Proposal for
EMOTIONAL STIMULATION IN THE CONTEXT OF EMERGENCY FOOD INTERVENTION IN THE TREATMENT OF MALNOURISHED CHILDREN: a randomized control trial

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Abbreviations

BMI – Body Mass Index

ES – Emotional Stimulation

HEW - Health Extension Worker

HC – Health Center

MUAC - Middle Upper Arm Circumference

NE – Nutritional Education

NGOs – Non-Governmental Organizations, Partner Agencies

OA – Outcome or Objective Assessor

RCT - Randomized Controlled Trial

SAM – Severe Acute Malnutrition

SD – Standard Deviation

TFU and OTP – Therapeutic Feeding Programs

TSC – Trial Steering Committee

Youth– Paid Young Volunteer

EXECUTIVE SUMMARY

Introduction

Our Clinical and Evaluation Team is pleased to submit a proposal to evaluate what we consider to be a groundbreaking intervention to accelerate recovery in malnourished infants in developing countries. The intervention to train mothers to provide emotional stimulation for their infants is remarkable because pilot investigation has demonstrated that it may be implemented by youths with a minimum of training and it leads to rapid weight gain in infants as well as overcoming the disruption in maternal interest in the child associated with malnutrition. Qualitative preliminary findings suggest that the intervention also leads to changes in parental behavior towards the child sustained months after the intervention. We now propose rigorously to test the inexpensive, practical and readily accessible intervention technique using local researchers and newly trained local staff. The question we address is whether this promising intervention is 'scalable' and whether previous results can be replicated and shown to be of sufficient strength against a credible control group to justify broad adoption across this country and possibly in other developing economies where malnourishment is a problem. The Evaluation Team brings together considerable knowledge and expertise of applying the intervention, training non-professionals to quickly acquire the therapeutic skills necessary, the medical expertise required for working with this clinical population, the cultural knowledge with the pool of young people capable of being trained in the intervention, and evaluation and research skills to deliver a compelling demonstration of effectiveness including knowledge of statistical methods and experience of psychometric and qualitative analyses; database management; and extensive experience of coordinating and managing health services research. The tight timescales make this an ambitious project. Its successful completion will rely on close collaboration between members of our team.

It is well accepted that education of children and young people is one of the most important ways that countries can achieve their goals of economic and social development to overcome poverty. However, effective as many of these efforts are, it is becoming increasingly clear they are much less so for a large group of children who fail to achieve their potential due to damage sustained at

an early stage of their lives. It has been estimated that at any one time in Africa, more than 200 million children under the age of five fall into this category. There are many biological and psychosocial risk factors responsible for this gloomy outcome[1], but malnutrition occurring at a very young age is known to be one of the most important remediable ones. One third of children whose development is compromised in this way, are known to be growth retarded (having a weight significantly lower than expected for their age and height)[2]. These developmental defects are usually not recognized until the child attends school when, not surprisingly, it is too late to correct them.

Description of the project in lay terms

Decades of research in developed countries have linked social and emotional development of children to certain aspects of the parental support they may or may not have received. Broadly these are – intellectual stimulus, sensitivity with appropriate response to their needs, and provision of emotional warmth. Studies have shown that food supplementation usually results in weight gain but has little to no benefit on emotional development[3 4]. However, in a review of 35 studies in which emotional stimulation was used in conjunction with nutritional supplementation, a small benefit was found, from the intervention, on intellectual skills of the children but was more marked for sociability, self-confidence and school entry[5-8]. These results imply that for normal emotional development of a malnourished child, parental contact with the child to provide the all-important emotional stimulation at an early stage of life is of critical importance. Recent studies have suggested that emotional stimulus, which is often lacking in the homes of young malnourished children, has achieved some success. In Jamaica, this was achieved in malnourished children under the age of 5 years who were visited in their homes by social workers over a period of six years[9 10]. Involvement of the mother in the provision of emotional stimulus was then used in Bangladesh. Children, aged between 6 months and 2 years, were taught a form of interactive play between mother and child, known as ‘play therapy’, by lay workers who had no previous experience of this type of work[12]. Original as this work was, it was hospital based and statistically unsound. Most recently, lay therapists teaching emotional stimulation within the home was used by the Conticinis in a part of Ethiopia where malnourishment of

children is relatively more common than elsewhere[11 13]. Malnourished children treated in this way showed, at follow-up, some apparent increase weight gain and improvement in emotional development. Unfortunately, once again these studies had one or more design defects which, at present, makes it impossible to recommend to governments the wider application of this potentially valuable form of treatment.

The Conticini Study (2008-09), on which our proposed study is based, was designed to test the hypothesis that acutely malnourished children recover more rapidly, physically and developmentally, if they are offered emotional stimulation combined with emotional stimulation and appropriate food rather than simply being fed in the health post by their mothers. The study was done in the Southern States Region in Ethiopia where there is considerable poverty and cyclical shortages of food. At that time, 4.8 million people in Ethiopia were experiencing severe food shortages and 75,000 children were registered with severe malnutrition. The child mortality throughout the country was 50/1000 children but obviously was much higher amongst those registered as malnourished. Five hundred and fifty five severely malnourished children, mostly aged between 1-3 years (85%), were visited every 3 weeks over the six months of the study, a proportion received education and emotional stimulation. The beneficial effects of emotional stimulation on the emotional and physical recovery of severely malnourished children observed in this study, seemed to confirm the results of other studies. The conclusions from these important results cannot be regarded as unequivocal because of the relatively small size of the control group and the absence of random allocation between groups.

The literature reviewed here is based on studies which have been institution based or which have been statistically difficult to conclude. For this reason, we propose a replication of the Conticini Study, to provide irrefutable evidence as to whether treatment of severely malnourished children by emotional stimulation is of such benefit that it can be recommended to the Ethiopian Government for general use throughout the country.

Addendum to executive summary

Design of Proposed Research Program

Creation of the Intervention Group and the Control Group will be randomized by health posts (HP) from where the malnourished children originate e.g. if HP 'A' is designated as Intervention then all children coming from there will be treated by emotional stimulation and food supplementation whereas if HP 'B' is designated as Control, children coming from there will be treated by nutrition advice and food supplementation only.

Food supplementation will be provided by the Regional Government for all malnourished children in the Trial, in the amounts recommended by the Ethiopian Government.

Selection of Therapists/data collector/outcome assessors will be by the regional authorities and selected staff of the trial management team. The selection of these individuals will be from health extension workers who are employed in health posts paid by the Government (HEWs) and young men and women (youth workers) who have volunteered to join the Project. Attention must be paid by the selectors to the intellectual competence and education of applicants for what is undoubtedly intellectually demanding work.

Emotional stimulation technique and details of data collection will be taught to Intervention Group therapists. Control Group therapists will be taught how to give nutrition advice and details of data collection. HEWs and youth workers will attend a 7 day training course before the Project gets underway. Two courses will be run – one who are to work with Intervention Group participants and another for those who will work with Control Group participants. It is essential that throughout the period of the Trial, HEWs/youth workers are informed of the objectives of the Trial but will not be told of the differences in the work they will be undertaking.

Supervisors of the work of the therapists will be selected and directed by the staff of the trial management team. How frequently a supervisor will visit the therapists has yet to be decided. It should be remembered that when the authors of this Grant Application met with some of the young workers from the previous study, they made it clear that supervision was valued by them and they asked if in future the visits of the supervisors could be more frequent.

The evaluation team

Professor Fonagy will oversee the research program of the Trial, ***Dr Alessandro Conticini***, as the Project Director, will be responsible for the organization of the 'fieldwork' of the Trial, in particular the reliability of the data collection by the youth workers and their supervision. ***Professor Beard,*** as Chairman of the Trial Steering Committee in London, will be responsible for overseeing the conduct of the Trial, including dealing with organizational issues such as data collection and analysis, medical issues arising during the course of the Trial and maintaining good liaison with officers of the Ethiopian Government.

BACKGROUND

Physical and Psychological Impact of Malnutrition

Education is vital for both individuals and countries in their struggle to emerge from poverty. A significant proportion of children's development is compromised to a marked degree in many developing countries. More than 200 million under five year olds in developing countries fail to fulfill their developmental potential[9]. A range of biological and psycho-social risk factors contribute to the compromised development of children in developing countries[1] and these risk factors have cumulative effects[14]. However, malnutrition is consistently reported as profoundly impeding child development in sensori-motor, socio-emotional and cognitive domains[15]. A third of children under five in developing countries have growth retardation, defined as height below 2 standard deviations[2], and prospective cohort studies consistently show strong associations between stunting and later cognitive deficits[3 16-18] even when socio-economic covariates are controlled for. In addition to cognitive and educational deficits in these children, emotional deficits have also been frequently reported, including apathy (the absence of positive affect)[19], insecure attachment[20], and an impeded readiness to engage in exploration and play[19 20]. Not surprisingly, with development these come to manifest as problems of behavioral control, self-directed attention, and the capacity to create age appropriate social relationships[4 21 22].

The association between nutritional status and the achievement of developmental potential is powerfully confirmed by randomized controlled trials that have measured the impact of providing food supplements on developmental status. Food supplements to improve children's nutritional status and development show concurrent benefits to motor development[23-27], cognitive development[23 24 27], cognitive ability[26] and socio-emotional development[23 24 27]. Behavioral benefits from nutritional supplements include reductions in apathy[28] and fussiness[27]. From the point of view of the present study it is important to note that long-term benefits are not invariably demonstrated and follow-ups often show limited[29] or no benefits to cognition or behavior[3 4] from food supplementation programs alone. Studies where there is

greater long-term involvement with mothers[26 30] are more likely to show supplementation to have benefits on behavior as well as cognitive development.

In summary then, there is robust evidence to indicate that malnutrition is associated with substantial psychological morbidities which affect sensori-motor, cognitive and socio-emotional development. It powerfully impacts on children's ability on school entry, which in turn is an important component in determining their progress in school. Biological risk factors, included in and associated with malnutrition (e.g. specific micro-nutrient deficiencies), impact on the development and functioning of the central nervous system[1] which may be a key mediator of long term developmental adverse outcomes. Experimental studies that have modified nutritional status have demonstrated a robust impact on these domains, although long term effects on behavior appear on the basis of systematic reviews to be a more elusive target.

The Impact of Malnutrition on Parenting

Malnutrition, however, is rarely an isolated risk factor. Inadequate cognitive stimulation has strong associations with malnutrition and robust findings indicate that in many developing countries only a small proportion of parents (10-40%) provide cognitively stimulating materials to their child and only up to a third involve themselves with their children in cognitively stimulating activities[1]. Consistent evidence from intervention studies proves that providing increased cognitive stimulation to young children increases their socio-emotional and cognitive competence.

