Milk or cowpea-containing peanut-based ready-to-use foods for school feeding of Ghanaian children 5-12 years of age to improve cognition

Clinical Trial Protocol

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Authors: Kevin Stephenson, Donna Wegner, Mark Manary

Contacts: Kevin Stephenson, email: k.stephenson@wustl.edu; Mark Manary, email: manarymj@wustl.edu

Kevin Stephenson and Mark Manary were responsible for data analysis

Protocol history

Version	Date	Author	Reason
1	February 2021	Mark Manary	
2	July 2021	Mark Manary	Change in LSWM testing procedure
3	September 14, 2022	Kevin Stephenson	• Change to procedure for calculating DCCS, FICA accuracy scores, and PCPS scores • Addition of sensitivity analysis comparing trial procedure vs. NIH Toolbox procedure for calculating DCCS and FICA accuracy scores
4	November 30, 2022	Kevin Stephenson	Addition of post-hoc analysis

Protocol Approval

Version	Date	Approver	Signature
1	February 2021	Prof Mark Manary	
2	July 2021	Prof Mark Manary	
3	September 14, 2022	Prof Mark Manary	
4	November 30, 2022	Prof Mark Manary	

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1 Revision history

Version 2: Pilot testing of the list sorting working memory test revealed that some of the program's default images were not familiar to rural Ghanaian school children, and thus not usable. These images were changed in favor of familiar animals/foods, as determined by team members who lived in Mion District, Ghana.

Version 3: Full details are available in the Statistical Analysis Plan. In brief, during a pre-planned, masked, descriptive analysis in which cognitive test results were not separated by study group, we identified that the NIH Toolbox scoring guide/tablet program's assumption of high accuracy scores on DCCS and FICA for all participants ≥ 8 years of age was not supported in this study cohort. Thus, the NIH Toolbox tablet program's default of automatically allotting participants ≥ 8 years of age 10 accuracy points on DCCS and 20 accuracy points on FICA was not likely to reflect the true abilities of the children in this cohort. However, because the NIH Toolbox program had automatically allowed these participants ≥ 8 years of age to skip the first 10 DCCS trials and first 20 FICA trials, their scores on these trials were unknowable. As a result, accuracy scores were computed as proportion correct out of all trials seen, scaled to 5, rather than number correct x 0.125 (which is also scaled to 5, as there were 40 trials total in both tests).

For PCPS, the NIH Toolbox scoring guideline recommends the score should equal the number of correct responses (out of 130) that can be completed within 85 seconds. We noticed several participants had high scores who appeared to be guessing their answers (approximately 50% accuracy). For example, a participant with a score of 39 / 85 correct answers would have been scored higher than a participant with 38 / 39 correct answers. Given this, we decided to calculate the PCPS score as number of correct responses minus the number of incorrect responses.

In a sensitivity analysis, the NIH Toolbox guideline-based, tablet-generated accuracy scores were used for analysis and results were compared with those derived from the scoring method used in this protocol.

Version 4: Post-hoc analysis was added to investigate whether degree of school attendance was an effect modifier in the 4 primary outcomes or the composite median ranking for PM-RUF vs. FP or PC-RUF vs. FP. This is because one mechanism by which a school food might improve cognition is via improving attendance, and thus we determined this should be investigated despite such an analysis not being pre-specified.

2 Introduction

2.1 Background and rationale

2.1.1 School feeding

School feeding has the potential to benefit millions of children worldwide, particularly in low-income settings, and offers several unique advantages as a strategy for food aid. These include an opportunity to capture the relevant population for aid, at school, targeting improved nutrition to a unique period of development in the human lifespan, the potential of such nutrition for improving physical growth, academic achievement, and cognition function, and the bonus of increasing school attendance via school feeding, which would further the aforementioned benefits. This confluence recommends school feeding as a promising platform for improving the lives of children through nutrition, particularly children whose habitual diets are deficient.

2.1.2 Cognitive development and nutrition

Childhood cognitive development has profound implications for an individual's academic and economic achievement, as well as for their communities. Many millions of children worldwide are at risk for not meeting their developmental potential, including with respect to cognition.[1] Improved nutrition has the potential to support better brain development. There exists a large body of animal model-based evidence on the effects of various aspects of nutrition on cognitive development, as well as human studies data, including with respect to breast milk, docosahexaenoic acid, and choline, among many others. Increasingly, cognition is being targeted in studies of severe and moderate malnutrition and their treatment. For example, our group recently published the results of a large, randomized, controlled clinical trial among children with severe acute malnutrition in Malawi that showed that improving the fatty acid profile of ready-to-use food (RUTF) by reducing the amount of omega-6 fatty acids and increasing the amount omega-3 fatty acids, including docosahexaenoic acid, led to improved neurocognitive development when tested 6 months after treatment.[2]

