive Trial and would be possible in two countries: Pakistan and Mozambique
- **Poverty index**
- **Gestational age at delivery**
- Community
  - **Community engagement**
    - **High vs. low** (defined as N meetings, N attendees/meeting, N topics covered)
  - **Community health workers**
    - Baseline level of education (defined as the entry requirement for the relevant training programme)
    - Intensity of initial training
    - Attendance at updates
  - **CLIP visits**
    - **Where the visits were conducted** (PHC vs. in the home)
    - **Intensity of CLIP visits**, measure of 'compliance' with the protocol, defined as women who had prescribed N antenatal visits based on gestational age at enrollment and delivery (vs. those who did not), and women who had prescribed N postnatal visits (vs. those who did not) - OR defined by quartiles of N visits/N weeks between enrollment and delivery.
    - **Clinical compliance** with CLIP recommendations for referral
      - Women who went to facility vs. those who did not
      - Women who were referred back to the community vs. those who were not
    - **Transport** (by ambulance, private car/taxi, other transport, walking)
- Health care system
  - **Density of community health care provider per population** – defined as the N population covered by each cHCP accounting for the new cHCP hired for CLIP
  - **Quality of care at PHC** - N health care providers at PHC-level
  - **Quality of care at referral facilities** - N attendees (total) at CPD events at referral facilities (total), N (%)

- Time (later vs. earlier)
  - **Definitive vs. pilot trials** (which would exclude Mozambique)
  - **Quartiles of study period**
  - **Temporal trends** (observed/expected)

## 2.5 Interim Analysis

An interim analysis is planned for each of the three sites once complete data (until 42 days postpartum) have been received for women making up half of the planned sample size for that country. In the event that the site is unable to reach planned sample size, due to logistical and pragmatic challenges, then the interim analysis will be conducted once complete pregnancies (until 42 days postpartum) are expected for women making up half of the projected sample size for that country. Projection of sample size for each country will be based on the observed recruitment rates in the Definitive trial as follows: 12 months of recruitment in Pakistan, 15 months of recruitment in India, and 11 months of recruitment in Mozambique. The average monthly recruitment will be calculated and applied to the remaining months of the trial, to obtain the final projected sample size. The interim analysis is reviewed by the Data Safety and Monitoring Board (DSMB). The stopping rule for both benefit and harm will require an observed difference between groups associated with an alpha <0.001. Reporting and handling of adverse events will be in accordance with Good Clinical Practice (GCP) guidelines.

## 2.6 Safety Data

Adverse events (AE) and Serious adverse events (SAE) will be compared between intervention and control clusters. Analysis will be for the composite (one/more of the events), as well as for each of the events.

### 2.6.1 Definition of Adverse Events (AEs)

- Following methyldopa administration in the community, a sBP<110mmHg on arrival at facility (maternal hypotension)
  - All cases of hypotension (reported in facility from community treatment in an intervention cluster) will be pulled and cross referenced with methyldopa administration in the same women to confirm if this AE was related to the treatment
- Following MgSO<sub>4</sub> administration in the community, either respiratory depression, coma or death during transport, as diagnosed upon arrival at facility
- Transport-related injury (life or limb) or death during transport
- Injection site haematoma or infection (following either community or facility administration of i.m. MgSO<sub>4</sub>)
- ≥ 20% of women referred to facility being sent back to their communities without follow-up (monitoring community engagement and the CLIP POM)
  - This will be measured as follows:

- Include only POM visits with referral that occurred >14 days prior
- This may be antepartum or postpartum visit
- Calculate percentage of POM visits with referral that did not result in any subsequent POM visit

### **2.6.2 Definition of Serious Adverse Events (SAEs)**

Adverse events that meet all of the following criteria:

- (i) Serious
- (ii) Unexpected (in nature, severity, or frequency), and
- (iii) Thought to be related to the study intervention

### **2.7 Extraction of per-pregnancy data**

Trial participants may provide data through multiple surveys. To analyze data on a per-pregnancy level, the following rules will be used to extract the data per pregnancy for analysis:

- For variables that record the presence (“Yes”) or absence (“No”) of a condition, the analyzed value will be “Yes” if this was answered in any of the forms, “No” if this and/or “unknown” was the only answer in any of the forms, and lastly “unknown” if this was the only answer in any of the forms
  - e.g. Dialysis (Yes/No/Unknown)
- For variables that record a choice out of a list of equally weighted options, and there can only be one answer per woman, the analysed value will be the last value entered
  - e.g. Delivery location (Home/Facility/On route/Other)
- For variables that record a choice out of a list of equally weighted options, and there can multiple answers per woman, each survey response will be analysed
  - e.g. Type of facility visited during the most recent admission
- For variables that record a numeric value, and there can only be one answer per woman, the analysed value will be the last value entered
  - e.g. Age
- For variables that record a frequency value, that is recorded at each survey, the analysed value will be the summation of all values entered
  - e.g. Number of visits to hospital

### **2.8 Individual patient data meta-analysis (IPD)**

At the completion of all three trials (Mozambique, Pakistan and India), an individual patient data (IPD) meta-analysis will be conducted (at UBC). For the IPD meta-analysis, we will analyse data for women recruited at  $\geq 20$  weeks, to standardise data to the latest public declaration of pregnancy (i.e., 20 weeks in Pakistan). If baseline outcome data are available and consistent across all three countries, these data will be used for adjustment in analysis. For power calculation, see Appendix section 4.2.