Studies assessing the impact of cognitive stimulation[10 24 31-34] yield effect sizes in the moderate to large range (d=0.5-1.0) with effects largely maintained at follow-up[33 35]. Engle and colleagues[5] systematically reviewed 35 studies where nutrition and health programs were combined with stimulation in realistic tests of effectiveness. Centre-based programs were found to have small to moderate effects on cognitive measures[6] but additionally benefited non-cognitive skills such as sociability and self-confidence and had long-term impacts, including on school entry[7 8]. Thus, experimental studies confirm that inadequate parental cognitive stimulation associated with malnutrition, unless reversed, will have

significant detrimental educational and emotional developmental effects.

Not surprisingly, the evidence also suggests parental engagement at an early stage is critical for normal educational development. Intervention in the first two years of life is more likely to have lasting beneficial effects[36-38]. Our systematic review also suggested that programs focusing on parenting and parent-child interaction were more likely to yield larger effect sizes and to have greater long-term effects[39-42]. Several studies have directly addressed maternal sensitivity and maternal responsiveness and reported beneficial effects on cognitive development[43], behavioral problems[44], and socio-emotional development[45-47]. As relatively more effective early year stimulation studies appear to include parents, this raises the question as to why parental behavior (particularly parental sensitivity) may be important in overcoming the long-term effects of child malnutrition.

Here we have to seek answers in the transactional nature of the parent-child relationship and the broader context of the role of the parent in the child's development. For biological, (evolutionary[48]), and behavioral reasons, a parent's involvement with a malnourished child is likely to be suboptimal. As we have seen, malnourished children are more apathetic, display less positive affect, and engage in lower levels of play[19 20]. The lack of responsiveness of the child can initiate a transactional process where the parent becomes relatively disengaged from the child and fails to provide the necessary levels of cognitive and emotional stimulation required for normal development (see below). Poverty and hunger can also compromise a mother's capacity to promote social and cognitive development in infancy through timely responses to the infants' distress (sensitive interactions). This perhaps reflects an evolutionarily underpinned tendency towards apparent disengagement from the physically vulnerable infant[49-51]. This may be of particular concern for the developing world with extremely high rates of poverty and, associated with this, high rates of maternal depression, consequently disengagement from the child may be very likely[52]. Prevalence rates for maternal depressive symptoms across developing countries range from 3-60%[44]. The average rate across developing countries is about 17% which is 2-3 times the expected level in Westernized countries. We know maternal depression is likely to affect childhood outcome

via its impact on maternal child rearing behavior[53]. We know that depressed mothers are less involved, less sensitive and more negative when interacting with their infants[54]. Of course such non-responsiveness may be caused by maternal malnutrition or be a natural response to non-responsive behavior of under-nourished infants, or a combination. Regardless of the beginning of this causal chain, available evidence is consistent with the hypothesis that infant malnutrition is associated with parental non-responsiveness.

Does this matter? To answer this question we will briefly consider the conclusions of extensive research carried out over the last 50 years on the impact of parenting on the early cognitive and social development of the child.

The Impact of Parenting on Normal Development

Decades of research in developed countries have consistently linked young children's cognitive and social and emotional competence to three aspects of parenting: 1) cognitive stimulation, 2) sensitivity and responsiveness and 3) emotional warmth[55]. The influence of maternal sensitivity on infant attachment is confirmed in studies carried out in developing countries[34 46] and the benefits of secure attachment are well accepted, not just in terms of the long term advantages for peer relationships and socio-emotional adjustment[56], but also for physical health, including fewer chronic and recurrent health problems, better health and lifestyle practices and lower health costs[57]. Accumulating evidence leads us to expect that the parameters of parenting quality described above will have the same positive impact on children with malnutrition[58 59].

A rich literature supports the long-term benefits, with observed long term outcomes including school success, higher employment and earnings, less welfare dependency and a reduction in crime rates[60-67].

But do these interventions work for developing countries? Intervention studies that have directly addressed maternal sensitivity and responsiveness through psycho-education or modeling techniques, showed positive impact on maternal behavior[45 68]. Cooper and colleagues report an impressive study, carried out in a South African peri-urban settlement, which assessed the efficacy of an intervention designed to improve the mother-infant relationship and the security of infant attachment. The authors reported significant benefit from a home

visitation program, undertaken by previously untrained lay community workers, who provided support and guidance in parenting for six months post-partum. This randomized controlled trial (RCT) reported a small effect size on parental sensitivity at six and twelve months and a marked reduction in parental intrusive behavior. More remarkably, the intervention was shown to increase infant security of attachment at 18 months with an odds ratio of 1.7. Critically, these benefits were achieved without substantially impacting on maternal depression, suggesting that even depressed impoverished mothers can benefit substantially from an intervention aimed to promote sensitivity and responsive parenting. A limitation of this study was the lack of intervention offered to the control group. Thus we cannot be certain if simply the additional attention offered to mothers rather than the specific intervention generated the group differences. Nevertheless, the study demonstrated that a home-based intervention delivered by trained lay therapists in the context of substantial socio-economic disadvantage had positive benefits, not only for maternal responsiveness but also for child emotional development.

Several important features of successful programs emerge from reviews[1 5 69 70]. These are: a) limiting interventions to those at greatest disadvantage, b) interventions in the first three years of life, c) a combination of attention to nutrition, physical health, cognitive stimulation and emotional wellbeing, d) the involvement of families, particularly parents, and offering them ways to facilitate their involvement in promoting the child's development, e) directing interventions at encouraging biologically prepared (natural) ways of early learning and intuitive parenting rather than introducing artificial (designed) models, f) combining scientifically validated approaches with traditional practices to produce a culturally acceptable blend, g) arriving at structured relatively simple intervention protocols that can be readily acquired by previously lay community workers, h) providing a well-structured training program that integrates monitoring of competences and support with supervision and outcomes monitoring, i) a sound theoretical and practical framework from which the intervention program is constructed and that allows theoretical and practical developments to directly feed into programmatic improvement.

HYPOTHESES

Based on the literature reviewed above, we feel justified in concluding that, due to a constellation of factors, parenting may frequently unfortunately be sub-optimal for children who are suffering from malnutrition. Sub-optimal parenting will undermine social development, increasing the risk of non-responsiveness on the part of the child, which in turn may undermine the parent's capacity to respond to the child with sensitivity. Several predictions follow from this transactional model. 1) Addressing malnutrition with food supplements does not address parenting factors associated with malnutrition. 2) Addressing malnutrition alone may not reverse the impact of parental disengagement undermining the normal development of the child. 3) Given the relationship of parental responsiveness and benefit from feeding programs, infants may not fully benefit from these programs unless the quality of parenting is also addressed. The challenge for implementation science in this context is with the identification of a simple easily communicated strategy, which enhances parental responsiveness but does not require the complex educational and training strategies which have been used to achieve this in studies in developed countries (for example the use of video supported training or methods requiring expert therapists[71]). We propose to improve on this situation using a simple intervention, which helps reengage mothers more fully with their malnourished child and simultaneously provide the child with emotional stimulation by training them in simple play activity.

Based on the review of the above literature, we believe that we are justified in concluding that the parental care of many malnourished children is sub optimal. From the studies we have reviewed it seems likely that emotional stimulation may well improve the quality of the interaction between the child and his mother and thus prove to have a substantial beneficial effect on the recovery of malnourished children. It seems likely that malnourished children, in response to emotional stimulation, will regain their appetite more rapidly and start to rebuild their energy stores earlier than babies in the Control group. This response will be shown among babies in the group where mothers are trained in playful interaction with their child by more rapid weight gain and, consequently, an earlier return home than that of the control group. Training in play will generalize to the home setting which also means that fathers will be

more likely to be drawn into the family circle, with the considerable benefit for the child's long-term well-being that this tends to bring

PRELIMINARY DATA

Previous work combining nutritional and psycho-social and emotional relief interventions in Ethiopia

Remarkable work has been reported by Quéré and Conticini[11 13] in Addis Ababa based on a National Strategy for the Psychological Support of Ethiopian Children[72]. They developed a highly effective intervention methodology, emotional stimulation (ES), to facilitate the physical and emotional development of malnourished young children. The program was developed to follow the profile of effective intervention programs for developing countries outlined above. The Emotional Stimulation program[13] imaginatively addresses Ethiopian cultural constraints while integrating the delivery of emergency food with emotional stimulation in a pragmatic, potentially readily up-scalable, efficacious package.

The Final Report of a test of effectiveness supported by the Pulitzer Foundation gives preliminary evidence of the program's potential[11]. It was tested in a sample of 555 children drawn from 34 intervention sites receiving therapeutic feeding via ACF Concern (NGOs) or the Ethiopian Government. 26 of these sites included emotional stimulation. Children recruited from 10 sites were not malnourished. In half of these sites (n=52) the children received emotional stimulation while the other five sites (n=52) did not receive it. As these data merely establish the possibility of implementing play coaching, the results are not going to be discussed here. A hospital setting for children with severe malnutrition provided a further opportunity for examining the impact of emotional stimulation on bodyweight and the observation of emotional status, but this was complicated by major concomitant disease in some of the children studied (n=29) and therefore these results will not be considered here.

20 of the sites (n=376) had children who were malnourished and whose emotional status and body weight were monitored over three months and compared with children from three sites (n=46) who were malnourished but did not receive any emotional stimulation. Of the 302 children for whom MUAC (middle upper arm circumference) scores were available, 84% had MUACs less than 110 mm indicating severe acute malnutrition (SAM). A further 12% had a MUAC of between 110-125 mm. The mean age of this sample was 25.4 weeks,

ranging between 6 and 60 weeks. The children were recruited from 18 medical health posts each affiliated to one of five medical centers. Each medical health post recruited on average 18 consecutive referrals for malnutrition (SD=4.6, range 8-25). Three of the health posts provided all the participants for the comparison group and received no input from the emotional stimulation team. 51% of the sample was female. 55% of them were looked after by their mother and 39% by both parents. Only 35% of the sample reported a family member who was employed.

There were two primary outcomes in the trial: the child's weight and scores on the Ages and Stages Questionnaire (ASQ). Weight was assessed at weekly intervals and was analyzed using mixed effects linear growth curve models using robust standard errors to provide conservative estimates of statistical significance. Mixed effect models use all available data but missing values were a significant problem in the analysis of this dataset after the seventh week, so models were constructed on the basis of the first half of the observation period. Gender and age were introduced as covariates into the model and their interaction with time was tested. **Figure 1** shows the mean weight gain during the first seven weeks of treatment in both groups. The means suggest the presence of a quadratic effect and therefore a quadratic polynomial of time was also included. The two level mixed effects model with random effects parameters for medical posts and participants and treating group, time and group x time interaction as fixed effects yielded a highly significant Wald statistic ($\chi 2$ (9) = 1004.4, p<.0001). As would be expected, change over the first seven weeks of treatment was highly significant (β = .19, 95% CI: 0.08 – 0.30, z = 3.24, p < .001). This means that, on average, children's weight may be expected to increase by nearly 3 ounces (85 g) each week. The quadratic effect of time was not significant (β = 0, 95% CI: -0.02 – 0.01, z = 0.94, p>.1). There was a slight gender effect (β = 0.35, 95% CI: 0.05 – 0.65, z = 2.33, p < .02) indicating that male infants tended to be heavier than females. There was a gender by time interaction (β = -0.04, 95% CI: -0.08 – 0.01, z = 2.1, p<.04) suggesting that weight gain was slightly more rapid for girls than for boys. Age was a highly significant predictor of weight (β = 0.11, 95% CI: 0.10 – 0.12, z = 21.1, p<.0001) and weight gain (β = .002, 95% CI: 0.0009 – 0.0036, z = 3.18, p<.001) indicating that older children gained weight

somewhat more rapidly.