2.1.3 School feeding and cognition

To date, four studies have examined the effects of school feeding on cognition in children. In Kenya, school snacks containing meat and milk were compared to a vegetable snack in a cluster-randomized trial.[3] It was shown that fluid cognition improved among those consuming meat, which provided 8.4 g of beef protein, compared to milk, which provided 5.6 g of milk protein. In Malawi, fluid cognition was compared at 2 schools, one which served corn/soy porridge and the other did not.[4] Cognition improved more over the course of a school year in the school which served food, though this was not a randomized trial. In Australia and Indonesia, a powder drink additive with micronutrients, DHA/EPA, both, or neither was provided for a year. In Australia, micronutrients improved results on tests representing verbal learning and memory; no such effects were identified in Indonesia.[5] In Ghana, an individually

randomized trial compared fortification of a cereal porridge with 3 quantities of milk or vegetable protein to a control and found that 8.8 g of milk protein improved cognition more than an isonitrogenous vegetable porridge or 4.4 g of milk protein.[6] In all three studies, the populations' habitual diets contained little animal source food, and were dominated instead by carbohydrate-rich staple crops. These studies suggest a possible benefit of animal-source foods in school feeding for cognition in children in similar settings.

This trial aimed to test whether an animal source food, non-fat milk powder, or cowpea, would improve cognition in rural Ghanaian children 5-12 years of age when added to peanut paste-based ready-to-use foods (RUFs), as compared with a micronutrient fortified porridge. In so doing, the trial was designed to yield insights into both the role of milk powder in school feeding in contexts like northern rural Ghana, and into the practicality of using ready-to-use foods in a school feeding program. This latter point could be of interest to the international food aid community, as daily production of school foods in low-income areas is time and resource intensive, realities which limit the coverage of school feeding programs. If school food RUFs can be made and distributed successfully, and are demonstrated to be acceptable to children, this could impact school feeding strategies. An analogy is the story of ready-to-use therapeutic food (RUTF) for the treatment of severe acute malnutrition (SAM). RUTF revolutionized SAM treatment in part by removing the burden of nutritious food production from caregivers and their communities. It is possible that school feeding programs could benefit similarly from RUFs.

2.2 Choice of comparator

Micronutrient fortified millet porridge was chosen as a comparator for several reasons. First, millet porridge is the most common local porridge in Mion District, and thus was known to be acceptable to children there. Second, the porridge was fortified with micronutrients both to improve the nutritive value of the porridge and to make the 3 school foods as similar as possible in their micronutrient profiles and thereby remove this variable from consideration for relative efficacy of the 3 foods. Third, the study sought to determine whether ready-to-use foods would be acceptable and feasible in comparison with the current standard, which is often a similar porridge composed of local ingredients. By design, however, the control was stronger than usual practice both in its micronutrient fortification and in its daily availability: the trial team hired for and funded preparation of the fortified porridge each school day to assure its availability, which is not the case in standard operations.

2.3 Choice of outcomes

The 4 primary outcomes are measures of fluid cognition from the National Institutes of Health Toolbox for Assessment of Neurological and Behavioral Function (NIH Toolbox Cognitive Battery®; NIHTB-CB). The NIHTB-CB was created over the course of 6 years by over 250 scientists.[7] It was subsequently validated in a large cohort, including at least 500 individuals 5-12 years of age.[8] NIHTB-CB testing is done using a tablet-based program that simplifies its

procedures, requires minimal training, allows for automated calculation of speed-of-answer-related scores where relevant, and reduces the opportunity for administrator effects on test outcomes. Recently, the NIHTB-CB has been adapted into a Spanish-language version.[9]

The 4 primary outcomes, the dimensional change card sort test (DCCS), flanker inhibitory control and attention test (FICA), pattern comparison processing speed test (PCPS), and list sorting working memory test (LSWM), are all measures of fluid cognition. Fluid cognition refers to the ability to process and integrate information and solve novel problems. These 4 tests were chosen for several reasons. Fluid (as opposed to crystalized or language-based) cognition was targeted because it is less reliant on prior learning, is less culture-dependent, and is considered more sensitive to biological processes. DCCS and FICA were chosen as tests of executive function. DCCS and FICA both test cognitive flexibility, while FICA also tests inhibitory control, sustained attention, and attention allocation. PCPS is primarily a test of processing speed. LSWM is a test of working memory. The remaining Toolbox fluid cognitive test, picture sequence memory test, was dropped, as it seemed to have the potential to be confusing when translated for use in our target population. Further details on the tests are provided within the Outcomes section of this study protocol.

The NIH Toolbox cognitive domain is recommended for ages 3-85. In the NIH Toolbox scoring guide, PCPS and LSWM are recommended for ages 7-85. Review of the primary validation work upon which this recommendation was made revealed that PCPS and LSWM scores had similar correlations with convergent and discriminant validity measures in those 3-6 years of age as in those 8-15 years of age.[10,11] The primary concern among children <6 seems to have been related to some individuals who did not complete the tests. Given the inclusion age in this trial of ≥ 5 years (rather than down to 3 years) and importance of including both working memory and processing speed fluid cognitive assessments, it was decided to include PCPS and LSWM despite 5-6-year-old children falling below the recommended age range, accepting that some participants may not complete testing adequately.