### **3.0 Additional Methodological Details**

#### **3.1 Statistical Tests**

Outcome rates will be compared using measures of effect size (difference in event rates, relative risks, etc) with 95% confidence intervals. Where needed, statistical tests will be two-sided, with significance levels of 0.05 for primary outcome, and 0.001 for secondary and other outcomes, unless stated otherwise.

The population standardized risk difference will be presented as an alternate summary of the benefit of the intervention rather than as a primary analytic endpoint.

#### **3.2 Software to be Used**

SAS / R.

#### 4. Appendix

##### 4.1 CLIP country trials Sample Size Calculations

Country	Mozambique	Pakistan	India
Unit of randomization	AP	Union Council	PHC
Population per unit of randomization	25,000	32,000	27,000
Annual birth rate (/1000/yr)	40	14	22
Births/2yr	2000	900	1200
MMR (/100,000 live births)	388	267	150
Intra-cluster co-efficient	0.002 <sup>‡</sup>	0.002*	0.001**
Incidence of maternal & perinatal/neonatal M&M control clusters	14.00%	9.60%	5.40%
intervention clusters	11.10%	7.70%	4.30%
Number of clusters (total)	12	20	12
Number of births in Definitive CLIP Trial (2 years)	24,000	18,000	14,400
Additional births from Pilot CLIP Trial (4 clusters/1 year)	0	1800	2400
Total number of births (Pilot & Definitive Trials)	24,000	19,800	16,800
Expected referrals at month 6 of Pilot Trial assuming 5% incidence of HDP	100 [81, 119]	45 [32, 58]	60 [45, 75]
Number of women to be referred at month 6 of Pilot Trial to meet 50% use target	50	23	30
Number of health facilities (total)	56		
PHC/RHC	10 BEmoc	42	22
EmOC	1 CEmoc		22

<b>Number of cHCPs (total)</b>	135 APEs (71 prior to study start)	400 LHWs	260 (215 ASHAs, 45 ANMs)
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**ANM:** assistant nurse midwife; **AM: Administrative Posts;** **ASHA:** accredited social health activist; **CHEW:** community health extension worker; **cHCPs:** community health care providers; **CHW** community health worker; **EmOC,** emergency obstetric care; **LGA:** Local Government Area; **LHW:** Lady Health Worker; **M&M:** morbidity and mortality; **MMR:** maternal mortality ratio; **PHC:** Primary Health Centre; **RHC,** rural health centre.

\* calculated from Sindhi miniPIERS facility data; † assumes same ICC as Sindh (urban population in Maputo); \*\* assumes half the ICC of Sindh. In these calculations, we have used risks at the lower end of the published ranges for that risk and milieu.

#### Assumptions:

- 10% loss of individual women to follow-up
- No loss of clusters to follow-up
- Alpha of 0.05, power  $\geq 0.80$
- Anticipated effect size of a 20% reduction in all cause maternal and perinatal/neonatal morbidity and mortality
- Also, we have assumed a ratio of maternal morbidity : mortality of 5:1 (may be as high as 10:1), and a ratio of perinatal/neonatal : maternal events of 5:1 (may be as high as 10:1 – permits overlap in outcomes)
- All sample sizes will be supplemented by the data collected in each single country Pilot CLIP Trial.

## 4.2 CLIP IPD Meta-analysis Power Calculations

The combined Definitive CLIP Trials (Mozambique, Pakistan and India) cohort of 60,600 deliveries in 44 clusters over 2 years, averaging 1377 deliveries per cluster per year, will provide the following power for the IPD meta-analysis:

- CLIP Definitive Trials Primary Outcome (Maternal & fetal/neonatal mortality & morbidity): assuming a 20% effect size (incidence reduced from 10.2% to 8.2%), we would have 80% power with an ICC of 0.006.
- Maternal mortality & morbidity (primary outcome for the IPD meta-analysis): assuming a 20% effect size (incidence reduced from 1.7% to 1.4%), we would have 60% power with an ICC of 0.001. To achieve 80% power will require an ICC of <0.001 which is unlikely.
- Maternal mortality: assuming a 30% effect size (incidence reduced from 1.7% to 1.2%), we would have 80% power with an ICC of 0.002. We hope to reduce the adverse maternal event rate by  $\geq 30\%$ , primarily through community mobilisation and antenatal care by CHCPs.

## 4.3 Withdrawal

- **Mozambique:** a woman who has received a Form D (pregnancy registration), who rejects further trial surveillance (Form E). In intervention clusters, there is then consent for POM and the package of care in response to a CLIP trigger, should one develop.
- **India:** Withdrawal is defined as a woman with a MN01 who declines having MN02. In intervention clusters, there is then consent for POM and the package of care in response to a CLIP trigger, should one develop.
- **Pakistan:** Withdrawal is defined as a woman with pregnancy registration who declines to have trial surveillance (antepartum/postpartum). In intervention clusters, there is then consent for POM, and then should a CLIP trigger occur, consent for the package of care