Groups were not significantly different in overall weight (β = -0.20, 95% CI: -0.85 – 0.45, z = 0.59, p>.1) although markedly different in weight gain (see below). As would be expected, change over the first seven weeks of treatment was highly significant (β = .19, 95% CI: 0.13 – 0.24, z = 6.46, p < .0001). This means that on average children's weight increased by nearly 1/5 of a pound each week. There was a significant effect of group on the rate of change (slope) of individual trajectories. The slope of increase in weight was significantly greater in the ES group than the control group (β = .16, 95% CI = 0.04 - 0.28, z = 2.68, p<.007). The size of the mean difference effect is small (d=0.23) but the differences were observed within seven weeks. There was a marginally significant quadratic interaction between group and time (β = -.01, 95% CI: -0.02 – 0.002, z = 1.66, p<.10) suggesting that there was a greater tendency in the ES group to gain weight rapidly and then decelerate in their weight increase over the period of observation.

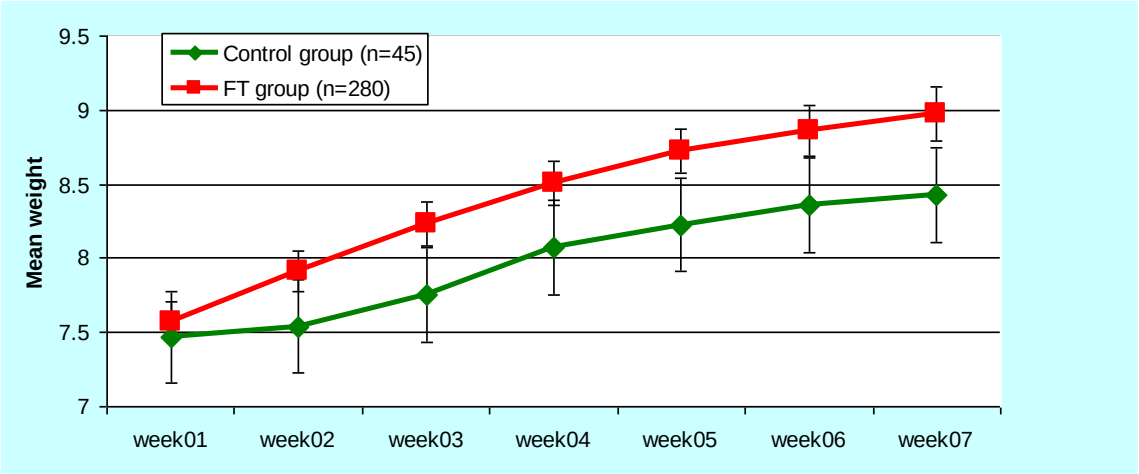


Figure 1. The mean weight of both groups during the first 7 weeks of treatment. The error bars represent 95% confidence intervals which are asymmetrical because of the unequal size of the groups. By week 5 the ES group is significantly heavier.

To estimate the longer term effects, we tentatively applied the above model to the full 13 weeks of the program. As there are very few observations for the control group after week 9 this analysis should be considered with great caution. **Figure 2** displays observed values and values fitted to a quadratic model. The figure suggests predicted weight gain continues in both groups but remains significantly different for at least 6 months. While the comparison was

obviously not undertaken for long enough to arrive at a definitive conclusion, the results may be taken as a proof of principle that the impact of emotional stimulation can be measured in terms of the rate of weight gain by the child.

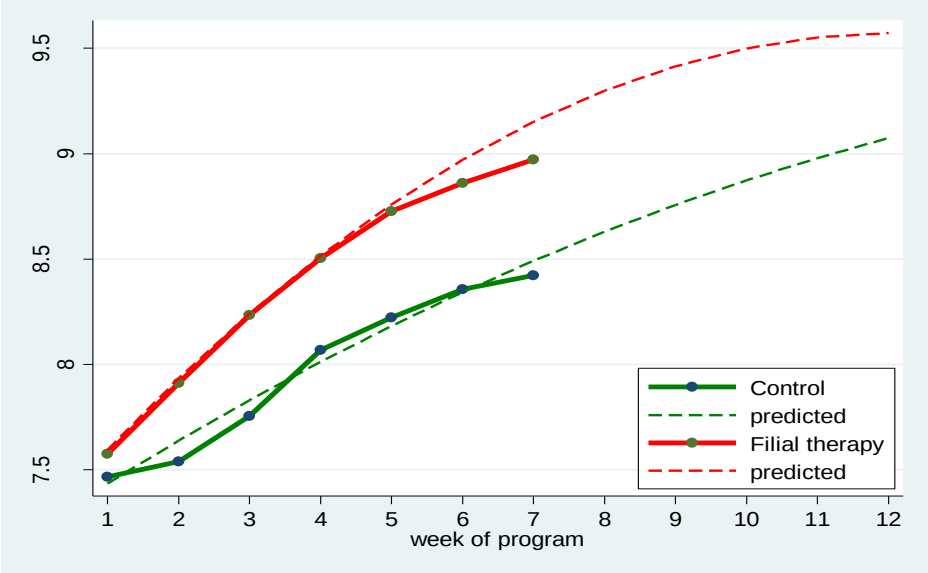


Figure 2
Mean weight for infants in feeding programs with and without supplementary emotional stimulation. Solid line represents observed values, dashed lines predicted observations based on mixed effects multilevel model with random effects regression model for medical post and time. Observed values are only displayed for 1st seven weeks because of the large number of missing observations.

The Ages and Stages Questionnaire was administered four times (at week one, five, nine and 13). ASQ scores are adjusted for age yielding a score adjusted for expectations on the basis of chronological age (RASQ). We applied a similar mixed effects linear growth curve model using robust standard errors to provide conservative estimates of statistical significance. Gender and age were again introduced as covariates into the model and their interaction with time was tested. **Figure 3** shows the mean age adjusted RASQ scores at the four measurement points. The means again suggest the presence of a quadratic effect and therefore a quadratic polynomial of time was also included in the two level mixed effects model with random effects parameters for medical health posts and participants. The model was highly significant, as indicated by the Wald $\chi 2$ statistic ($\chi 2$ (9) = 296.2, p<.0001). With the gain in body weight and the passing of time there was a significant improvement in RASQ scores (β = -.22, 95% CI: -.34 – -0.10, z = -3.5, p < .0001). This means that on average there was an improvement in ratings (decrease is errors) but this appeared to decelerate as indicated by the significant quadratic effect (β = 0.008, 95% CI: 0.0008 – 0.01, z = 2.2, p<.03). There was no gender effect (β = -0.07, 95% CI: -0.37 – 0.22, z = 0.49, p > .10) or gender by time interaction (β = 0.004, 95% CI: --0.02 – 0.03, z = 0.27, p<.04). Age was a predictor of RASQ (β = -0.14, 95%

CI: -0.024 – -0.003, z = 2.5, p<.02) and change (β = .001, 95% CI: 0.0003 – 0.0025, z = 2.60, p<.009) indicating that older children had better scores but improved somewhat more slowly. The groups were not significantly different overall (β = 0.004, 95% CI: -1.08 – 1.09, z = 0.01, p>.1). There was a highly significant effect of ES on the rate of improvement (slope) of individual trajectories (β = -.25, 95% CI = -0.38 – -0.12, z = 3.80, p<.0001) with very substantial differences between the groups favoring the ES intervention by the 4th time of testing (d=1.93). There was a quadratic aspect of the differences between individual growth curves of participants from the two groups indicated by the significant quadratic interaction between group and time (β = 0.009, 95% CI: 0.002 – 0.016, z = 2.36, p<.02) suggesting that there was a steeper improvement and then leveling off of ASQ scores in the ES group than in the controls. **Figure 3** illustrates the observed mean scores on the Ages and Stages Questionnaire and the scores predicted in this multi-level model.

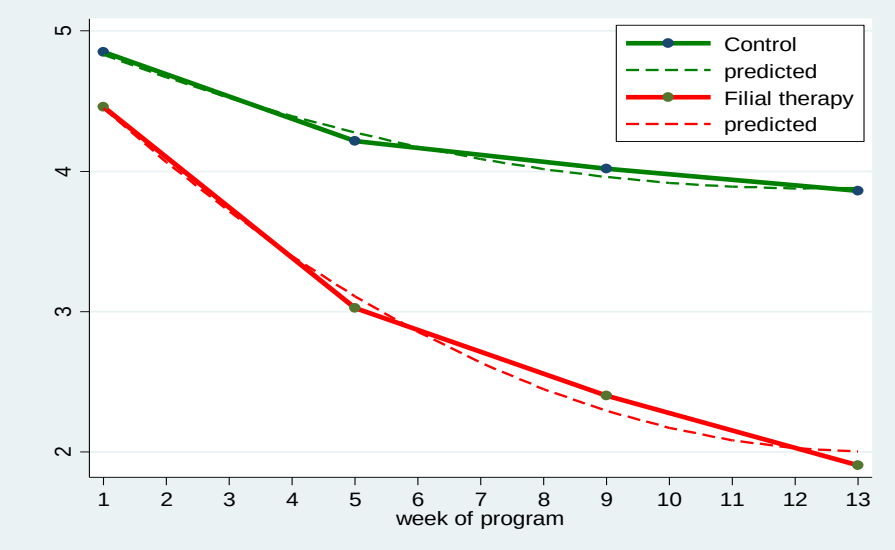


Figure 3
Mean ASQ adjusted for chronological age for infants in feeding programs with and without supplementary emotional stimulation. Solid line represents observed values, dashed lines predicted observations based on mixed effects multilevel model with random effects regression model for medical post and time.

The combination of ES coaching with the health extension program succeeded in reducing mortality rates. Increased speed of recovery led to substantial changes on the cognitive and emotional development scales of robust psychometric instruments. Although long-term follow-up data are not available, there is every reason to expect that these promising results will translate into increased resilience, both physical and mental, in the face of future stresses. The brevity and accessibility of the intervention along with the substantial

observed improvement recommends it highly for scaling up the intervention from a regional to a national level.

