High versus low intensity interventions for perinatal depression delivered by non-specialist primary maternal care providers in Nigeria: a cluster randomized controlled trial

(the EXPONATE trial)

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Summary

Background: Contextually appropriate interventions delivered by primary maternal care providers (PMCP) might be effective in reducing the treatment gap for perinatal depression.

Aim: To compare a high intensity (HIT) with a low intensity psychological intervention (LIT) for perinatal depression.

Methods: Cluster randomized clinical trial, conducted in Ibadan, Nigeria between June 18, 2013 and December 11, 2015 in 29 maternal care clinics allocated by computed-generated random sequence (15 HIT; 14 LIT). Interventions were delivered individually to antenatal women with DSM-IV major depression by trained PMCP. LIT consisted of basic psychosocial treatment specifications in the WHO Mental Health Gap Action Programme – Intervention Guide while HIT consisted of LIT plus 8 weekly problem-solving therapy sessions with possible additional sessions determined by scores on the Edinburgh Postnatal Depression Scale (EPDS). Primary outcome was remission of depression at 6 months postpartum (EPDS< 6).

Results: There were 686 participants, 452 and 234 in HIT and LIT arms, respectively, with both groups similar at baseline. Follow-up assessments, completed on 85%, showed remission rates of 70% in the HIT arm and 66% in the LIT arm: risk difference 4% (95%CI: -4·1%, 12·0%), adjusted odds ratio 1·12 (95%CI: 0·73, 1·72). HIT was more effective for severe depression (OR 2·29, 95%CI 1·01, 5·20; p=0.047) and resulted in higher rate of exclusive breastfeeding. Infant outcomes, cost-effectiveness, and adverse events were similar.

Conclusions: Except among severely depressed perinatal women, we found no strong evidence to recommend high intensity in preference to low intensity psychological intervention in routine primary maternal care.

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INTRODUCTION

Perinatal depression, occurring during pregnancy or shortly after childbirth, is a common disorder, affecting between 10-15% of women during this period[1]. In Nigeria reported prevalence rates range between 10 and 30%.[2,3] While prenatal depression is associated with greater risk of premature delivery, low birth weight of infants and greater risk of adverse obstetrical outcomes,[4,5] postnatal depression might interfere with mother-infant interactions, and impair infants' cognitive and emotional development.[6,7] Furthermore, mothers with perinatal depression are more likely to miss their infants' routine immunization visits and delay help-seeking for potentially serious childhood illnesses.[8]

In spite of evidence suggesting that integration of the care of perinatal depression into routine maternal care is the most efficient way to bridge the treatment gap for the condition, it is estimated that less than 50% of cases of perinatal depression are detected by primary health care professionals in routine clinical practice.[9] Systematic reviews of studies in high income countries show that, in most instances, perinatal depression can be effectively managed with psychological and psychosocial interventions.[10] There is growing evidence from low and middle-income countries (LMIC) that such interventions can be effectively implemented by trained and supervised non-physician primary health care workers with benefit for both mothers and their children.[11,12] In most LMIC, especially countries in sub-Saharan Africa, where primary care providers are few and often burdened with a heavy workload, it is important to determine how intense such an intervention needs to be for it to be effective in bringing about remission from perinatal depression. The primary hypothesis of the current study is that an intervention package consisting of primary care worker-administered problem-solving treatment delivered within a stepped-care approach will be more effective than enhanced care as usual at alleviating perinatal depression 6 months after childbirth.

METHODS

Study design

This study was a cluster randomized controlled trial in which the unit of randomization was eligible and consenting primary maternal care clinics in selected local government areas, and the unit of analysis was individual women participants. A full description of the study methods has been published.[13] The study was conducted in Oyo State in south-western Nigeria. Nine local government areas (four urban and five rural) were randomly selected for the study. Appropriate institutional ethics approval was obtained from the University of Ibadan/ University College Hospital Ibadan Ethical Review Committee.

Participants

Participating clinics had to provide both antenatal and postnatal services. Participants were all consecutive pregnant women registering for antenatal care at the participating clinics. These women were approached for screening if they were aged between 16 and 45 years, with a foetal gestational age of between 16 and 28 weeks. Women who consented to be screened and spoke Yoruba, the language of the study, were administered the Edinburgh Postnatal Depression Scale (EPDS).[14] Women who scored ≥12 on the EPDS were administered further questions, derived from the short version of the Composite International Diagnostic Interview[15] to confirm the presence of major depression according to DSM-IV criteria and the absence of psychotic symptoms and bipolar disorder. Women with major depression, who had no psychotic symptoms, were not actively suicidal, who provided signed informed consent and were going to be available in the study area up until 12 months following childbirth, were invited into the study and enrolled after consent. A full baseline assessment took place within 72 hours of recruitment. Participants in both arms of the study were provided with their EPDS score and asked to give this information to the attending primary maternal care provider (PMCP) for the latter to initiate treatment

according to the arm of the study. While screening and recruitment took place at the maternal and child care clinics (MCC), baseline and other outcome assessments took place at participants' homes or other places of their choice.

Randomization and masking

Clinics were randomized to deliver either a high intensity intervention or enhance care as usual delivered individually to patients by primary care workers who provided routine antenatal and postnatal care to the women. Eligible and consenting maternal care clinics were stratified by local government area and allocated to intervention or control arm using a computer-generated random number sequence. Allocation was conducted by one of the authors (AAM) using anonymous codes for clinics and local government areas provided by other members of the research team.

All outcome assessments were conducted in participants' homes by experienced research interviewers who had received two-week training in trial procedure, were not involved in participants' recruitment and were blind to participants' treatment arm.

Procedures

High Intensity Treatment (HIT)

In the HIT arm, in addition to the enhanced usual care (see below), providers offered a stepped-care treatment using a manualised psychological intervention package. We have earlier provided details of the development and piloting of a stepped care intervention for depression in primary care. [16] A full description of the intervention package used in this study has been published (and is available from the authors on request).[13] The core component was a locally adapted form of Problem Solving Treatment for Primary Care (PST-PC). In this intervention, the patient is guided

through a step-by-step process of breaking down current psychosocial stressors, and exploring and trying out options for their resolution, including the use of personal resources as well as available social support.