## 4.4 The Geo-Temporal analysis

The Geo-Temporal analysis will serve to; 1) elucidate the spatial variation in community level risk for adverse maternal outcomes, 2) Identify the factors that promote maternal resilience in the different communities under study, and 3) illustrate changing rates of adverse outcomes through the timeline of the CLIP trials. The population level estimates of variables of interest will be calculated using data from the surveillance cycles, while community rates of adverse outcomes will be calculated by combining the maternal deaths and severe morbidities recorded through facility surveillance. Geographically Weighted Regression (GWR) will be used showcase the spatial variation in associations between the choice variables, and rates of adverse maternal outcomes. Communities with less than expected rates of adverse outcomes, based on their community characteristics, will be further assessed using GWR against the predetermined community resilience variables to identify the factors that are associated with maternal resilience. Key place specific factors promoting maternal resilience will be weighted and combined into an index measuring maternal resilience. Summaries of predetermined indicators of both primary and secondary outcomes of the trial will be calculated and mapped using the ArcGIS software on a quarterly basis for the entire timeline of the trial data. This will enable the creation of geo-temporal visualizations and data indicating the changing rates of outcomes throughout the timeline of the trial.

#### 4.5 Health Economics – Plan of analysis

Parameter estimates for costs and effectiveness will be derived from the CLIP surveillance questionnaire. The unit costs will be multiplied by identified health resource utilization to calculate the total cost per pregnancy, including both pregnant woman and newborns. The total cost will be calculated as the sum of the health resource utilization cost, cost of implementing the CLIP package of care, cost of routine pregnancy care and societal costs. The annual equivalent costs in local currency of selected CLIP countries will be converted to US dollar. The pregnancy outcomes (i.e. health of mother and baby) will be modelled as the effectiveness of the CLIP interventions. This will include no-adverse outcomes (healthy mother and newborn at the time of delivery) and adverse outcomes (death and/or disability of mother and baby) observed in the intervention and control groups. Using the data and parameter estimates specific to each CLIP country, the incremental cost-effectiveness ratios (ICER)s will be calculated first from a healthcare system perspective and then from a societal perspective. The country-specific ICER will be calculated as incremental cost per adverse pregnancy outcome. Comparison will be made between the country-specific ICER and the per capita value for the gross national income for the year 2015.

Given the uncertainties involved in CEA, we will use probabilistic sensitivity analysis to produce cost-effectiveness plots. The confidence region surrounding the cost-effectiveness ratio will be estimated using appropriate statistical methods, including bootstrap and Monte Carlo simulations. Life tables based on data from the World Health Organization's Southeast Asia and African regions or the West level-26 model will also be used in a sensitivity analysis. Country-specific health system budget impact analysis will be conducted to facilitate policy decisions for resource allocation.

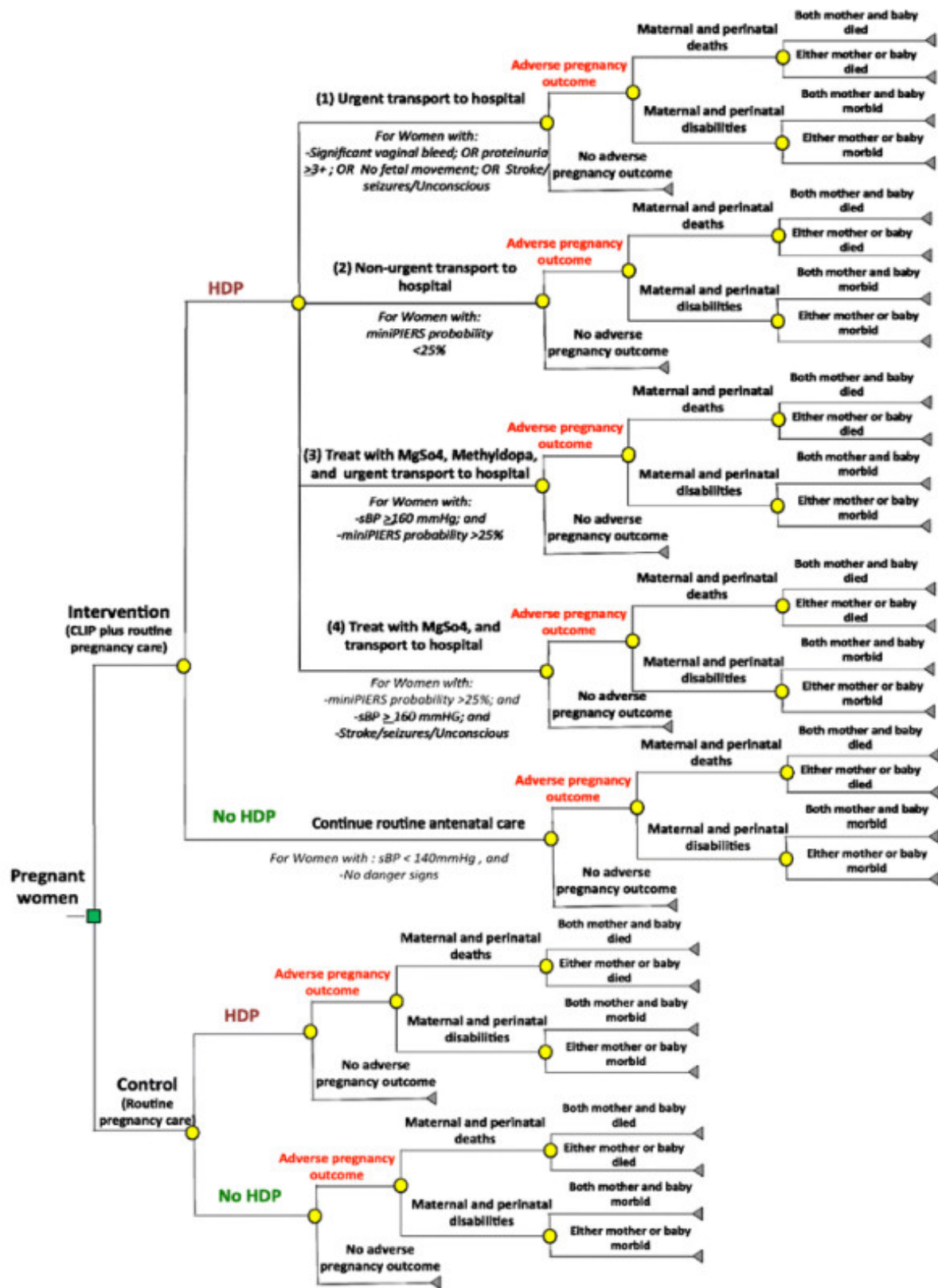
Our primary analysis for this study will be model based, guided by previous work in high-income countries as no LMIC modelling in pre-eclampsia has been done. We will use parameter estimates for costs and effectiveness coming from the CLIP Trial (see Figure 1). The unit costs will be multiplied by identified health resource utilization to calculate the total cost per pregnancy, including both pregnant woman and newborns. The total cost will be calculated as the sum of the health resource utilization cost, cost of implementing the CLIP package of care, cost of routine pregnancy care and societal costs. The annual equivalent costs in local currency of selected CLIP countries (PKR—Pakistani Rupee; INR—Indian Rupee, NGN—Nigerian Naira and MZN—Mozambican Metical) will be converted in US dollar exchange rate as of 2015. The pregnancy outcomes (i.e. health of mother and baby) will be modelled as the effectiveness of the CLIP interventions. This will include no-adverse outcomes (healthy mum and newborn at the time of delivery) and adverse outcomes (death and/or disability of mother and baby) observed in the intervention and control groups. Using the data and parameter estimates specific to each CLIP country, the ICERs will be calculated first from a healthcare system perspective and then from a societal perspective. The country-specific ICER will be calculated as Incremental cost per adverse pregnancy outcome. ICERs for the system perspective as the reference case will be of interest to country-specific health policy makers for resource allocation decisions, when switching from routine pregnancy care to CLIP plus routine pregnancy care, should CLIP be found effective. Critically, however, the ICER from a societal perspective will facilitate discourse on the full opportunity cost in the context of the selected CLIP country. In accord with the recommendation of the Commission for Macroeconomics and Health, we will compare the country-specific ICER with the per capita value for the gross national income of each of the four selected CLIP countries for the year 2015.