The preliminary study offered evidence of the normalization of intervener-rated developmental quotients in both malnourished and non-malnourished groups offered emotional stimulation (the 'treated group'), greater weight gain in the malnourished treated group compared to the malnourished untreated group in the first six weeks following enrolment, and earlier discharge from treatment in those receiving emotional stimulation than those in the non-treated group. Parents of the children in the treated group substantially changed their perception of their child, seeing them as less lethargic, less inattentive, less irritable and less intolerant than prior to the intervention. Two thirds were seen to have improved on these dimensions whilst only 10% appeared to have worsened over the course of emotional stimulation.

Several strong features of this study should be noted, including the large sample, the involvement of 23 health extension workers and the same number of Youths supporting them, the highly organized training offered to both groups of interventionists, the supervisory training offered, the systematic data collection, the presence of an untreated comparison group, and a measure of adherence to the treatment protocol amongst others. However, this initial landmark study has several important limitations that could be readily addressed in further investigations. A) The malnourished comparison group was relatively small in size; B) the outcome assessments were not conducted without knowledge of which group the child was in ('non-blind'); C) the assignment of sites to treatment was not random; D) some of the outcome measures may have been reactive (where treatment interacts with the accuracy of measurement by for exampling getting to know a child in the treatment arm better than a child in the control arm of a trial); E) the statistical analyses applied to the findings could have included an examination of the association of weight gain with change in emotional status that could improve the claim for a causal association.

Despite these limitations the findings are very impressive and provide an excellent platform for a replication in an adequately powered double-blind cluster randomized trial. The current investigation proposes to extend these

findings and test the hypothesis that emotional stimulation will serve to enhance the bond between the mother and her infant and the impact of this will be clear on key variables, such as the speed of weight gain on the part of the infant.

RESEARCH DESIGN AND METHODS

Overview and setting

In this study we will test the hypothesis that encouraging social stimulation of the infant through maternal play impacts on the physical development of the infant and leads to faster weight gain in malnourished children. We propose a cluster randomized superiority trial comparing ES with nutrition education alone (NE) for families who meet criteria for being malnourished. Each of 24 intervention sites will be staffed by a health extension worker (HEW) and a Youth, both of whom will have been trained in ES or NE, and a further Youth assigned to evaluation. We have obtained agreement from political leaders at federal and regional governmental level to support the study. Sadly because of adverse climate conditions, including excessive rain, referrals from Therapeutic Feeding Programs (TFU and OTP) are not anticipated to be a problem. The project manager has exceptionally strong links with sites and all sites that have been approached agreed, at least in principle, to participate in a rigorous RCT.

The organization of the therapeutic feeding program in Southern Ethiopia seems to lend itself well to cluster randomized RCT. RCTs have been performed in the area in the past and are possible. Although there are some local variations, health care is offered through medical centers, each of which has several health posts which are linked to communities (kebele). Each health post has one or usually two health extension workers who are familiar with a number of health packages (16) and would be the first individuals to be consulted in case early signs of malnutrition such as diarrhea. Health centers have professional medical care including nurses and each health centre is likely to cover about half of a woreda. Referrals from health centers go to hospitals and referrals in case of severe malnutrition are linked to explicit criteria.

The design calls for randomization of 12 health posts to ES. The other health posts will receive the same amount of expert time but no training in the emotional stimulation intervention, they will benefit from extra nutritional education (NE) offered to mothers following an analogous protocol to ES. We have opted for cluster randomization as it is unlikely that meaningful informed

consent for individual randomization could be obtained from eligible individuals and in this way consent needs only to cover participation of an intervention program and the administration of research measures. It is not assumed that the current implementation of NE is uniform across the sites, and to create appropriate comparability training and supervision of HEWs and Youths will be developed following UNICEF guidelines and its delivery will be monitored for each person randomized to this arm of the study. The key part of the program is training of HEWs and Youths including OAs in both the ES and NE protocols. The cost of this training and the effectiveness of it in terms of standards of delivery are a critical part of this evaluation. In order to establish if this project could be brought to scale, the training input will be carefully monitored in terms of cost, effectiveness and value.

Recruitment of participants will take place for 2 months commencing between 1 and 6 weeks after the inauguration of the program at each site. The study will run for six months and the capacity for TFU for individuals meeting inclusion/not meeting exclusion criteria is conservatively estimated to be approximately 18 children at each of the sites. The number of eligible cases will be substantially higher; based on our past experience of ES implementation, the proportion of families accepting this treatment is likely to be close to 80% of those to whom it is offered. In the sample size and power calculations based on our experience in implementing this program successfully to a similar sized sample, we have assumed that most, if not all, of the ES treatment capacity at each site will go towards cases participating in the trial who have agreed to research participation. We are confident that health posts will not offer ES or NE to those who had not consented to participation. Not only would this potentially skew the sample, it would also act to reduce recruitment to the study, since families would know that they could increase their chances of obtaining the treatment by refusing consent to the research. Given the therapeutic equipoise that exists between ES and NE for this group of children in Ethiopia, we believe that this is an ethically appropriate and defensible position.

Design

This will be a cluster randomized controlled clinical trial. We aim for the trial to be pragmatic as far as possible, to have very few exclusion criteria and to match routine practice in all possible respects consistent with rigorous evaluation. Throughout we aim to pay attention to establishing systems for training and treatment that are consistent with the intervention being brought to scale across several regions of the country where malnutrition is a significant clinical problem. Allocation of health posts to the trial arms will be by minimization. Health posts will be randomly drawn from a pool of 24 health posts across 6 medical centers, stratifying for differences between health posts in terms of a) the relative poverty of the site calculated in terms of the prevalence of malnourished children; b) distance from the nearest medical centre; c) and average age of children presenting to the health post. Minimization along these lines is necessary because there is some heterogeneity between health posts and the relatively small number of health posts in each arm (k=12) means that chance differences between the arms could easily influence treatment response.

In the initial phase of the trial HEWs and Youths will be trained with 7 days of training. Recruitment and treatment will take 9 months. Treatments will be offered over a period of 12 weeks for individual families. The primary outcome will be BMI. An alternative categorical measure will be the Ethiopian Weight classifications using the WHO 2005 norms. Secondary outcomes will include indicators of physical development (height, MUAC), cognitive and emotional development. The quality of interaction between parent and child during spontaneous play will also be assessed. Other secondary outcome measures used with a selected sub-sample of children will yield development indicators of cognitive development on a standardized measure (The Bayley Scales to be administered to a sub-sample of randomly identified cases by a supervisor trained in the assessment of infants).

Setting

Treatments will be offered by services collaborating in this ES trial at the 24 sites. At this stage there is insufficient information available to us to

characterize the settings fully and the proposal assumes that characteristics of the 34 sites familiar to the researchers in the pilot trial, reported above, are representative of the remaining settings. On the basis of these data we anticipate a significant variability in children's age associated with health posts, no substantial variability associated with gender balance, the identity of the primary caregiver (both parents or mother alone) or the employment status of the primary caregiver. Nevertheless, these characteristics of the setting will be monitored and, if necessary, adjusted for using minimization. The study will be conducted in the Southern Region of Ethiopia with a training hub in Awassa Town. The Conticinis built up a good link with the Regional Health Officers of the Southern States Region in 2008-09 after the successful completion of an ethical review of their proposed Study. We would like to use the same Region and a very similar protocol, albeit with different health posts, HEWs and Youth Workers.

Target population

The selection criteria listed below are aimed to be as broad as possible in order to help consumers of the research make decisions about the generalizability of the findings and test the intervention against the aim to bring the ES intervention to scale. Inclusion and exclusion criteria will be applied rigidly. In general we will aim to increase generalizability by using the minimum number of entry criteria. The task of establishing an infant target population based on the status of being severely undernourished is a challenging one as, in most contexts, this term gestures towards a heterogeneous group. At the same time, we also recognize that the referral routes of poverty, under-nourishment, developmental delay in sensory motor, cognitive, language and social emotional development often identify the same young children and families with very similar needs when they have reached a particular crisis point.

Taking this into consideration, we have defined inclusion criteria for eligibility for enrolment into ES or NE. Those invited to enroll will share at least 2 of the following features indicative of 'risk status' that can be considered severe and which serve as generic inclusion criteria: (i) malnutrition; (ii) developmental delay (iii) family poverty. We will put in place demographic, clinical and individual functioning measures to assess these attributes and test the

assumption of relative homogeneity despite different recruitment sites. Under-nourishment will be determined according to criteria defined by the 'Protocol for the Management of Severe Acute Malnutrition' [73] issued by the Ethiopian Federal Ministry of Health. These criteria are (a) a weight/height or weight/length ratio of less than 70%, which is a z score larger than 3 using the WHO 2005 standards (in other words more than 3 standard deviations outside population norms). (b) In the absence of an accurate measure of body length or height a MUAC score less than 110mm with an upper arm length of greater than 65cm. (c) Alternatively the presence of bilateral pitting oedema may be used.

These measures will be taken at first visit to the health post. In our preliminary study sample 82% met the MUAC criteria for Severe Acute Malnutrition (SAM) i.e. would have been eligible for this study on criterion (b). Although height information is not available for this sample, we suspect that the remaining 18% met criterion (a). At all sites objective assessors will obtain information concerning family visit all the homes to inquire (a) whether there is a child at the appropriate age and (b) whether the child is undernourished. This will be the screening triage stage of the trial. Developmental delay will be assessed using the Ages and Stages Questionnaire but will not be used as part of the entry criteria. Family poverty is challenging to establish but is so pervasive in this population that its discriminatory value is minimal. We anticipate that at all sites we will have an opportunity to identify all suitable families meeting the general inclusion criteria and invite them to be included in the study. Inclusion and exclusion criteria are listed in **Table 1**.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria:

1. Age greater than 6 months and less than 5 years.
2. Undernourishment defined as 3 SD (70%) below WHO published norms of height or forearm skinfold thickness less than 110mm.
3. Sufficient family involvement to support intervention.
4. Passing the appetite test.

Exclusion criteria:

1. The presence of serious medical complications requiring referral for inpatient treatment (see Table 2).
2. The presence of clinically apparent congenital abnormalities.
3. Preterm birth (<37 weeks gestation) or birthweight >2SD below weight weight/gestation limit.

Following the triage stage, there will be a medical check for complications that will include an appetite test. Appetite tests need to be carried out because they

frequently reveal classical IMCI diseases in malnourished children who show no sign of these diseases and reveal cases of metabolic malnutrition not indicated by anthropometric measurement. As both significant infection and major metabolic abnormality represent immediate risk of death, an appetite test following SAM guidelines is required. Some cases may pass the appetite test but show symptoms indicative of a medical disorder. These are listed in **Table 2** and are considered to be exclusion criteria for this trial.