The intervention, which was commenced within one week of subjects being enrolled into the study, was delivered in three steps determined by the patient's score on the EPDS, time since enrolment and gestational status. Step one comprised eight sessions of psychological interventions delivered weekly in the antenatal period. Step two commenced six weeks after delivery during the mother's routine post-natal visit. Depending on participants' EPDS scores (<12 or ≥ 12), providers delivered either four fortnightly top-up sessions of the problem-solving treatment or eight, weekly intervention sessions. At the completion of step two, participants who still had EPDS scores of 12 or more proceeded to step three in which they were reassessed by the community physician with a view to initiating pharmacotherapy in addition to continuing with the psychological intervention or referral to a specialist service. Each session of the psychological intervention lasted approximately 30–45 min. Mothers in the HIT arm of the study also received parenting skills training, which included information on issues such as the importance of routine antenatal visits, adequate nutrition and rest, the care of and nutrition for the new-born and information on how to engage and stimulate the infant. All sessions were individual based.

The intervention was delivered by the PMCP who had received an initial three-day training and a two-day top-up training (one month later) on the delivery of the intervention and had ongoing structured support and supervision from primary care physicians who, in turn, could consult with a psychiatrist when needed. The support, supervision and specialist consultation were provided by mobile phones except when face-to-face assessment was indicated. Patients also received

automated mobile phone voice messages and calls from the PMCP to remind them of clinic appointments and homework related to the therapy session.

Enhanced Care as Usual (Low Intensity Treatment (LIT))

Following a recent official health policy of the government, specifying the mhGAP as the pathway to scaling up mental health care in the country, participants in the comparator arm were offered enhanced usual care constituting the Low Intensity Treatment (LIT). The PMCP in the LIT arm received a one and half day training on the use of the WHO Mental Health Gap Action Programme – Intervention Guide (mhGAP-IG) and were given copies of the mhGAP-IG as well as a manual describing the nature and standard treatment approaches for perinatal depression. The providers thus delivered intervention using the basic specifications of mhGAP-IG to women identified through the screening and assessment procedures conducted by research staff. The mhGAP-IG basic specifications, as previously stated, consist of psychoeducation, addressing current psychosocial stressors, and reactivation of social network. No structured sessions were stipulated and no stepped care procedure was specified; the number/frequency of visits and content of the psychosocial interventions were at the discretion of the PMCP.

Outcomes

The primary outcome was remission from depression at six months postpartum, defined as an EPDS score of less than six (which, from our pilot experience, validly operationalizes our protocol pre-specified outcome of no longer meeting DSM-IV criteria for major depression). Maternal secondary outcomes were: 1) depressive symptoms (as shown by EPDS scores over the follow-up period), 2) disability (measured with the WHO Disability Assessment Scale (WHODAS)),[17] parenting skills (measured with the Maternal Adjustment and Maternal Attitudes Questionnaire (MAMA),[18] and the Infant Toddler version of the Home Inventory for Measurement of the

Environment (HOME-IT)),[19] and 3) experience of stigma (measured with the 12-item Discrimination and Stigma Scale (DISC-12))[20]. The EPDS, WHO-DAS and DISC-12 have been previously validated and used in Nigeria.[3] Infant secondary outcomes consisted of 1) growth and health at 6 months (measured by height and weight, history of completed immunization and history of any illness, including fevers and diarrhoea); 2) nutrition at 6 months (measured by history of breastfeeding); and 3) motor and cognitive development at 12 months (as assessed with the Bayley's Scale for Infant Development. We used the Client Service Receipt Inventory – PND version to collect service use data for the estimation of cost-effectiveness.[21] A full description of the measures, with evidence of previous use and their validation in our setting, was published earlier.[13]

We monitored fidelity and quality of care in the HIT arm by reviewing the clinical records of all participants, documenting contacts, sessions attended, and consultations and referrals to physicians and psychiatrists. The clinical records were designed to capture each step and structure of the PST. Independent assessments of quality of delivery of and adherence to the structure of the PST in the HIT arm were conducted by senior members of the research team on 18 PMCP by direct observation. Either session 2 or 5 was rated on 9 dimensions. The dimensions included quality of eye contact, appropriate probes relevant to the PST session, listening and use of cues and were rated on a 3-point scale of Very Good, Good, or Poor. Of a total 180 ratings (from 20 sessions), 58% were rated very good, 32% good, and 10% poor.

Evaluation of the process of care in the LIT arm was conducted by reviewing all case records of contacts to retrieve documented evidence of provider's attention to patient's depression (either by treatment mentioned or clinical progress reported).

To enable an assessment of the relative cost-effectiveness of HIT versus LIT, primary study outcomes were linked to estimates of the service costs incurred in each arm. A service use questionnaire that had been previously piloted and used in the local context was administered alongside other measures at baseline and 3, 6 and 12 months follow-up. Simplified costing templates and local data inputs were used to generate a set of unit costs and prices for all inpatient and outpatient service use components, as well as the cost of the interventions themselves.

Statistical analysis

Data from previous trials among women with perinatal or postnatal depression in Pakistan and Chile[22,23] suggested a remission rate of about 50% and 75% in control and intervention arms respectively. As the study compared a high intensity intervention versus enhanced care as usual, we conservatively sought to detect an absolute difference of 15 percentage points (40% remission in LIT and 55% remission in HIT groups respectively) at six months after birth. An individually-randomized trial requires 186 participants per arm for analysis to detect this difference with 80% power and 5% two-sided alpha. Using pilot study data, we estimated the intra-cluster correlation coefficient (ICC) for the primary outcome to be 0·026, 85% collection of primary outcome data, and cluster size for analysis of 43. We therefore started the trial aiming to recruit 18 clinics and 916 individuals. Participant recruitment was slower than anticipated, so we recruited and randomised a further 11 clinics in January 2014, giving a total of 29 in the study. In August 2014 prior to the planned completion of participant recruitment, we undertook a formal review of sample size and found some assumptions in the original estimate were inaccurate: (1) there was an imbalance in the ratio of women recruited of around 1·9 in favour of the HIT arm; (2) there was variation in cluster size that was non-ignorable when estimating the design effect; and (3) we examine the remission rate among the control (LIT) arm participants who had reached the primary follow up and found this to be much higher than expected at around 84%. (We did not examine remission in the intervention arm or between group effect). We no longer considered an absolute

difference of 15% to be plausible with such high remission in the low intensity arm, and estimated sample size for a smaller difference of 11·5%. An individually-randomized trial requires 258 participants for analysis with allocation ratio of 1·9 and same power and alpha as before. With projected mean cluster size for analysis and standard deviation both of around 24, the design effect is 2·2,[24] giving a total of 670 to be recruited with 85% collection of primary outcome data. In essence, our study was fully powered (80%) to detect a difference of 11.5%.