Given the uncertainties involved in CEA, we will use probabilistic sensitivity analysis to produce cost-effectiveness plots. The confidence region surrounding the cost-effectiveness ratio will be estimated



using appropriate statistical methods, including bootstrap and Monte Carlo simulations. Life tables based on data from the World Health Organization's Southeast Asia and African regions or the West level-26 model will also be used in a sensitivity analysis. Children in LMICs bear a disproportionately large share of the total disease burden, because of the cause structure of the disease burden by age could influence overall distribution of DALYs. As reported on previous cost-effectiveness studies in LMIC, no-age-weighting in the reference case was used on sensitivity analysis. Country-specific health system budget impact analysis will be conducted to facilitate policy decisions for resource allocation, when switching from routine pregnancy care to CLIP plus routine care, should the intervention be found effective.

Figure 1 (next page) Decision analytic tree model for economic evaluation of CLIP. HDP, hypertensive disorder of pregnancy



HDP = Hypertensive Disorder of Pregnancy

## Tables in CLIP Statistical Analysis Plan

<b>Table 1 Design of the Pilot Trial .....</b>	<b>1</b>
<b>Table 2 Design of the Definitive Trial.....</b>	<b>2</b>
<b>Table 3 Data fields used in the analysis of baseline and demographic variables .....</b>	<b>3</b>
<b>Table 4 Baseline outcome variables collected, by country .....</b>	<b>4</b>
<b>Table 6 Data fields used in the analysis of POM acceptance of referral.....</b>	<b>5</b>
<b>Table 7 Data fields used in the analysis of primary outcome.....</b>	<b>6</b>
<b>Table 8 Data fields used in the analysis of secondary outcomes .....</b>	<b>7</b>
<b>Table 9 Data fields used in the analysis of other outcomes.....</b>	<b>7</b>
<b>Table 10 Data fields used in the analysis of adverse events .....</b>	<b>9</b>

**Table1** Design of the CLIP Pilot Trials

	<b>Pakistan</b> (Hyderabad and Matiari districts in Sindh Province)	<b>India</b> (Belgaum and Bagalkot districts in Karnataka State)
<b>Timeline</b>	Feb 2014 – Dec 2014	Feb 2014 – Oct 2014
<b>Number of control clusters</b>	2	2
<b>Number of intervention clusters</b>	2	2
<b>Data collection</b>	Ongoing pregnancy registration; Regular household surveys on quarterly basis; Facility surveillance in public tertiary level hospitals only	Using MNH Registry with three time points of data collection: Pregnancy identification; Within 7 days of delivery; 42 days postpartum