Table 2. Medical complications that indicate that patients should be excluded from the trial and be referred for inpatient treatment

- Bilateral pitting oedema Grade 3 (+++)
- Marasmus-Kwashiorkor (W/H<70% with oedema or MUAC<11cm with oedema)
- Severe vomiting/ intractable vomiting
- Hypothermia: axillary's temperature < 35°C or rectal < 35.5°C
- Fever > 39°C
- Number of breaths per minute:
  - 60 resps/ min for under 2 months
  - 50 resps/ minute from 2 to 12 months
  - >40 resps/minute from 1 to 5 years
  - 30 resps/minute for over 5 year-olds or
  - Any chest in-drawing
- Extensive skin lesions/ infection
- Very weak, lethargic, unconscious
- Fitting/convulsions
- Severe dehydration based on history & clinical signs
- Any condition that requires an infusion or NG tube feeding.
- Very pale (severe anaemia)
- Jaundice
- Bleeding tendencies
- Other general signs the clinician thinks warrants transfer to the in-patent facility for assessment

Patients failing the appetite test and/or showing medical complications should be referred for inpatient treatment. If the indications of complication are dealt with and appetite returns, patients may be recruited for the trial if they are referred back to the outpatient setting. A diagram showing the recruitment pathway is included as **Figure 4**.

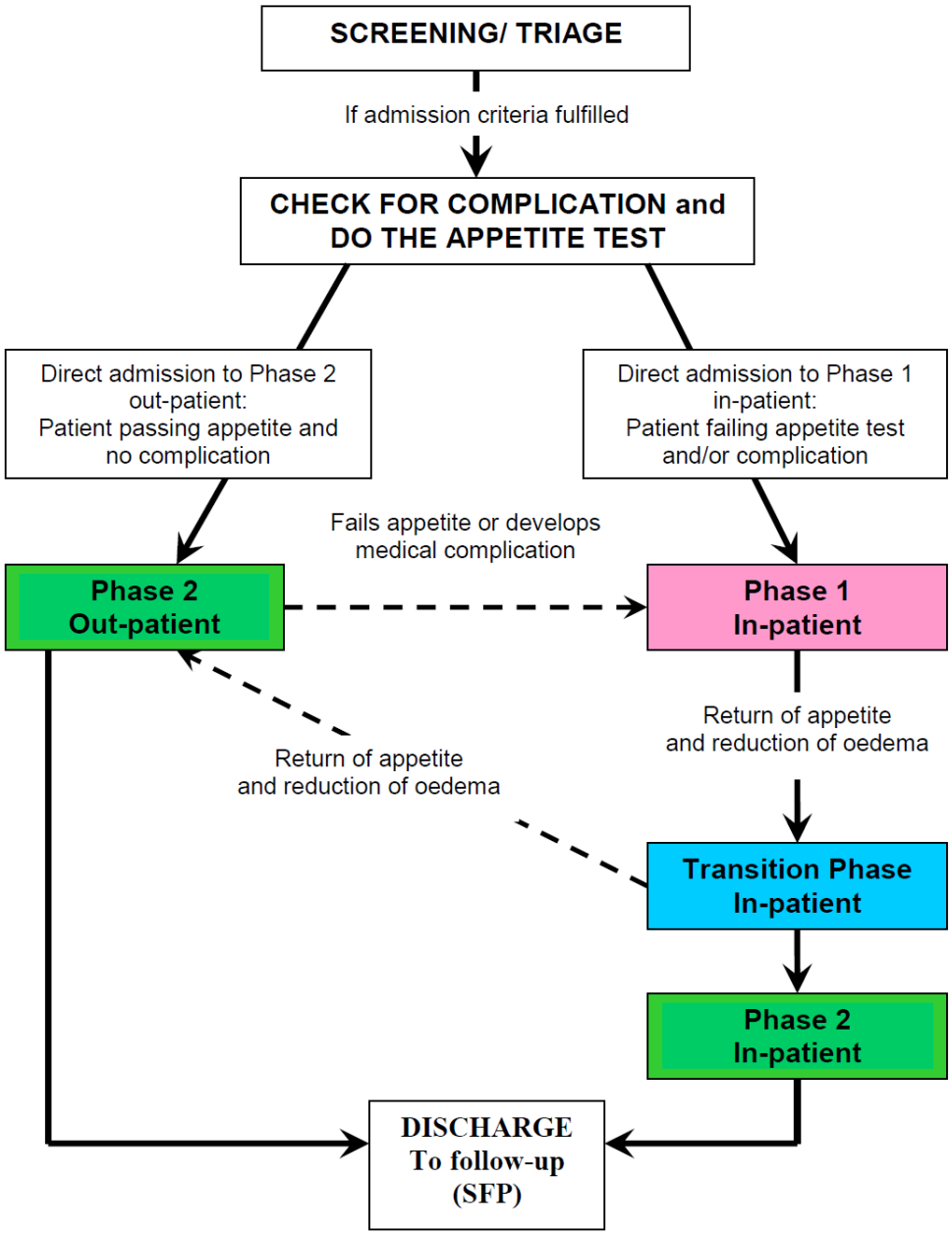


Figure 4. The schema for decision making in recruiting participants for the ESCEFI Trial. Patients are assessed for inclusion criteria at the screening stage and exclusion criteria in the medical assessment. Screening is carried out by trial staff. Checking for complications is carried out by HEWs or nurses. Dashed lines indicate moving between inpatient and outpatient treatment. Patients who do not respond to outpatient treatment (**see Table 3**) are referred for assessment and inpatient treatment. Patients for whom inpatient treatment was successful and who are returned to outpatient treatment may be recruited for the trial if they meet entry and no longer meet exclusion criteria.

Patients may be excluded from the study during the course of the trial exceptionally. Indications for this are serious medical complications, failure of the appetite test or fulfilling the criteria for failure to respond to treatment. These criteria are listed in **Table 3.**

Out Patients	
Criteria for failure to respond	**Time after admission**
Primary failure to respond	
Failure to gain any weight (non-oedematous children)	21 days
Failure to start to lose oedema	14 days
Oedema still present	21 days
Secondary failure to respond	
Failure of Appetite Test	At any visit
Weight loss of 5% of body weight	At any visit
Weight loss for two successive visits	During OTP care
Failure to gain more than 2.5g/kg/d for 21 days (after loss of oedema (kwashiorkor) or after day 14 (marasmus)	During OTP care

Table 3. Criteria for discontinuing patients in the trial and referring for medical evaluation with a view to inpatient treatment

Outcome measures

Our primary outcome is the incidence of severe and moderate malnutrition defined by anthropometric measures (MUAC, weight and height). The criteria for severe malnutrition, described above, are either 70% of the median WHO 2005 weight for height or weight for length ratio or a MUAC score of less than 110mm. The criteria for moderate malnutrition for children up to the age of 5 and height between 45-120 cm are included in the SAM management protocol. The severity of under-nourishment will be categorized as ‘none’ (100% of the median weight), ‘mild’ (<85% of the median weight), ‘moderate’ (80-75% of the median weight), ‘moderate to severe’ (75-70%), ‘severe’ (<70%) and ‘very severe’ (<60%). Weight and length/height measurement will be carried out at each visit to the health post. The method of obtaining height and weight will be the standard one specified in the SAM management protocol. Every effort will be made to weigh and measure the child at each visit. If for technical reasons this is not possible MUAC measurement will substitute and the category of malnutrition will be imputed. This categorization offers a six point scale of malnutrition which is normally reduced to a binary category with cut-offs at 70% (severe) or 80% (moderate). The hypothesis examined in this study is the time taken to remission from severe under-nourished status, measured in weekly

intervals, and the proportion of cases in either arm of the trial that remit within the study period. A comparable analysis will be possible to compute the proportion of cases and the time taken to reach the mild under-nourished category or better. This will be based not on weekly measurement but measures taken at the formal assessment points in the study.

It is anticipated that a substantial number of children will reach the trial criteria for remission and will no longer be attending the health post for treatment. The measurement points will be at baseline, 6 weeks and 12 weeks. It is important to identify as far as possible the key moderators of the effects of ES. We will collect demographic information relevant to outcomes, in particular gender, age, family structure. The latter variable is included because post-hoc analyses of our preliminary study showed that the primary caretaker being the mother or grandmother was associated with weight gain but not significantly with the intervention. In order to understand the way this new intervention works and perhaps enhances the effectiveness of current services, from the viewpoint of both the users and providers, we will also undertake a range of quantitative and qualitative measures. The latter will include interview based investigation of the key stakeholders in the service systematically sampled from the 24 sites. This was undertaken with great success in Conticini study, although the information gathering was more informal than intended in the ESCEFI Trial.

(a) Principles of measurement

The secondary measures are selected according to a clear set of principles. Measures will be made across multiple domains (physical indicators, cognitive function, family function, parent satisfaction, comorbid problems and economic costs), using multiple methods (physical measurement, ratings based on interviews, questionnaires), and multiple sources (the child, the mother, the therapist) to maximize the clinical validity of the outcome assessments and minimize bias arising from any single source of information. Where possible, measures will be made by objective assessors (OAs), blind to treatment allocation. Many of the measures have been selected because they were part of the ambitious pilot project, which this trial represents an attempt to replicate, and which will provide prior data against which the current sample may be compared.

(b) Domains of measurement

Baseline/Background Measure

Mothers' Demographic Information regarding family background, educational background, medical history, and maternal life course outcomes (subsequent child bearing and work status) will be collected at baseline assessment (at the beginning of treatment).

Maternal Mental Health and Perception of the Child

The General Health Questionnaire (GHQ)[74-76] will be used to give an indication of the mother's emotional wellbeing. This is a well-documented screening instrument for detecting emotional disorders in community settings and in non-psychiatric settings. The questionnaire originally contained 60 items, but there is currently a range of shorter versions including the GHQ-30, GHQ-28, GHQ-20 and GHQ-12. The scale asks whether the participant has experienced a particular behavior or symptom recently and includes several items commonly endorsed by individuals presenting with physical symptoms strongly linked to emotional difficulties. Each of the items can be scored on a Likert scale from 0 (not at all) to 3 (much more than usual) points. The GHQ may also be analyzed in a dichotomous fashion; in this case each item receives a value of 0 (0 or 1 points) or 1 (2 or 3 points). The GHQ is brief, simple and easy to complete. It has been translated into a number of languages[77-81] and has been used extensively in different contexts and cultures [82-84].

In addition we will use the **Pearlin and Schooler's**[85] seven- item scale measures maternal sense of mastery by asking mothers to respond to the extent that they feel some control over their life's chances, as opposed to feeling ruled by fate. Responses indicating agreement to disagreement are based on a seven- point scale. Higher scores indicate a higher sense of mastery. Mastery scores were negatively correlated with depression scores and positively correlated with self-esteem scores[86]. We predict an increased sense of mastery associated with the ES intervention.