Analyses were conducted using Stata/SE 13.1. We used appropriate descriptive statistics (chi square test and t-test) to examine balance between the arms at baseline and to describe outcomes at 6 and 12 months follow up. In view of the high follow-up rate, the main approach to analysis was modified intention to treat at the individual level, that is, analysis according to randomised group regardless of adherence with allocation and without imputation of missing outcome data. We used multivariable mixed effects regression models (logistic or linear dependent on outcome type), with clinic and local government area included as random effects, and baseline value of the outcome, if measured, as a covariate, in order to estimate between-arm effects and 95% confidence intervals. For the primary outcome, we conducted sensitivity analyses with further adjustment for any variables displaying between-arm differences at baseline, and by multiple imputation of missing outcome data using chained equations. We conducted a per-protocol subgroup analysis of the primary outcome according to baseline severity of depression by including an interaction term between arm and baseline EPDS score (<16, ≥16) in the primary regression model. We conducted a pre-specified analysis of EPDS as a continuous outcome at 6 months and also over the 12-month postnatal follow up period using repeated measures analysis by including follow up occasion (3, 6, 9, 12 months) as a random effect in the regression model. We analysed other secondary outcomes using a similar approach as for the primary outcome.

For the economic analysis, mean service costs were computed for each study arm and then linked to primary outcomes through a series of multivariate regression analyses that controlled for baseline differences in cost as well as key demographic characteristics. Due to the skewness of cost data, the non-parametric bootstrapping technique was employed to generate confidence intervals around mean costs and cost-effectiveness ratios (N = 1000 replications were made).

The conduct of the study and its adherence to approved procedures were monitored by an independent Data Monitoring and Ethics Committee which reported to another independent body, the Trial Steering Committee. The trial is registered with the ISRTCN registry at isrtcn.com; Trial number ISRCTN60041127.

RESULTS

All 137 primary care clinics located in the nine local government areas were assessed for eligibility. Of the 49 providing comprehensive maternal care and therefore eligible, 29 consented to participate and were randomized (Figure one). Data to further describe participating clinics prior to randomisation were not collected. A total of 9352 women were screened, of whom 727 (7·7%) scored at least 12 on the EPDS and 686 were recruited. Even though the proportions screening positive who were subsequently recruited were similar in both arms, a higher proportion of women screened positive in the HIT arm (9·4% vs. 5·8%), due primarily to two clinics with high screen positives rates (Online Figure). Participant recruitment took place between June 18, 2013 and October 14, 2014, while the final 12-month postnatal follow-up was concluded December 11, 2015. Follow up was high at both six (85%) and 12 (79%) months follow up and was similar in both arms. Refusals were very few at both time points. Most of those not followed up had either moved to new addresses that could not be traced or were not available after multiple efforts (at

least four attempts) were made to interview them. No demographic or clinical features were significantly associated with refusal to participate or with attrition.

Table 1 shows the sociodemographic and clinical features of trial participants at baseline. This was a sample of young women with mean age under 25 years and about 11 years of education. About four in five were married, most were in the second trimester at time of recruitment, and about 50% were primiparous although this was slightly higher in the HIT group than LIT. The trial was focused on persons with moderate to severe perinatal depression. A mean score of 14 on the EPDS suggests that most indeed had moderate depression. Participants in both groups showed similar levels of adjustment to pregnancy and of disability, as indicated by scores on the MAMA and WHO-DAS scales, respectively. Importantly, even though rates of recruitment were different between trial arms, baseline features were very similar except for parity. Pregnancy outcomes were similar between the arms (Online Table 1). Over 90% of pregnancies resulted in a live birth, of which over 98% were singletons.

At the primary follow up six months after childbirth, similar proportions of women in both arms had recovered from depression and there was no evidence of any between-group difference, (adjusted risk difference of 4%, 95%CI: -4·1%, 12·0%). (Table 2). Additional adjustment by baseline parity, and multiple imputation for the 107 women who did not provide primary outcome data made no material difference to the results. There was some evidence that the HIT was more effective than LIT among women who had higher EPDS scores at baseline (interaction odds ratio 2·29, 95% CI 1·01, 5·20, p = 0.047).

The HIT arm had significantly lower mean level of disability than the LIT arm at 6 months (adjusted mean difference -0.6 (95% CI -1.1, -0.0, p = 0.045) and lower mean EPDS score at 12 months

(adjusted mean difference (-0.9 (-1.7, -0.2, p= 0.012) (Table 3). Over the 12-month postnatal period mean EPDS scores were lower in the HIT arm than in LIT. Mean scores at 3, 6, 9 and 12 months were 3·4, 3·7, 3·4, 3·5 and 4·7, 4·5, 3·8, 4·6 in HIT and LIT arms respectively. The between-group difference averaged over all four follow up time points was -0·8 (95% CI -1·3, -0·2, p=0·007) in favour of HIT. There were no other significant differences in secondary maternal outcomes.

Infants of mothers in both arms were similar in weight, height and head circumference at 6 months (Online Table 2). They were also similar in regard to measures of cognitive and motor development. The proportions of infants who had been administered scheduled immunizations or who had experienced any physical illness were also similar across groups. However, mothers in the HIT arm were twice as likely to have complied with the recommendation to feed babies exclusively on breast milk than mothers in the LIT arm (19% vs. 10%; odds ratio 2·17, 95% CI 1·27 – 3·73; p = 0·005).