**Table 2** Design of the CLIP Definitive Trials

	<b>Mozambique</b> (Maputo and Gaza Province)	<b>Pakistan</b> (Hyderabad and Matiari districts in Sindh Province)	<b>India</b> (Belgaum and Bagalkot districts in Karnataka State)
<b>Timeline</b>	Feb 2015 -	Mar 2015 -	Nov 2014 -
<b>Number of control clusters</b>	6	10	6
<b>Number of intervention clusters</b>	6	10	6
<b>Data collection</b>	Ongoing pregnancy registration; Regular household survey every six months with ongoing facility data collection; Maternal and Perinatal verbal autopsies for all deaths	Ongoing pregnancy registration; Regular household surveys on quarterly basis; Facility surveillance in public tertiary level hospitals only; Maternal and Perinatal verbal autopsies for all deaths	Using MNH Registry with three time points of data collection: Pregnancy identification; Within 7 days of delivery; 42 days postpartum

**Table 3** Data fields used in the analysis of baseline and demographic variables

<b>CRF</b>	<b>Section</b>	<b>Field</b>
Pregnancy registration	Demographic information	<ul style="list-style-type: none"><li>• Age</li><li>• Years of school</li><li>• Partner in house (Mozambique only)</li></ul>
Pregnancy registration	Obstetric history	<ul style="list-style-type: none"><li>• Parity</li><li>• High blood pressure</li><li>• Seizures</li></ul>
Pregnancy registration	Gestational age assessment	<ul style="list-style-type: none"><li>• EDD / LMP</li></ul>
Pregnancy registration	Medical history	<ul style="list-style-type: none"><li>• High blood pressure</li><li>• Seizures</li></ul>
Regular surveillance	Cost of newborn interventions / admissions	<ul style="list-style-type: none"><li>• Time to facility</li></ul>
Baseline survey	Household information	<ul style="list-style-type: none"><li>• Poverty index</li></ul>

**Table 4** Baseline outcome variables collected, by country

	<b>Pakistan</b>	<b>Mozambique</b>	<b>India</b>
N MWRA (married women of reproductive age)	x	x	x
Age of MWRA	x	x	x
Number of MWRA with one or more delivery/ abortion reported in last 12 months (n(%))	x	x	x
Number of pregnancies resulting in a live birth (n(%))	x	x	x
Number of pregnancies resulting in a still birth (n(%))	x	x	x
Number of pregnancies resulting in a miscarriage (n(%))	x	x	x
Pregnancies complicated by high blood pressure (n(%))	x	x	x
Pregnancies complicated by eclampsia(n(%))	x		x
Pregnancies complicated by seizure(n(%))		x	
Pregnancies complicated by severe headache (n(%))	x		
MRWA deaths reported n(%)	x	x	x
Maternal deaths		x	x
Age of woman at death (mean +/- sd)	x	x	x
<b>Children deaths within 1 week (early neonatal death)</b>	<b>x</b>	<b>x</b>	<b>x</b>
<b>Children deaths between 1 week and 1 month (late neonatal death)</b>	<b>x</b>	<b>x</b>	<b>x</b>
Maternal morbidity			x
Blood transfusion			x
Hysterectomy			x
Antepartum haemorrhage			x
Coma			x
Failure to form clots			x
Fever & symptom			x
Headache and stiff neck			x
Cough and shortness of breath			x
Abd pain or uterine tenderness			x
Flank pain			x
Foul smelling vag discharge			x
Received Anti-shock garment			x
Received Bimanual uterine compression			x
Received Brace sutures			x
Received CPR			x
Received Dialysis			x
Received Internal iliac artery ligation/devascularisation procedure			x
Received Mechanical ventilation			x
Seizure (fits)			x
Stroke			x

Neonatal Morbidity			x
Breathing problems			x
Feeding problems			x
Lethargy			x
Coma (neonatal)			x
Seizure (neonatal)			x
Umbilical stump infection			x
Skin infection			x
Jaundice			x
Diarrhea/vomiting			x
Bleeding			x

**Table 5** Decision rule for POM acceptance of referral

Follow-up response (Did you go to hospital?):	Yes			No			Missing		
	Accept	Refuse	Missing	Accept	Refuse	Missing	Accept	Refuse	Missing
Response given immediately following recommendation:	Accept	Refuse	Missing	Accept	Refuse	Missing	Accept	Refuse	Missing
Acceptance	✓	✓	✓	X	X	X	✓	X	Missing

**Table 6** Data fields used in the analysis of POM acceptance of referral

CRF	Section	Field
PIERS on the Move	Visit	<ul style="list-style-type: none"> <li>Transport</li> </ul>
PIERS on the Move	Follow-up	<ul style="list-style-type: none"> <li>Went to hospital after last home visit</li> </ul>