Qualitative Survey

This is based on the interview used in the pilot study in Ethiopia[11]. The

interview establishes attitudes about the child as well as perception of the mother's family situation. It is a brief interview that needs to be administered by the person working with the family. It will be used pre and post treatment. This interview includes asking the parent to rate the child on a five point frequency scale on four attributes related to malnourished status: lethargy, inattentiveness, irritability and intolerance. In the pilot study substantial shifts were observed in the parent's perception of the child.

Child Measures

Child Health Outcome indicators will be collected through routine measurement of weight, height and skin-fold thickness. Data will also be collected on a range of symptoms of malnutrition. In TFU settings, the child is measured for weight and height already, while in OTP the child is only measured for weight. This project proposes to include a measurement of height also in OTP settings for children who are enrolled into the program. In addition before starting treatment, eating habits of children recruited for the trial will be elicited using a standardized schedule to be administered by the OA. Information gathered will include the amount of food taken by child per diem recorded by mother e.g. no food, occasional food, regular food. This schedule will be repeated with each follow-up occasion.

The **Ages and Stages Questionnaires: Social-Emotional (ASQ:SE)** has been developed to provide information specifically addressing the social and emotional behavior of children ranging from 3 to 65 months of age[87 88]. The measure has been extensively used in cross-cultural contexts[89 90]. The measure yields separate scale scores for self-regulation (the child's ability or willingness to calm or settle down or adjust to physiological or environmental conditions or stimulation), compliance (the child's ability or willingness to conform to the direction of others and follow rules), communication (the child's ability or willingness to respond to or initiate verbal or non-verbal signals to indicate feelings, affective or internal states), adaptive functioning (the child's success or ability to cope with physiological needs such as sleeping, eating, safety), autonomy (the child's ability or willingness to self initiate or respond without guidance i.e. moving to independence), affect (the child's ability or willingness to demonstrate his or her own feelings and empathy for others) and

interaction with people (the child's ability or willingness to respond to or initiate social responses to parents, other adults and peers).

Bayley Scales of Infant Development will be administered to evaluate the development of the infant or child in a small subsection of young children[91]. It is an assessment-based measure that describes a child's (between the ages of 2 months and 42 months) mental and motor functioning and includes a behavior rating scale. The Scales require about 45 minutes and must be administered by a trained and experienced evaluator so it will only be administered to a random sub-sample of the children recruited for the study. The mother is present during the evaluation and may assist in the presentation of various items and activities to the child. The Bayley was standardized on a national sample of 1,262 infants and children and correlates (r=.57) with the Stanford Binet reported for children aged 24-30 months. The split half reliability coefficients are reported as ranging from .81 to .93 on the Mental Scale and .68 to .92 on the Motor Scale. The instrument has often been used in studies on the impact of nutrition supplements in developing countries[92-95].

Mother-child interaction

We will record mother-child interactions and the observed interaction will be coded using the Global Rating Scale (GRS) [97]. Several aspects of the interaction will be coded including the parent's attitude, the extent of support for the child, the quality of communication between the parent and the child, the child's capacity to explore with parental support, parental tolerance and discipline, parental confidence in interaction with the child and the presence of inappropriate, odd or threatening behaviors. In particular an RAs will be trained to note evidence of spontaneous show of affection by mother to baby – touching, stroking, kissing. These aspects are incorporated in various scales of the coding system (warmth, sensitivity etc).

Supervision of Assessments

Although the measures intended to be used in the trial are simple, and many of them routine, the administration of even simple measures in this environment can be complex and challenging. The trial will put in place comprehensive and vigorous supervision of objective assessors, who will be extensively trained and thoroughly supervised throughout the trial, with reliability on each of the

measures assessed by supervisors for 25% of the cases at each point of measurement. The budgetary calculations allow for this unusually intense level of supervision.

Sample Size

A minimum of 432 participants (216 in each arm) will be recruited. The sample size calculation is motivated by a secondary outcome (achieving clinically significant increase of body weight), as reliable figures for the reduction of malnourished status associated with ES are not available because height was not measured in the preliminary study (see above). The expected difference in proportion of our trial is derived from the major Indian and South American effectiveness trials, as well as our pilot investigation.

We assume that each site (health post) will have at least 18 families with infants meeting the inclusion criteria during the recruitment period who agree to participate. In our calculations we also assume that 6 medical centers will participate and these medical centers will have 24 health posts in their area of administration overall. No centre will have less than 3 or more than 6 health posts. On the basis of past experience with the same population, 65% of families with children between 6 months and 5 years presenting to the health post are likely to meet criteria and 80% of these will agree to enrolment. This implies that each site will be expected to be able to recruit and offer treatment to 18 families over the recruitment period. Assuming that 5% weight difference is clinically significant and observing, on average, 1kg weight difference achieved between ES and the control groups over a 6 week period, using WHO 2005 norms for the variation of child weight at age 6-60 months, this sample size will give 86% power to detect a 5% difference in weight using a 2-level random-effects model with health post and child as random effects. To take account of within-Youth/HEW correlation of outcomes in the ES arm, we assumed an interclass correlation of 0.02 and a total of 48 therapists, giving design effects of 1.22 in the ES arm and 1 in the NE arm, and thus reducing the power to 83%.

Participant Recruitment

The process of recruitment is fundamental to the success of this research trial. In addition to criteria that apply to recruitment for any trial (the clear application of eligibility criteria, a standard procedure for obtaining informed consent, etc.), recruitment for this trial must be especially sensitive to the community context and be based on effective partnerships with partner agencies (NGOs) and strong relationships with HEWs and Youths, the communities and the families of the undernourished young children. Given the relatively large number of sites and limited possibility of statistically moderating site-specific effects, the trial team will work in strong collaboration with the team based in Addis Ababa, and supervisors coordinating the intervention at each site, to achieve the high levels of accrual necessary to ensure sample comparability and reasonable generalizability. We are able to make a tentative projection regarding recruitment developed on the basis of the pilot trial referred to above[11], but fully recognize the need for allocating time for recruitment and opportunities for training and continuous professional development for supervisors, HEWs and Youths. The appropriate line items for training and supervision in our budget reflect our attention to this priority.

Families will be approached by the HEW and recruited to the intervention (either ES or NE) with equal enthusiasm to retain therapeutic equipoise. The site will determine which of the two invitations a family receives. In either case they are asked to agree to be trained in the intervention once a week for 12 weeks. Further, they are asked to meet with an objective assessor after agreement to participate, at baseline, 6 weeks and12 weeks. They are told that at any time, they can discontinue involvement in the trial and that this will not affect their participation in the food program. They will also be asked to consent to potentially being followed up several months hence, in case resources become available for examining the long term effects of the program.

Accrual

Anticipated recruitment paths are shown **Figure 5**. We have made very conservative assumptions based on the Final Report of the pilot Trial[11]. It is likely that with time fewer inappropriate referrals will be made but we assume that only 65% of those referred to health posts will be considered appropriate referrals for this trial. For the moment we assume that 35% will clearly not

meet the ‘at severe risk’ of malnourishment or will meet exclusion criteria and fail triage. Data from the pilot study suggests that approximately 80% of cases meet triage criteria and over 90% considered to be appropriate for the trial go through to providing consent. We conservatively estimate that in the more heterogeneous recruitment context of this trial, the ratio of referrals to randomized will be closer to 52%. Once again on the basis of the pilot trial, we anticipate drop-outs during the intervention to be extremely low at 5%, and during the follow up period a further 5% may be lost, so 90% of participants to be available at 24 weeks for at least one of the primary outcome variables. Intent-to-treat analysis will include all participants who had consented to the trial.

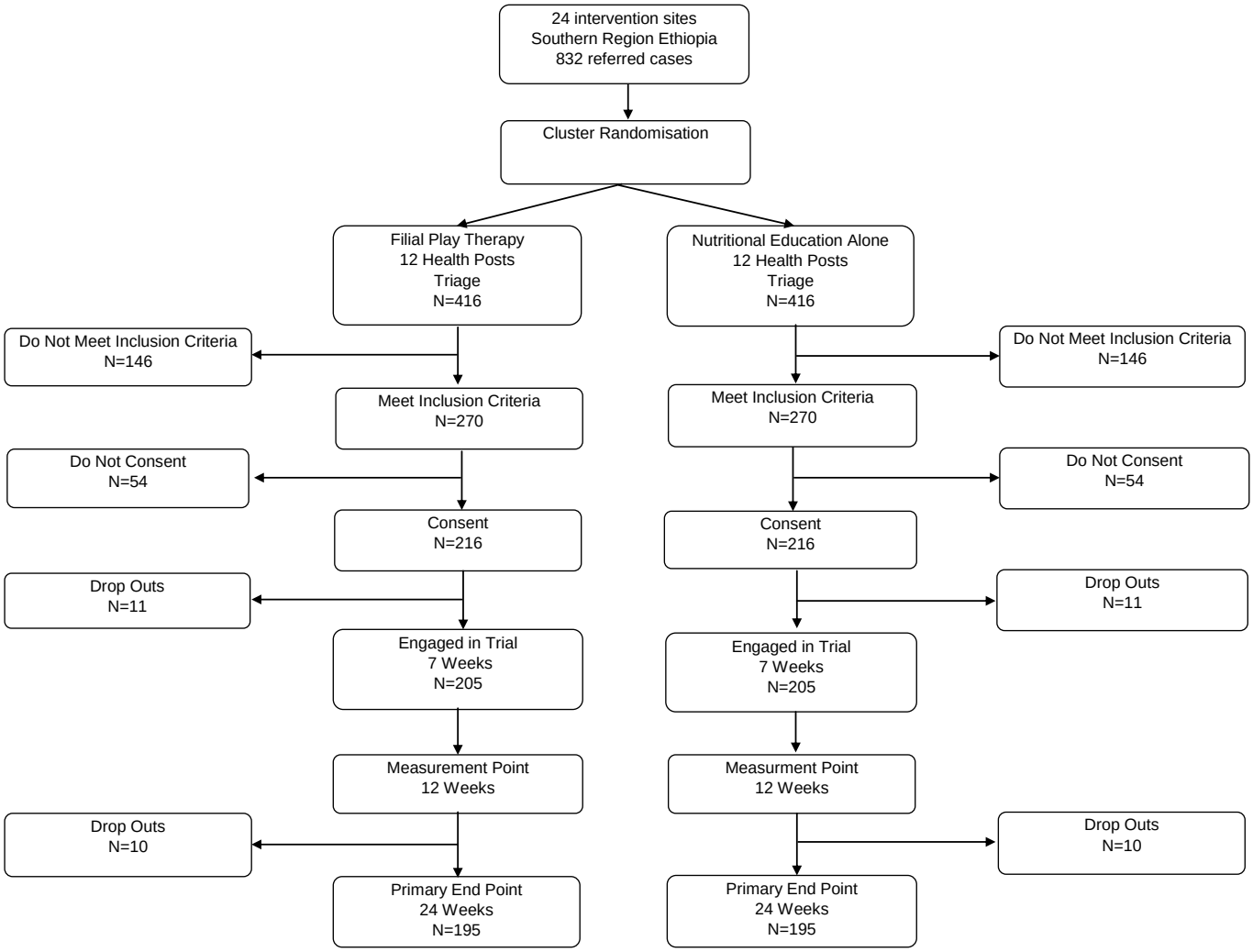


Figure 5. Consort Diagram Representing Recruitment and Expected Drop-Out from the trial.