Every participant in the HIT arm received at least one session of psychological intervention, about 90% received at least four sessions and 61% completed the initial prenatal eight treatment sessions. At least one postnatal session was received by 85% of the mothers, with 78% receiving two sessions. Consultation was made to doctors for about 3% of the women following their first assessment by the PMCP. None of the participants was prescribed an antidepressant medication.

About 95% of participants in the LIT had two prenatal treatment contacts with the PMCP, 60% had three contacts and only 10% had four contacts. One postnatal treatment contact was made by 30% of the women.

There were three maternal deaths, all in the HIT group, none of which was from suicide. Eight miscarriages were recorded: five in the LIT arm and three in the HIT arm. There were 36 stillbirths, 25 (6%) in the HIT group and 11 (5%) in the LIT group. None of the adverse events were judged by the independent Trial Steering Committee to be related to the study procedures.

Costs and cost-effectiveness

Service costs per participant per month reduced appreciably and to a similar degree from their baseline values in both groups (ONLINE Table 3), falling from Naira 981 to 788 (at 6 months) and 379 (at 12 months) in the HIT group, and from Naira 809 to 485 (at 6 months) and 142 (at 12 months) in the LIT group. Total estimated costs over the full one-year period following baseline were approximately double in the HIT group (Naira 7,028 per participant) (US$ 46.85) compared to the LIT group (Naira 3,600 per participant) (US$ 24.00). Converted to US dollars (US$ 1 was worth Naira 150 in 2015), these costs appear relatively lower – reflecting very modest use of services in general – but may nevertheless impose a financial burden on families contributing towards the cost of services in the local context via direct payments (out of pocket payments).

Cost-effectiveness was assessed at 6- and 12-month follow-ups. Changes in service costs were linked to changes on the EPDS, with results showing that reductions in service cost over time were slightly greater in the LIT group, while outcomes were only marginally in favour of HIT. The extra cost per one-point improvement on the EPDS with HIT compared to LIT was Naira -653 (95% CI, -5108 to 3975) at 6 months and Naira -128 (95% CI, -1360 to 1186) at 12 months. Cost-effectiveness was also assessed with respect disability, and for this outcome the cost per one-unit improvement on WHODAS was Naira 186 (95% CI, -1055 to 1408) at 6 months and Naira 58 (95% CI, -521 to 568) at 12 months. In summary, HIT represents a cost-effective alternative to LIT, but since LIT was associated with similar changes in health, functioning and cost, there is no significant difference for the more intensive strategy.

DISCUSSION

We found no evidence of any significant difference between HIT and LIT in the proportion of women who recovered from depression at 6 months after birth nor did we detect any cost-effectiveness advantage for HIT. However, our data suggest that HIT may be more effective than LIT for the subgroup of women with more severe depressive symptoms at baseline. We also found some evidence that participants in the HIT group had fewer depressive symptoms as measured by mean EPDS score at the 12-month outcome as well as over the course of the 12 months follow up after birth, indicating a greater level of symptom remission in the HIT group, but this effect may not be clinically significant. Other than significantly lower disability at 6 months, there was no evidence of any differences between the groups in the levels of attitude to motherhood, experience of stigma and in the quality and quantity of stimulation they provided to their infants at home at 6- and 12-month outcomes. Unlike as noted by others,[22] infant outcomes at 6 months including growth, reported illnesses and exposure to scheduled immunizations as well as cognitive and motor development at 12 months were also similar between the groups. However, mothers receiving the high intensity intervention were more likely to have provided exclusive breastfeeding to their infants than those receiving the low intensity intervention at six months, a benefit that may be explained by the parenting skills training component of the HIT.

The study did not find substantial evidence to indicate that the HIT is superior to the LIT except among women with high baseline depression. The outcomes from the two interventions were also comparable to what has been reported in the literature either with the use of medication or psychological approaches.[12,22,23] Extending observations made in high-income countries that show the effectiveness of psychological and psychosocial interventions for common perinatal mental disorders,[10] there are now several studies providing similar evidence for such forms of intervention in low and middle income countries.[11] A recent meta-analysis of 13 studies conducted

in LMIC showed that interventions delivered by mostly non-specialist health workers, within task-shifting or task-sharing approaches, provide significant benefit to mothers with perinatal depression as well as their infants.[12]

The major findings of our study confirm the feasibility of this task-sharing model of care in the setting of the study. Even though they differed in intensity and structure, both interventions met some of the essential features of psychological interventions delivered by non-specialists that have been found to be effective in LMIC for perinatal depression: active psychotherapeutic components delivered within an understanding of the contextual social problems of the women and with sensitivity to cultural and language factors.[25] When those features are present, even simple, low intensity interventions are commonly effective for perinatal depression.[26]

The rate of depression in this sample is lower than is often reported.[1] Even though a score of 10 or higher on EPDS has a specificity of 91.5% for DSM-IV major depression among perinatal women in Nigeria,[27] we have used a higher cut-off score in order to focus on depression of at least moderate severity. A higher proportion of women screened positive in the HIT compared to the LIT arm. This was due primarily to two clinics which served communities with large populations of migrant farm workers. However, both arms were similar in regard to age, gestational age, education, pregnancy outcomes and baseline EPDS scores.[28]

The fact that PMCP were willing and able to use the mhGAP-IG as a clinical support tool in this trial suggests that the tool may have potentials for scaling up care for perinatal depression. However, the design of the study involved screening and assessment of women for the presence of perinatal depression by the study research team. There thus remains the need to demonstrate whether with training and with the use of the mhGAP-IG, these frontline providers can reliably

detect the condition themselves. The strengths of EXPONATE include the use of validated tools with proven cultural appropriateness and acceptability in the setting[29,30] and its focus on depression of at least moderate severity and therefore of undoubted clinical significance. The major limitation is the use of an enhanced care as usual, rather than a typical care as usual in the setting where most women with perinatal depression are either not detected or offered evidence-based treatment.[29] It is also possible that the reasons for a lack of clear difference between the two trial arms include, spontaneous remission of women with the less severe forms of the condition, a non-real world implementation of the mhGAP-IG in which detection of depression was by research assistants rather than by the providers, the use of non-specialists to supervise providers in the HIT arm or the fact that the performance of the PMCP was not uniformly good. Also, even though efforts were made to blind the outcome assessors, the possibility of unmasking and hence some information bias cannot be totally excluded. Another limitation is that, even though the CIDI has been extensively used and validated by us,[30,31] and the trained interviewers has wide experience with its use, no formal test of reliability for its items were conducted for this study.