**Table 7** Data fields used in the analysis of primary outcome

CRF	Section	Field
Regular surveillance	Demographic information	<ul style="list-style-type: none"> <li>• Deceased</li> </ul>
Regular surveillance	Maternal conditions and interventions	<ul style="list-style-type: none"> <li>• Cardiopulmonary resuscitation (CPR)</li> <li>• Mechanical ventilation</li> <li>• Dialysis</li> <li>• Blood transfusion</li> <li>• Disseminated intravascular coagulation (DIC)</li> <li>• Antepartum haemorrhage</li> <li>• Anti-shock garment</li> <li>• Hysterectomy</li> <li>• Stroke</li> <li>• Seizure</li> <li>• Coma</li> <li>• Obstetric sepsis</li> </ul>
Regular surveillance	Perinatal outcomes	<ul style="list-style-type: none"> <li>• Birth outcome</li> <li>• Death within one week of birth</li> <li>• Death between one week and one month of age</li> </ul>
Regular surveillance	Perinatal outcomes	<ul style="list-style-type: none"> <li>• Feeding difficulty</li> <li>• Breath difficulty</li> <li>• Seizure</li> <li>• Lethargy</li> <li>• Coma</li> <li>• Hypothermia</li> <li>• Umbilical cord infection</li> <li>• Skin infection</li> <li>• Bleeding</li> <li>• Jaundice</li> <li>• Central nervous system related morbidity</li> </ul>



**Table 8** Data fields used in the analysis of secondary outcomes

<b>CRF</b>	<b>Section</b>	<b>Field</b>
Regular surveillance	Delivery information	<ul style="list-style-type: none"> <li>• Location of delivery</li> </ul>
Regular surveillance	Birth preparedness	<ul style="list-style-type: none"> <li>• Where to deliver</li> <li>• Skilled birth attendant</li> <li>• Transportation plan</li> <li>• Funds saved for emergencies</li> <li>• Permission to go seek care</li> </ul>
Regular surveillance	Care-seeking behaviour	<ul style="list-style-type: none"> <li>• Care sought from health care provider</li> <li>• Visits to primary health centres</li> <li>• Visits to higher level facilities</li> </ul>

**Table 9** Data fields used in the analysis of other outcomes

<b>CRF</b>	<b>Section</b>	<b>Field</b>
Regular surveillance	Delivery information	<ul style="list-style-type: none"> <li>• Location of delivery</li> <li>• Blood pressure measured</li> <li>• Antihypertensive medications</li> </ul>
Regular surveillance	Pre-eclampsia knowledge	<ul style="list-style-type: none"> <li>• Abnormal bleeding after delivery</li> <li>• High blood pressure during pregnancy</li> <li>• High blood pressure can cause death of pregnant women</li> <li>• Seizures during pregnancy</li> <li>• Headache</li> <li>• Visual disturbance</li> <li>• Chest pain</li> <li>• Shortness of breath</li> <li>• Nausea and vomiting</li> <li>• Abdominal pain</li> <li>• Vaginal bleeding</li> </ul>

CRF	Section	Field
		<ul style="list-style-type: none"> <li>• Unconsciousness</li> <li>• Stroke</li> <li>• Seizures</li> <li>• Unusual swelling</li> </ul>
Regular surveillance	Medications and adverse effects	<ul style="list-style-type: none"> <li>• Received MgSO4</li> </ul>
PIERS on the Move	Visit	<ul style="list-style-type: none"> <li>• MgSO4</li> </ul>
PIERS on the Move	Follow-up	<ul style="list-style-type: none"> <li>• Followup_MgSO4</li> <li>• Haematoma</li> <li>• Infection</li> </ul>
Regular surveillance	Functional disability	<ul style="list-style-type: none"> <li>• Take care of newborn</li> <li>• Wash babies' clothes</li> <li>• Prepare meals</li> <li>• Clean the house</li> <li>• Get water</li> <li>• Work in the fields</li> <li>• Go to the market</li> <li>• Return to work/paid employment</li> </ul>

**Table 10** Data fields used in the analysis of adverse events

<b>CRF</b>	<b>Section</b>	<b>Field</b>
PIERS on the Move	Visit	<ul style="list-style-type: none"><li>• Methyldopa</li><li>• MgSO4</li><li>• Visit date</li></ul>
PIERS on the Move	Follow-up	<ul style="list-style-type: none"><li>• Physical injury during transport</li><li>• Haematoma at injection site</li><li>• Infection at injection site</li></ul>
Facility Surveillance	Visit information	<ul style="list-style-type: none"><li>• Reason for seeking care</li><li>• Status on arrival</li></ul>
Facility Surveillance	Clinical characteristics on arrival	<ul style="list-style-type: none"><li>• Blood pressure</li></ul>
Facility Surveillance	MgSO4-related adverse effects	<ul style="list-style-type: none"><li>• Haematoma at injection site</li><li>• Infection at injection site</li></ul>

**The Community-Level Interventions for Pre-eclampsia (CLIP)  
cluster randomised trials in Mozambique, Pakistan, and India:  
an individual participant data meta-analysis – Appendix**

**CLIP Trial Data Sharing Statement**

## CLIP Trials Data Sharing Statement

The CLIP Trial data are de-identified participant-level data. Once the primary CLIP manuscripts, individual participant data meta-analysis, and papers based on the other pre-defined analyses are published as per the Statistical Analysis Plan (SAP), the data will be freely available to academically-active entities (e.g., universities, NGOs, multilaterals), with the CLIP Principal Investigator (Peter von Dadelszen) or named delegate as a named co-investigator, for the purposes of pregnancy-related research and within the limits of the informed consent obtained. Access will be through the CLIP Trials Data Access Committee\*, contacted at 'PRE-EMPT@cw.bc.ca', as referenced on our website at 'https://PRE-EMPT.bcchr.ca'. A full data dictionary and all study documents will be available. Access will be through written application. When approved, a quote for the costs of preparing the data will be provided to the applicant.