Randomization

We are planning a cluster randomized design rather than imposing randomization at individual level for several reasons: (1) randomizing individuals to two treatments requires informed consent being given by participants to meet minimal ethical standards and at the time of writing we are not certain if meaningful informed consent could be gained from individuals approached; (2) if participants were individually randomized within each site and both ES and NE interventions were provided in each location the likely 'leakage' or contamination between the two treatments arms could very well distort the findings, particularly risking that the principles of the ES treatment

would be adopted by neighboring families, thus reducing the likelihood of finding substantial differences between individuals randomized to the two arms of the trial; (3) the blindness of OAs would be hard to assure if OAs were fully informed about the two types of interventions (the preliminary plan is that OAs are not informed about the nature of interventions or indeed that there are two different types, their task would be simply to assess the effect of the interventions carried out without knowing the categorical differences between these or them having expectations about the superiority of one over the other); (4) we feel consenting and enrolment will be easier if families only have to agree to participate in additional meetings with a therapist and an OA rather than having to make a decision about accepting a random choice between two types of interventions; (5) there would probably be insuperable practical problems with individual randomization, particularly if minimization was also required with a computer-generated adaptive minimization algorithm that incorporates a random element with stratification factors. It seems to us both feasible and easier to apply stratification factors at site level (number of malnourished children, distance from nearest medical centre and average age of children presenting at the health post). Even though there will be no individual matching of participants, demographic and clinical factors will be monitored, see above, and should site specific differences occur, these will be modeled in the hierarchical linear models proposed, see below.

Planned Interventions

Experimental intervention

ES is an integrative, manualized, licensed program with an accumulating evidence base for engaging families of children exhibiting problems associated with malnourishment. The program is based on emotional stimulation which in turn is a multicomponent intervention including psycho-dynamic, cognitive behavioral and existential therapeutic routes. It lends itself well to dissemination to lay therapists following a short training period and extensive practice and supervision. The ability to effectively disseminate the treatment is essential if this strategy to enhance resilience in Ethiopian children is to be brought to scale in this country. Preliminary results[11] indicate that (a) HEWs and paid young volunteers (Youths) are able to learn the method and (b) that it

is effective in their hands not only in dramatically altering parenting attitudes but also in changing the child's growth trajectory (weight gain and cognitive development). ES trained therapists and ES supervisors will not be allowed to see participants in the NE arm of the trial, although professional consultants in the study team may well be engaged in provision of NE. On site supervision will ensure that Youths and HEWs are supported in their implementation of the therapy. Supervisors will also be charged with determining the quality of the therapy and offer further training and ultimately replace those who do not adhere to the therapy manual.

Nutritional Education

Numerous interventions in developing countries have combined the provision of therapeutic food with a supportive educational intervention covering infant's and caregiver's dietary needs as well as advice concerning hygiene and a range of other concerns which health visitors often address in the developed countries. There are numerous programs currently in common use in Southern Ethiopia; we have opted for the Ethiopian Federal Ministry of Health [73] package. Training in and delivering this package would be considered by most health professionals to be of intrinsic value. In order for a positive outcome to be compelling for health professionals, the intervention has to be shown to be superior to a treatment that does not contain the same active ingredient (in this case emotional stimulation) which is under scrutiny. While this is often referred to in the medical literature as a 'placebo' condition, there is no equivalent to a 'sugar pill' in psychosocial interventions. The best we can hope for is (a) that the control condition carries the same level of expectation of good outcome on the part of the families as the 'experimental' treatment condition (ES); (b) it matches the treatment condition in terms of the attention the family receives; (c) the person assessing the outcome of both treatments remains objective i.e. they have no knowledge of the treatments and do not know when collecting data about the effectiveness of the treatment (e.g. weighing children, collecting health measures) what kind of treatment the family under assessment has received. For this reason the control condition must be as similar to the active treatment as possible so that the objective assessor (OA) cannot 'guess' which treatment the family received. In order to ensure blindness OAs will be specific to sites and will not be aware that there are different expectations in regard to

the two arms of the trial, more importantly, nor will those delivering the training in nutritional education. The change to routine procedures in a cluster randomized trial (where sites rather than individuals are randomized) should not interfere with the normal delivery of either type of intervention. Further, the use of NE as a control condition is ethical, as the trial is offering treatment to both groups (not an inert sugar pill).

Training

Training of therapists for the ES and NE interventions is a key part of the protocol and considerable resources are directed towards ensuring that a high level of fidelity is achieved, by youths and HEWs, in delivering the intervention protocol to an appropriate standard. The trainings are organized at local centers for both supervisors and HEWs. They take seven days, including a test where participants' competence in delivering the protocol is assessed by supervisors. The supervisors' training, including an assessment of the supervisors by the trainers, is more rigorous and we anticipate that it will take 10 days. We anticipate that it will be necessary to offer training to more health extension workers and youths in both arms of the trial than is necessary to deliver the protocol. Supervisors will identify those HEWs and youths who do not meet minimal criteria in competence of delivery of the program. The assessments will be based on role play exercises, to be carried out in the training setting following the methodology for the assessment of medical competences using the Objective Structured Clinical Examination (OSCE) technique.

Controlling for Confounding Factors

Confounding factors will be controlled for using an attention control group. Here an alternative intervention is offered, which is carried out over the same length of time, in the same circumstances and by people with same level of training as those in the ES arm. The content is aimed at the mother and not at the relationship between child and mother. We hope other confounding factors will be equivalent between the two arms of the trial. A further possible source of bias is the expectation of the assessors. This will be controlled for by keeping the assessors blind to treatment allocation. If blinding is not possible, we intend to create equivalent expectations in the assessors in relation to the two

intervention arms.

Participant Adherence

Dropping out of treatment is common during preventive interventions for early childhood problems[70]. In this context, however, the capacity of ES to maintain families in treatment when compared with NE may be an important consideration in relation to effectiveness. The standard treatment for malnutrition in Ethiopia is by 'emergency food'. This is understood by all therapists and the communities most likely to have the problem of malnutrition, so it is unlikely to be a problem asking mothers to join the Control group unless they are in the Southern Region. In the pilot study following the recruitment procedure outlined above, it seems that well over 90% of those recruited for either arm of the trial were retained for the purposes of data collection. We recognize that participation in the various treatment protocols will have lower adherence than data collection as data collection visits are incentivized for both families and young persons by feedback on weight and progress which families, by and large, welcome. To ensure a comprehensive 'intent to treat' analysis, the primary outcomes consist of data recorded formally, which can be measured even if participants have dropped out of treatment, and are only willing to take part in the briefest of research appointments.

Participant Burden

The respondent burden for this set of instruments, when administered in person is approximately 15 minutes for the parent and 30 minutes for the child. These measures have been used successfully with subjects from various ethnic backgrounds. The OA will read all instruments to subjects so literacy will not be a requirement. We appreciate that open-ended questions are sometimes hard for this ethnic group, in particular, questions aimed at subjective experience are challenging for these participants to answer. We have removed some difficult, sometimes inappropriate, questions from these instruments and we have made extensive efforts to overcome language barriers by translating and back-translating.

There are specific challenges we face in association with bringing in an

objective assessor, in addition to the HEW and the Youth, to work with others, children and families. We anticipate that as these individuals do not have the same history as the Youths carrying out the treatment, some understanding of the dynamics of the family will inevitably be lost. In order to mitigate a loss of information confirming subtle aspects of interaction, Youths will collect information in relation to their observations and these will be used to provide a background to help interpret the 'objective' data that OA's provide.

There is a further challenge in using objective assessors, in that therapists use the form assessment questionnaires as an entry point to establishing alliance with the family. In order to mitigate loss of the more helpful aspects of data collection by the therapists, therapists will continue to collect demographic information. Supervisors will support the introduction of objective assessors and will continue supervising on site. These supervision sessions will last 2.5 hours and most of the supervision will take place in small groups in a non-judgmental, non-threatening way that emphasizes maintaining rapport with the family.

Trial management

There will be only one trial centre based in headquarters in Addis Ababa. There will be two committees with overlapping membership responsible for the governance of the trial. The trial management committee (TMC) will be an Ethiopia-based group under the chairmanship of the Research Director; this committee will be responsible to a London-based trial steering committee. There will be five individuals closely involved in leadership of the program. The trial management committee will include the Project Manager, the Senior Clinical Director and ex-officio, the Principal Investigator and the Chair of the trial steering committee will meet regularly by phone. A user-representative who took part in the pilot project will also contribute to discussions of the TMC. The Research Director will oversee the work of the Project Manager and Senior Clinical Director. The Research Director will be accountable to the TSC for the running of the trial.

The Project Manager will be in overall charge of the day to day running of the trial. The clinical programs will be coordinated by an experienced therapist and

a Senior Clinical Director who will train all supervisors and coordinate training events. The Project Manager will oversee the training of OAs and their supervision by research supervisors. The Principal Investigator will oversee data collection, data management and data storage, as well as the statistical analysis of the data collected.

In the first phase of the study we will set up a trial steering committee (TSC) to monitor the progress of the project, to advise the research team on matters arising during subsequent phases and also to carry out data monitoring. The TSC will sign off on the protocol at its first meeting and will meet at least quarterly over the course of the trial, perhaps more regularly during the preparatory and final stages of the project. The group will be based in London and will meet in person and by telephone conference where necessary. It will be made up of a Chair with medical qualifications, the PI, the Research Director, and independent researchers and statisticians with experience relevant to the project. The committee will be chaired by Professor Richard Beard, who initiated the trial and has overseen it over the planning stages (pro-bono).

There will be a Youth, working alongside a HEW, administering the intervention at each site. 24 HEWs and 24 Youths will be responsible for delivering the two arms of the trial; 12 HEWs and 12 Youths will be trained in ES and the same number trained in NE. The management of these clinical staff will be under supervisors, three responsible for ES and three responsible for the NE intervention. The supervisors will be under the management of the Senior Clinical Director. The Senior Clinical Director will have day to day management responsibility in relation to both Youths, HEWs and supervisors working on the project.