Our findings show that even though a high intensity psychosocial intervention has some added benefits, a low intensity evidence-based intervention, consisting of the basic treatment specifications for depression described in the mhGAP-IG, may be sufficient to bring relief to majority of women with perinatal depression in primary maternal care service. A low intensity intervention may be more feasible as well as affordable to deliver within routine service in busy primary maternal care clinics in low resource settings.

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Contributors

OG drafted the report, with input from AAM, BDO, RA and DC. All authors reviewed the drafts and approved the final version. OG, AAM and RA were responsible for the design of the trial. OG and BDO designed and delivered the intervention training and with LK, DG and PZ were responsible for the assessment tools. OG, BDO, LK and LBO supervised trial conduct. LK, TB, WT were responsible for database design and management; WT, TB and AAM conducted the statistical analyses. DC supervised the economic analysis.

Declaration of interests

We declare no competing interests

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Table 1: Baseline demographic and clinical characteristics

	HIT Group (n=452)	LIT group (n=234)	Total (n=686)
Age (years)			
Mean[SD]	24·5 [5·6]	24·9 [5·8]	24·7 [5·7]
Years of education			
Mean[SD]	10·6 [3·0]	10·4 [3·2]	10·6 [3·1]
Marital status N (%)			
Married	363 [80%]	185 [79%]	548 [80%]
Single	84 [19%]	49 [21%]	133 [19%]
Widowed	1 [<0·5%]	0	1 [<0·5%]
Divorced	2 [<0·5%]	0	1 [<0·5%]
Parity			
Primiparous	230 [56%]	103 [49%]	333 [54%]
Multiparous	179 [44%]	109 (51%)	288 [46%]
Gestational age			
Mean[SD]	21·8 [3·7]	22·6 [4·0]	22·1 [3·8]
Baseline MAMA score			
Mean[SD]	24·2 [3]	24·6 [3·5]	24·3 [3·2]
Baseline WHODAS score			
Mean [SD]	18·2 [4·8]	19·5 [6·3]	18·6 [5·5]
Baseline DISC-12 score			
Mean [SD]	19·6 [5·7]	20·4 [6·4]	19·8 [6·0]
Baseline service cost (Naira)			
Mean per month (SD)	981 [4821]	809 [2500]	923 [4176]

EPDS: Edinburgh Postnatal Depression Scale. Contains 10 questions with each ranging 0 (best) to 3 (worst).
MAMA: Maternal Adjustment and Maternal Attitude questionnaire. Contains 12 questions each ranging from not at all to very much.
WHODAS: WHO Disability Assessment Scale. Contains 12 questions each ranging from 1 (best) to 5 (worst), plus 3 additional questions about number of days in the past month they had the difficulties.
DISC-12: Discrimination and Stigma Scale. Contains 16 questions each ranging from not at all to a lot.

Table 2. Primary outcome, sensitivity and subgroup analyses

Outcome					
Binary	**HIT (n=379)**	**LIT (n=197)**	**Adjusted odds ratio (95% CI)[a]**		**p-value**
Remission* at 6months					
Yes n (%)	267 [70.5]	131 [66.5]			
No, n (%)	112 [29.6]	66 [33.5]	1.3 [0.8,2.0]		0.343
Multiple imputation of missing outcome					
Remission* at 6months					
Yes n(%)	307 [68%]‡	148 [63%]‡	1·10 [0·73,1·67]		0·714
No, n (%)	145 [32] ‡	86 [37] ‡			
Subgroup analysis of primary outcome					
Remission* from depression at 6 months postnatal			**Subgroup specific crude Odds Ratio (95% C.I)**	**Interaction effect (95% CI)^**	**p-value for Interaction**
EPDS score < 16 at baseline					
Yes	213 [72%]	99 [76%]	0·81 [0·47,1·40]		
No	82 [28%]	32 [24%]			
EPDS score ≥ 16 at baseline					
Yes	54 [64%]	32 [48%]	1·93 [0·96,3·87]	2·29 [1·01,5·20]	**0·047**
No	30 [36%]	34 [52%]			

***Remission is defined as EPDS score lower than 6.**
[a]Adjusted by baseline EPDS score, baseline parity, MCC and LGA that participants belong to. Maternal care clinics and local government areas are included as random effects
‡Predicted totals from multiple imputation

Table 3: Effect of intervention on secondary outcomes at 6 and 12 months

Outcome	**Mean(SD)**				**Intra-cluster correlation at 6 months, (95% CI)**
	HIT	**LIT**	**Adjusted mean difference (95% CI)[a]**	**p-value**	
EPDS score at 6 months	3.7 [4.1]	4.5 [4.4]	-0.8 [-1.7, 0.1]	0.065	0.03 [0,0.08]
MAMAS score at 6months	19.9 [4.2]	20.6 [5.1]	-0.7 [-1.5, 0.1]	0.098	0.01 [0.0, 0.04]
HOME-IT at 6months	27.0 [4.8]	26.8 [4.6]	0.2 [-0.9, 1.2]	0.757	0.02 [0.0, 0.13]
WHODAS at 6months	13.7 [3.1]	14.3 [3.6]	-0.6 [-1.1, -0.0]	**0.045**	0.02 [0.0, 0.06]
DISC at 6months	14.1 [3.8]	14.8 [4.6]	-0.5 [-1.2, 0.2]	0.174	0.04 [0.0, 0.09]
EPDS score at 12 months	3.5 [3.9]	4.6 [4.6]	-0.9 [-1.7, -0.2]	**0.012**	-
WHODAS at 12months	13.7 [2.7]	13.9 [2.6]	-0.2 [-0.7, 0.3]	0.435	-

[a]Adjusted by baseline EPDS score, MCC and LGA that participants belong to. MCC and LGA are included as random effects