By submitting an application form, the investigator agrees that s/he has read, understood and agrees to the terms and conditions below:

1. S/he is an academically-active researcher affiliated with an entity able to engage in a data transfer agreement;
2. S/he warrants that the information entered is to the best of her/his knowledge full and correct;
3. S/he agrees that the Data Sharing Agreement will only be used for the specific project outlined in the application;
4. S/he represents that s/he has obtained the necessary approvals to transfer the data and/or receive the data under this Data Sharing Agreement;
5. S/he understands that the responses provided will form part of a legally-binding document;
6. S/he understands that the Agreement is not valid until a fully-executed copy, with signatures from all parties, is emailed to PRE-EMPT@cw.bc.ca); and
7. S/he understands that no modifications can be made to the Data Sharing Agreement and if modifications are made, the Data Sharing Agreement will be rendered invalid.

There is no pregnancy-specific repository for us to access, but once the primary papers for the CLIP Trials have been published, we will be depositing a copy of our data in the HBGDki repository at the Bill & Melinda Gates Foundation, our funder. The permitted uses and disclosures of these data are as follows:

1. The Foundation will limit the use and disclosure of the CLIP data to conduct research related to achieving the goals of the Foundation as represented above. The Foundation may also de-identify the data set and aggregate it with other de-identified information.
2. The Foundation will restrict access to the CLIP data to individuals involved in the Foundation's research who have a need to access the CLIP data to carry out their duties as they relate to the Permitted Uses and Disclosures identified above, and any such access will be consistent with the assurances and obligations set forth in this Agreement. The Foundation will use appropriate safeguards to prevent use or disclosure of the CLIP data other than as permitted by this Agreement.
3. The Foundation will report to HBGDki Collaborator any use or disclosure of the CLIP data not provided for by this Agreement of which the Foundation becomes aware.

4. The Foundation will ensure that any agents, including subcontractors, to whom it provides the CLIP data, if any, agree to the same restrictions and conditions that apply to the Foundation with respect to such information.

*\* The **Data Access Committee** is made up of the following individuals: Peter von Dadelszen and Laura A. Magee (King's College London, UK); Zulfiqar A Bhutta (Aga Khan University, Karachi, Pakistan and the Hospital for Sick Children, Toronto, Canada); Rahat N Qureshi (Aga Khan University, Karachi, Pakistan); Ashalata A Mallapur (S Nijalingappa Medical College, Bagalkote, India); Mrutyunjaya B Bellad and Shivaprasad Goudar (KLE Academy of Higher Education and Research's JN Medical College, Belagavi, India); Khátia Munguambe, Charfudin Sacoor, and Esperança Sevene (Centro de Investigação em Saúde da Manhiça, Manhiça, Mozambique)*

**The Community-Level Interventions for Pre-eclampsia (CLIP)  
cluster randomised trials in Mozambique, Pakistan, and India:  
an individual participant data meta-analysis – Appendix**

**Checklists**

## Checklist of Items to Include When Reporting Harms in Randomized, Controlled Trials\*

Standard CONSORT Checklist: Paper Section and Topic	Standard CONSORT Checklist: Item Number	Descriptor	Reported on Page Number
Title and Abstract	1	If the study collected data on harms and benefits, the title or abstract should so state.	NA (title) 4 (abstract)
Introduction Background	2	If the trial addresses both harms and benefits, the introduction should so state.	5
Methods		List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs unexpected events, reference to standardized and validated definitions, and description of new definitions).	
Participants	3		6-7
Interventions	4		7
Objectives	5		10-11
Outcomes	6	Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent).	8-9
Sample size	7	Describe plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of recurrent events , specification of timing issues, handling of continuous measures, and any statistical analyses).	6 NA
Randomisation			
Sequence generation	8		
Allocation concealment	9		
Implementation	10		
Blinding (masking)	11		7
Statistical methods	12		9-10
Results			
Participant flow	13	Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment.	11 11
Recruitment	14	Provide the denominators for analyses on harms.	11-12 11
Baseline data	15		
Numbers analysed	16	Present the absolute risk per arm and per adverse event type, grade and seriousness, and present appropriate metrics for recurrent events, continuous variables and scale variables, whenever pertinent <sup>†</sup> .	12 (Table 1)
Outcomes and estimation	17	Describe any subgroup analyses and exploratory analyses for harms <sup>‡</sup> .	12-13 (Table 1)
Ancillary analyses	18		13-14
Adverse events	19		13
Discussion			
Interpretation	20	Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalisability and other sources of information on harms <sup>‡</sup> .	14
Generalizability	21		16
Overall evidence	22		18

\*This proposed extension for harms includes 10 recommendations that correspond to the original CONSORT checklist.

<sup>†</sup>Descriptors refer to items 17, 18 and 19. <sup>‡</sup>Descriptor refers to items 20, 21 and 22.