There will be 24 OAs under the management of the Project Manager based at the research sites working in a number of teams. The teams will work semi-independently from each other to ensure blindness in coding and interviewing. They will be able to support each other in doing assessments in order to maximize the possibility of blindness (also enforced by instruction to families) so that site A will have an OA from team 1 and someone doing qualitative interview with the same family from team 2. OAs and the trial co-coordinator

will meet regularly across sites as often as feasible.

Involvement of HEWs

HEWs are involved for a number of reasons. It would not be possible to carry out the project without their collaboration. They know the mothers well and when mothers come to the health centres because they have a malnourished child that is when our staff and the HEWs will collect the data required for the Study. All reports back from HC's show that the HEWs enjoy the involvement and did not find that it impeded their work. In this Study, a trained local (youth) therapist will be attached to the HC who will liaise closely with the HEW. In addition a further HEW will be attached as an objective observer. The HEW will collect most of the data from the mother. Close liaison with the Study team is valuable because HEWs are trusted by the mothers.

Working with local groups

The local Project Team will be encouraged to collaborate as closely as possible with local academic groups. There may be some measures which require administration by a locally trained expert. The up-skilling of local youths could be considered to be a direct benefit or of added-value to Ethiopia, although we recognize that this is not the same as establishing collaboration with local academics.

Agreeing study methods with service providers

On confirmation of funding we will make contact with NGO project leads of each service, send them an outline copy of our proposal and ask them to send us an update on progress with plans for setting up and evaluating their local service. We will arrange to visit each pilot site at the earliest convenient time. Each visit will include a senior member of the project team. During this initial visit we will explain the overall aims of the project and obtain feedback on the acceptability and feasibility of our proposed national evaluation. We will establish a link with a specific member of staff in the responsible NGO, who will be invited to play a more active role in the project through membership of the Trial Steering Committee and acting as a link person between the project team and the local service. We will obtain updated information about the local project timetable and the start date for the service. We will collaborate with local service providers in finalizing measures that will be used to evaluate outcomes

and agree arrangements for maintaining regular contact with the service during the remainder of the project.

Ethical considerations

Families will be identified and approached about the possibility of trial involvement by the HEW, informed by the treating team and asked for their consent to be enrolled into the research. If consent is given, the OA will be asked to perform the baseline tests. In collaboration with the HEW the OA will establish whether families meet inclusion criteria and do not meet any exclusion criteria. In consenting, all parents will be told that they can discontinue participation at any time. While the families will not be paid for trial participation, they will be offered compensation for time lost in participating in the research.

Risks and anticipated benefits for trial participants and society, including how benefits justify risks

There is minimal risk from enrolment, research measures and either treatment. Both ES and NE will be delivered by individuals used to working with families and children of this age with severe health problems. Those who agree to participation in the trial will be involved in a number of interviews and assessments (up to 1.5 hour for baseline assessment, 30-60 minutes for follow up assessments) which may be somewhat burdensome but do not carry specific risk. Given that participant families will agree to provide access to confidential information, including the child's health status, there is potential risk of accidental breakdown of confidentiality which must be met by stringent data-handling safeguards. Benefits to participants will include the provision of intensive high quality care from uniquely trained HEWs and the supervising clinicians in the ES arm of the trial. Benefits to society will be predominantly through the potential to discover a clinically and economically effective intervention for a social problem that causes considerable distress not only to the family members involved, but to the social group directly affected by the long term consequences of emotional developmental problems associated with poor infant-parent relationships. This is a very significant cost to public services as well as the individuals and families concerned.

Informing potential trial participants of possible benefits and known risks

This will be, as outlined above, through the discussion with the recruiting HEW clinician.

Procedures for Consenting

We will obtain verbal consent, including permission to follow-up the family remaining in effect for four years. For consenting families, the outcome assessor (OA) will administer pre-testing questionnaires during initial contact with the child and family.

Time period for retention of relevant trial documentation

AC will be responsible for archiving records which will be kept for at least 5 years as per the Research Governance requirements.

Expected Serious Adverse Event

Epidemiological data suggest that with a sample of this size it is possible that some children may suffer from major health problems or serious injury during the course of the study. In the event of unexpected deaths associated with the trial, the Trial Steering Committee would consider the implications for continuation of the trial and may wish to speak to someone representing the research project about such deaths as well as to local HEW staff who have provided treatment. If required, the site AC and VC staff would be available for such meetings.

Data analysis

Data analysis will take place in London at University College London. We will use a multilevel growth-curve model organized at three levels: individual assessments of BMI (‘Measure’); participants (‘Child’); site (health posts). Week of testing will be coded as number of weeks from presentation, with zero being baseline at presentation. The primary dependent variable is BMI. We will also use multi-level models for the secondary outcome measures.

Analyses will be by intention-to-treat: that is, including each individual in their

randomized group regardless of the intervention actually received, and performing sensitivity analyses to explore the impact of any missing data. If there is significant missing data this will be dealt with using multiple-imputation methods (which are widely implemented in a variety of statistical software packages101).

To test whether the relationship between intervention and BMI is mediated by changes in the infant-mother relationship we will carry out a mediational analysis, fitting a saturated model tested with 500 bootstrap iterations of model 74 of the PROCESS algorithm of Hayes.

We will also carry out a range of exploratory analyses using a multilevel model to assess the effect of any variables showing systematic differences between the intervention and control groups at baseline.

The Competences of the Team

The research team provides a unique and essential combination of individuals with knowledge of both local conditions and trial methodology, as well as the clinical skill required to carry out the trial. **Dr Alessandro Conticini** will be **Project Manager** of the trial; he has led the successful previous study of ES and brings to the trial 3 essential skills. First, his background in UNICEF as a senior manager equips him with extensive knowledge of under-nourishment issues and their management in Ethiopia. He has worked in Ethiopia as a UNICEF officer, as well as a head of an NGO in more recent years. Second, his current work in the Southern region of the country has provided him with unique local knowledge, and as director of an NGO he has administrative skills in recruitment and support for both clinical and research staff. Third, Dr Conticini's PhD from the University of Manchester is in economics, particularly in connection with developing countries. This background provides him with a valuable capacity to scrutinize the cost-benefit aspects of differences observed in the course of the trial. He has also published extensively and will be important in disseminating findings to inter-governmental and non-governmental organizations.

Valerie Quéré, Senior Clinical Director, has worked therapeutically with children using therapeutic play and creative art. She has unique experience in

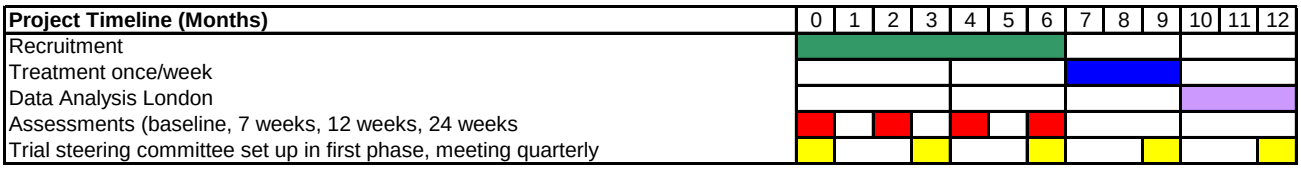
applying these skills to children in Ethiopia. She has established the Ethiopian Centre for Child Psychological Support Association and was a leader in developing this as a platform for emotional stimulation. She promoted the implementation of play therapy strategy with UNICEF support, and developed and applied a clinical governance system to ensure ethical, safe and effective play therapy practice with children. She has overseen the training of 65 Ethiopian practitioners to certificate level, 25 to diploma level and 23 trained as clinical supervisors. As clinical lead to the trial (a senior clinical director) she brings her management and supervision experience in supporting implementation of the emotional stimulation project in Ethiopia (UNICEF and Pullitzer Foundation). In addition to her experience setting up play therapy, she developed an integrated and multi-sectoral case management of children who are victims of abuse. She brings to the project her legal experience; Ms Quéré is a lawyer who has been program coordinator for juvenile justice in Capital's Defense for Children International (NGO). She has been working in Ethiopia since 2005, has extensive knowledge of the country and was a key architect of the Justice for Children project of UNICEF in Ethiopia. The use of emotional stimulation as a way of moderating childhood maltreatment emerged as part of her work as project officer in Justice for Children.

Peter Fonagy, who will be **Principal Investigator and Research Director,** has primarily focused on early social experience in his work, identifying genuinely formative aspects of the family environment which influence subsequent personality functioning, including the quality of social relationships, future wellbeing and mental health. His longitudinal studies, which linked the quality of parent-infant attachment to theory of mind development, have important implications for strategies for early prevention not accounted for by genetic influences. In collaboration with Read Montague and Lane Strathearn, he showed that parents' attachment history (quality of relationships to their own parents), assessed before the birth of their child, predicted the strength of their own reward system's response to the infants and identified a potential neural mediation for the transgenerational transmission of patterns of attachment. The link between human attachment and social cognition led Fonagy and colleagues to develop a model of and a highly effective treatment approach for borderline personality disorders (BPD). Mentalization Based Treatment (MBT)

is now one of the two evidence-based psychological treatments used for severe PD and is widely practiced in the UK, Europe and the USA. As a separate line of work, Fonagy contributed to establishing the evidence-based movement in psychological therapy, including founding the Centre for Outcome Research and Effectiveness at UCL which has been responsible for 19 out of 20 of the NICE guidelines for treatment of mental health problems. He has chaired the NICE GDG on childhood and adolescent depression and was responsible for developmental contributions on the ASPD guidelines. He has been invited to serve on the conduct disorder GDG currently in the process of being set up. He is involved as PI or Co-PI in several large RCTs of psychosocial treatments for adolescents including multisite studies of the treatment of conduct problems and depression (with Ian Goodyer), and smaller scale RCTs of borderline personality disorder, self-harm, eating disorder, and treatment resistant depression. He is currently director of the Mental Health and Wellbeing Program of the UCL's Academic Health Science Centre which involves partnership with 5 NHS Community Trusts covering a population of 3 million. Fonagy has published over 300 peer reviewed papers, 15 books and 175 chapters over a scientific career spanning almost 30 years.

Emeritus Professor Beard, who will chair the Trial Steering Committee, was head of the Department of Obstetrics and Gynaecology at the Imperial College School of Medicine (St Mary's Hospital in London) from 1972-1996. He has an exceptionally distinguished record of research achievements and has long been involved with research in perinatal medicine. He was the first clinician to introduce electronic fetal monitoring into the UK and in 1969, with Professor Pryse-Davis, he was the first to confirm the association of fetal/neonatal brain swelling with severe perinatal hypoxia. In 1980-84, he was the obstetric expert adviser to the Social Services Select Committee of the House of Commons, investigating 'Perinatal Mortality in the UK'. He was also an advisor to the Chief Medical Officer of the British Government and has held important medical advisory positions in Ethiopia, including Chairing a review of Ethiopian medical education. Currently he is an advisor to the Pulitzer Foundation.

Figure 6. Project Timeline



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