ONLINE TABLE 1: Pregnancy outcomes

	HIT group (N=452) N (%)	LIT group (N=234) N (%)	Total (N=686) N (%)
Pregnancy outcome			
Live birth	417 (92%)	208 (89%)	625 (91%)
Stillbirth	25 (6%)	11 (5%)	36 (5%)
Unknown	10 (2%)	15 (6%)	25 (4%)
Sex of live births			
Male	214 (51%)	94 (45%)	308 (49%)
Female	203 (49%)	114 (55%)	317 (51%)
Types of live births			
Single	410 (98%)	206 (99%)	616 (98%)
Twin	7 (2%)	1 (<0.1%)	8 (1%)
Triplet	0	1 (<0.1%)	1 (<0.1%)

ONLINE TABLE 2: Infant secondary outcomes

Outcome	HIT group	LIT group	Adjusted^ mean difference (95% CI)	P value
Mean infant weight at 6 months, kg (SD)	6·6 (1·0)	6·8 (1·1)	-0·1 (-0·3, 0.1)	0·213
Meant infant height at 6 months, cm, (SD)	57·7 (4·3)	57·9 (4·3)	0·3 (-1·6, 0·9)	0·601
Bayley's scores at 12 months:				
Cognitive scaled score, (SD)	11.8 (2.4)	12.1. (3.7)	-0.3 (-0.8, 0.3)	0.344
Receptive scaled score, (SD)	7.7 (1.6)	7.8 (1.5)	-0.2 (-0.5, 2.0)	0.306
Expressive communication scaled score, (SD)	9.1 (2.5)	9.4 (2.2)	-0.2 (-0.7, 0.2)	0.365
Fine motor scaled score, (SD)	10.2 (2.1)	10.3 (1.9)	-0.1 (-0.4, 0.5)	0.947
Gross motor scaled score, (SD)	9.7 (3.0)	9.9 (3.1)	-0.2 (-0.8, 0.3)	0.468
			Adjusted^ odds ratio (95% CI)	**P value**
Infant completed immunization at 6 months, N (%)	279 (78%)	132 (74%)	1.1 (0.70, 1.76)	0.669
Infant reported illness at 6 months, N (%)	277 (73%)	144 (73)	0·97 (0·66, 1·43)	0·881
Infant nutrition at 6 months: Exclusive breastfeeding, N (%)	72 (19%)	19 (10%)	2·17 (1·27, 3·73)	0·005

^ Adjusted for maternal care clinic and for local government area

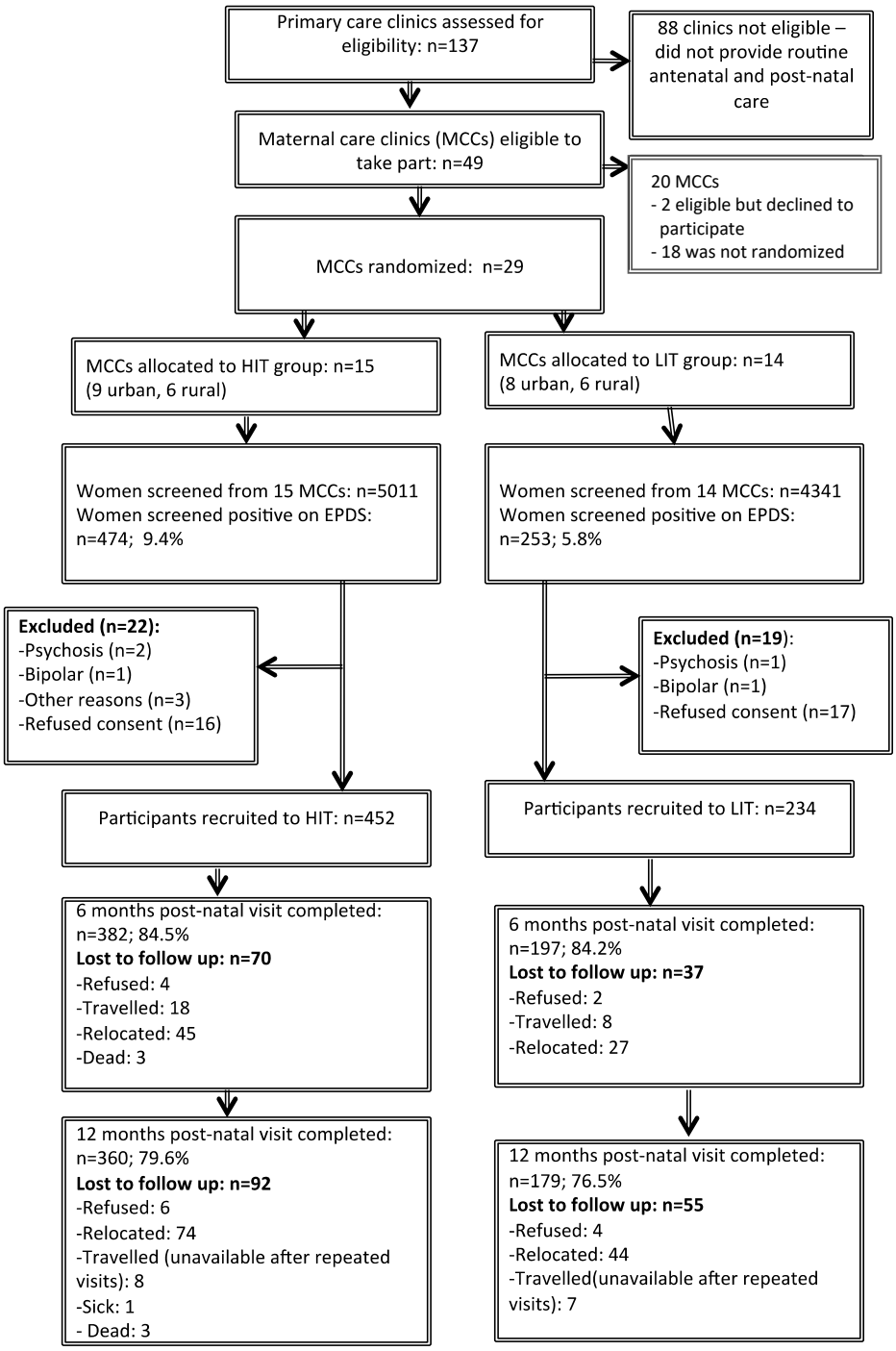
ONLINE TABLE 3: Costs and cost-effectiveness of the interventions at 6 and 12 months postpartum