**CONSORT Extension for Abstracts Checklist: items to include when reporting a randomised trial in a journal or conference abstract**

<b>Item</b>	<b>Description</b>	<b>Reported on page &amp; line number</b>
Title	Identification of the study as randomised	1-2
Authors *	Contact details for the corresponding author	39-41
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	51-54
<b>Methods</b>		
Participants	Eligibility criteria for participants and the settings where the data were collected	54-55
Interventions	Interventions intended for each group	55-57
Objective	Specific objective or hypothesis	N/A
Outcome	Clearly defined primary outcome for this report	57-58
Randomisation	How participants were allocated to interventions	N/A
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	58
<b>Results</b>		
Numbers randomised	Number of participants randomized to each group	60-61
Recruitment	Trial status	N/A
Numbers analysed	Number of participants analysed in each group	66-67
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	66-68
Harms	Important adverse events or side effects	68-70
Conclusions	General interpretation of the results	72-74
Trial registration	Registration number and name of trial register	53
Funding	Source of funding	76
*this item is specific to conference abstracts		

## CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard checklist item	Extension for cluster designs	Page No *
<b>Title and abstract</b>				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) <sup>1,2</sup>	See table 2	3-4
<b>Introduction</b>				
<b>Background and objectives</b>	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	N/A
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	N/A
<b>Methods</b>				
<b>Trial design</b>	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		N/A
<b>Participants</b>	4a	Eligibility criteria for participants	Eligibility criteria for clusters	6
	4b	Settings and locations where the data were collected		7-8
<b>Interventions</b>	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	N/A
<b>Outcomes</b>	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons		N/A
<b>Sample size</b>	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or $k$ ), and an indication of its uncertainty	11-12 Table 1
	7b	When applicable, explanation of any interim analyses and stopping guidelines		N/A
<b>Randomisation:</b>				
<b>Sequence generation</b>	8a	Method used to generate the random allocation sequence		6-7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	6-7
<b>Allocation concealment mechanism</b>	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	6-7
<b>Implementation</b>	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	N/A
	10b		Mechanism by which individual participants were included in clusters for	7

	10c		the purposes of the trial (such as complete enumeration, random sampling) From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	6
<b>Blinding</b>	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		N/A
	11b	If relevant, description of the similarity of interventions		N/A
<b>Statistical methods</b>	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		12-13
<b>Results</b>				
<b>Participant flow (a diagram is strongly recommended)</b>	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	11 Table 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	13
<b>Recruitment</b>	14a	Dates defining the periods of recruitment and follow-up		Table 1
	14b	Why the trial ended or was stopped		N/A
<b>Baseline data</b>	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	11 Table 1
<b>Numbers analysed</b>	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table 2
<b>Outcomes and estimation</b>	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or $k$ ) for each primary outcome	12-13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		N/A
<b>Ancillary analyses</b>	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		13-14
<b>Harms</b>	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms <sup>3</sup> )		13
<b>Discussion</b>				
<b>Limitations</b>	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		17
<b>Generalisability</b>	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	18
<b>Interpretation</b>	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		14-18
<b>Other information</b>				
<b>Registration</b>	23	Registration number and name of trial registry		3

<b>Protocol</b>	24	Where the full trial protocol can be accessed, if available	6
<b>Funding</b>	25	Sources of funding and other support (such as supply of drugs), role of funders	4, 18
* Note: page numbers optional depending on journal requirements			

### Extension of CONSORT for abstracts<sup>1,2</sup> to reports of cluster randomised trials

Item	Standard checklist item	Extension for cluster trials	Page No
<b>Title</b>	Identification of study as randomised	Identification of study as cluster randomised	<b>1 (Line 1)</b>
<b>Trial design</b>	Description of the trial design (e.g. parallel, cluster, non-inferiority)		<b>3 (Lines 51-54)</b>
<b>Methods</b>			
<b>Participants</b>	Eligibility criteria for participants and the settings where the data were collected	Eligibility criteria for clusters	<b>3 (Lines 54-55)</b>
<b>Interventions</b>	Interventions intended for each group		<b>3 (Lines 55-57)</b>
<b>Objective</b>	Specific objective or hypothesis	Whether objective or hypothesis pertains to the cluster level, the individual participant level or both	<b>N/A</b>
<b>Outcome</b>	Clearly defined primary outcome for this report	Whether the primary outcome pertains to the cluster level, the individual participant level or both	<b>3 (Lines 57-58)</b>
<b>Randomization</b>	How participants were allocated to interventions	How clusters were allocated to interventions	<b>N/A</b>
<b>Blinding (masking)</b>	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment		<b>3 (Line 58)</b>
<b>Results</b>			
<b>Numbers randomised</b>	Number of participants randomised to each group	Number of clusters randomized to each group	<b>3 (Lines 60-61)</b>
<b>Recruitment</b>	Trial status		
<b>Numbers analysed</b>	Number of participants analysed in each group	Number of clusters analysed in each group	<b>4 (Lines 66-67)</b>
<b>Outcome</b>	For the primary outcome, a result for each group and the estimated effect size and its precision	Results at the cluster or individual participant level as applicable for each primary outcome	<b>4 (Lines 66-68)</b>
<b>Harms</b>	Important adverse events or side effects		<b>4 (Lines 68-70)</b>
<b>Conclusions</b>	General interpretation of the results		<b>4 (Lines 72-74)</b>
<b>Trial registration</b>	Registration number and name of trial register		<b>3 (Line 53)</b>
<b>Funding</b>	<b>Source of funding</b>		<b>4 (Line 76)</b>

### REFERENCES

- 1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283
- 2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20
- 3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	NA
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	8,9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 (11)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 1; Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-14, Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14 Table 3, Table S2
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-17
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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