	6 months post-partum		12 months post-partum	
	HIT	**LIT**	**HIT**	**LIT**
Total service cost (naira) Mean (SE)	788 (286)	485 (196)	379 (143)	142 (59)
Mean difference (95% C.I)[a]	303 (-373 to 1001)		237 (-34 to 567)	
Change in cost since baseline (Mean, SE)	-193 (369)	-324 (247)	-602 (265)	-667 (168)
Mean difference (SE)	131 (452)		65 (323)	
Effectiveness analysis				
Incremental cost effectiveness ratio, EPDS (95% C.I)	-653 (-5108 to 3975)		-128 (-1360 to 1186)	
Incremental cost effectiveness ratio, WHODAS (95% C.I)	186 (-1055 to 1408)		58 (-521 to 568)	

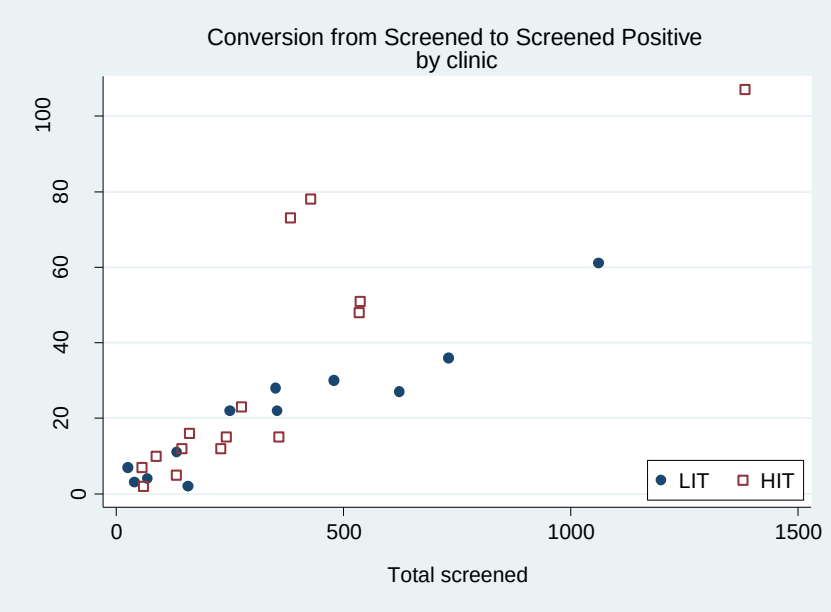
CI, confidence interval; **#**, Nigerian naira.

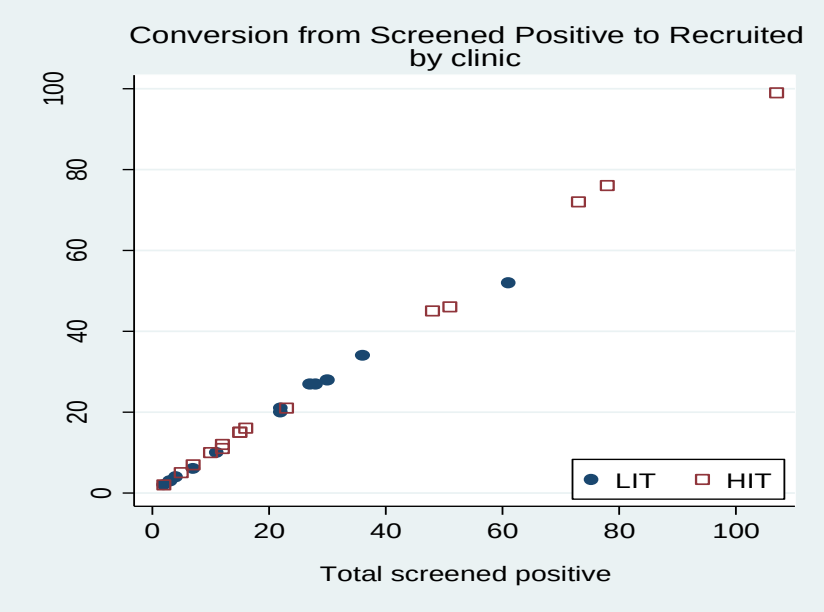
[a]The value for the LIT arm subtracted from the corresponding value for the HIT arm for the mean difference and 95% bootstrap C.I.

FIGURE 1


Primary care clinics assessed for eligibility: n=137
88 clinics not eligible – did not provide routine antenatal and post-natal care
Maternal care clinics (MCCs) eligible to take part: n=49
20 MCCs
- 2 eligible but declined to participate
- 18 was not randomized
MCCs randomized: n=29
MCCs allocated to HIT group: n=15 (9 urban, 6 rural)
MCCs allocated to LIT group: n=14 (8 urban, 6 rural)
Women screened from 15 MCCs: n=5011
Women screened positive on EPDS: n=474; 9.4%
Women screened from 14 MCCs: n=4341
Women screened positive on EPDS: n=253; 5.8%
Excluded (n=22):
-Psychosis (n=2)
-Bipolar (n=1)
-Other reasons (n=3)
-Refused consent (n=16)
Excluded (n=19):
-Psychosis (n=1)
-Bipolar (n=1)
-Refused consent (n=17)
Participants recruited to HIT: n=452
Participants recruited to LIT: n=234
6 months post-natal visit completed: n=382; 84.5%
Lost to follow up: n=70
-Refused: 4
-Travelled: 18
-Relocated: 45
-Dead: 3
6 months post-natal visit completed: n=197; 84.2%
Lost to follow up: n=37
-Refused: 2
-Travelled: 8
-Relocated: 27
12 months post-natal visit completed: n=360; 79.6%
Lost to follow up: n=92
-Refused: 6
-Relocated: 74
-Travelled (unavailable after repeated visits): 8
-Sick: 1
- Dead: 3
12 months post-natal visit completed: n=179; 76.5%
Lost to follow up: n=55
-Refused: 4
-Relocated: 44
-Travelled(unavailable after repeated visits): 7

ONLINE FIGURE: Recruitment charts





References

1. Gelaye B, Rondon M, Araya R, Williams M. Epidemiology of maternal depression, risk factors, and child outcomes in low- and middle-income countries. *Lancet Psychiatry* 2016; **3**: 973 - 82.
2. Aderibigbe YA, Gureje O, Omigbodun O. Postnatal emotional disorders in Nigerian women: A study of antecedents and associations. *Br J Psychiatry* 1993; **163**: 645-50.
3. Uwakwe R, Okonkwo JE. Affective (depressive) morbidity in puerperal Nigerian women: validation of the Edinburgh Postnatal Depression Scale. *Acta Psychiatr Scand* 2003; **107**(4): 251-9.
4. Bonari L, Pinto N, Ahn E, Einarson A, Steiner M, Koren G. Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry* 2004; **49**: 726-35.
5. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry* 2010; **67**: 1012-24.
6. Field T. Prenatal depression effects on early development: A review. *Infant Behav Dev* 2011; **34**: 1-14.
7. Stein A, Pearson RM, Goodman SH, et al. Effects of perinatal mental disorders on the fetus and child. *Lancet* 2014; **384**: 1800-19.
8. Prince M, Patel V, Saxena S, et al. No health without mental health. *Lancet* 2007; **370**: 859-77.
9. Hearn G, Hiff A, Jones A, et al. Postnatal depression in the community. *Br J Gen Pract* 1998; **48**: 1064-6.
10. Dennis CI, Ross IE, Grigoriadis S. Psychosocial and psychological interventions for treating antenatal depression. *Cochrane Database Syst Rev* 2007; (3): CD006309.
11. Clarke K, King M, Prost A. Psychosocial Interventions for Perinatal Common Mental Disorders Delivered by Providers Who Are Not Mental Health Specialists in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *PLoS Med*; **10**(10): e1001541.
12. Rahman A, Fisher J, Bower P, et al. Interventions for common perinatal mental disorders in women in low- and middle-income countries: a systematic review and meta-analysis. *Bull World Health Organ* 2013; **91**: 593-601.
13. Gureje O, Oladeji B, Araya M, et al. Expanding care for perinatal women with depression (EXPONATE): study protocol for a randomized controlled trial of an intervention package for perinatal depression in primary care. *BMC Psychiatry* 2015; **15**: 136.
14. Cox J, Holden J, Sagovsky R. Detection of postnatal depression: development of teh 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**: 782-6.
15. Kessler RC, Calabrese JR, Farley PA, et al. Composite International Diagnostic Interview screening scales for DSMIV anxiety and mood disorders. *Psychol Med* 2013; **43**(8): 1625-37.
16. Oladeji BD, Kola L, Abiona T, Montgomery AA, Araya R, Gureje O. A pilot randomized controlled trial of a stepped care intervention package for depression in primary care in Nigeria. *BMC Psychiatry* 2015; **15**: 96.
17. World Health Organization. WHO-Disability Assessment Schedule II In: Organization. WH, editor. Geneva, Switzerland: World Health Organization; 1999.
18. Kumar R, Robson K, Smith A. Development of a self-administered questionnaire to measure maternal adjustment and attitudes during pregnancy and after delivery. *J Psychosom Res* 1984; **28**: 43-51.
19. Caldwell BM, Bradley RH. HOME Inventory Administration Manual - comprehensive edition. University of Arkansas for Mediacl Sciences and University of Arkansa at Little Rock, Little Rock, USA; 2003.

20. Lasalvia A, Zoppei S, Van Bortel T, et al. Global pattern of experienced and anticipated discrimination reported by people with major depressive disorder: a cross-sectional survey. *Lancet* 2013; **381**: 55 - 62.
21. Chisholm D, Conroy S, Glangeaud-Freudenthal N, et al. Health services research into postnatal depression: results from a preliminary cross-cultural study. *Br J Psychiatry* 2004; **184** (suppl. 46): s45-s52.
22. Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behavior therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomized controlled trial. *Lancet* 2008; **372**: 902-9.
23. Rojas G, Fritsch R, Solis J, et al. Treatment of postnatal depression in low-income mothers in primary care clinics in Santiago, Chile: a randomized controlled trial. *Lancet* 2007; **370**: 1629-37.
24. Eldridge SM, Ashby D, Kerry S. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method *Int J Epidemiol* 2006; **35**(5Pp): 1292-300.
25. Adeponle A, Groleau D, Kola L, Kirmayer L, Gureje O. Perinatal depression in Nigeria: perspectives of women, family caregivers and health care providers. *Int J Ment Health Syst* 2017; **11**:27: doi: 10.1186/s13033-017-0134-6. eCollection 2017.
26. Chowdhary N, Sikander S, Atif N, et al. The content and delivery of psychological interventions for perinatal depression by non-specialist health workers in low and middle income countries: A systematic review. *Best Pract Research Clin Obstetr and Gynaecol* 2014; **28**: 113 - 33.
27. Adewuya AO, Ola BA, Dada AO, Fasoto OO. Validation of the Edinburgh Postnatal Depression Scale as a screening tool for depression in late pregnancy among Nigerian women. *J Psychosom Obstet Gynaecol* 2006; **27**(4): 267-72.
28. Tan W, Gureje O, Montgomery AA, et al. Investigating recruitment imbalance in EXPONATE, a cluster randomised trial. *Trials* 2017; **18 (Suppl 1)**: P190.
29. Gureje O, Odejide AO, Olatawura MO, et al. Mental illness in general health care: an international study. In: Üstün TB, Sartorius N, eds. Mental illness across the world in General Health Care: An international study. London: John Wiley & Sons; 1995: 157-73.
30. Gureje O, Lasebikan VO, Kola L, Makanjuola VA. Lifetime and 12-month prevalence of mental disorders in the Nigerian Survey of Mental Health and Well-Being. *Br J Psychiatry* 2006; **188**: 465-71.
31. Gureje O, Olowosegun O, Adebayo K, Stein DJ. The prevalence of non-affective psychosis in the Nigerian Survey of mental Health and Wellbeing. *World Psychiatry* 2010; **9**: 50-5.