2.4 Hypotheses

2.4.1 Primary hypotheses

Among rural Ghanaian children 5-12 years of age, when offered each school day for a school year:

1. Peanut/milk ready-to-use food (PM-RUF) will improve fluid cognition as compared with a micronutrient fortified millet porridge (FP) as measured by 4 NIH Toolbox tests: DCCS, FICA, PCPS, LSWM
2. Peanut/cowpea ready-to-use food (PC-RUF) will improve fluid cognition as compared with FP as measured by 4 NIH Toolbox tests: DCCS, FICA, PCPS, LSWM.

2.4.2 Secondary hypotheses

Among rural Ghanaian children 5-12 years of age, when offered each school day for a school year:

1. PM-RUF and/or PC-RUF will improve a composite median ranking of the 4 primary outcomes as compared with FP
2. PM-RUF and/or PC-RUF will improve height-for-age z-score and body mass index-for-age z-score compared with FP
3. PM-RUF and/or PC-RUF will improve speed and accuracy sub-scores for DCCS and FICA as compared with FP
4. There will be heterogeneity in the effects of PM-RUF and PC-RUF based on participant age at baseline and participant sex
5. RUFs will be acceptable and feasible options for school feeding in rural Ghana

3 Trial design

3.1 Trial framework

The superiority framework is used for this trial. All comparisons will be presented on the basis of establishing superiority of PM-RUF and/or PC-RUF vs. FP.

3.2 Trial design

This is an investigator-blinded, 1:1:1 individually randomized, parallel group clinical trial designed to determine whether offer of school feeding with PM-RUF or PC-RUF vs. FP for a school year improves 4 NIH Toolbox measures of fluid cognition: DCCS, FICA, PCPS, or LSWM.

4 Study setting

This study will take place in Mion District in rural Northern Ghana at 6 schools: St. Anthony in Sang, Gumah, Kpiligine, Mbatinga, Salankpang, Afayili. Eligibility screening, consent, randomization, questionnaire completion, anthropometric measurements, and cognitive measurements will all take place at these 6 schools.

5 Eligibility criteria

Inclusion criteria are age 5.0-12.0 years and attendance at one of 6 participating schools within the first 6 weeks of school. Exclusion criteria are diagnosis of severe acute malnutrition, presence of a chronic debilitating illness, peanut or milk allergy, or caregiver intention to move out of the school district in the following year.

6 Interventions

6.1 Ingredients, production, packaging

The two ready-to-use school foods have been and will be prepared by Project Peanut Butter in Kumasi, Ghana. All production processes were in accordance with the CODEX Alimentarius code for production of low moisture foods, CXC 75-2015 (https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXC%2B75-2015%252FCXC_075e.pdf). The process is one of dry mixing powders, such as grains, milk, micronutrients, or sugar with liquid lipids, such as vegetable oils and peanut. Packaging will be in 80g individually sealed, metalized polyethylene terephthalate packets under nitrogen. These foods were approved for human use by the Food and Drug Administration of Ghana. As a part of this process, they have been tested for *salmonella* and *enterobacter spp* and found to contain none; continued testing will occur as per Project Peanut Butter Quality Control processes.

Fortified Porridge will be made onsite daily by hired staff by adding 5.5 cups of millet powder to 10L of water and bringing the mix to boil for 35 minutes. 300mL of the porridge will be distributed daily to each participant in uniform bowls with a marking to indicate the level to fill. A packet containing the micronutrient content listed below will be added to each bowl prior to participant consumption.

The ingredient recipes of the two experimental foods are listed below. Ingredients will be sourced in local Ghanaian markets in Kumasi, Ghana.

Ingredient	**Peanut cowpea -ready-to-use food**	**Peanut milk -ready-to-use food**
Peanut, g (%)	36.7 (46)	28.7 (36)
Palm oil, g (%)	10.3 (13)	10.3 (13)
Sugar, g (%)	9.1 (11)	9.1 (11)
Maize, g (%)	8.0 (10)	-
Cowpea, g (%)	14.9 (19)	8.0 (10)
Milk, g (%)	-	22.9 (27)
Micronutrients, g (%)	1 (1)	1 (1)

6.2 Nutrient content of the interventions

Nutrient content of the three interventions is displayed in the table below.

Nutrient	Peanut/milk ready-to-use food	Peanut/cowpea ready-to-use food	Fortified Porridge
Energy, kcal	402	416	412
Protein, g	17.6	14.5	11.9
Fat, g	24.7	28.9	5.4
Essential amino acids, g	7.13	4.78	5.16
Calcium, mg	341	46	45
Vitamin B12, mg	1.6	0.6	0.6

Micronutrient content of the three interventions is displayed in the table below.

Micronutrient	Peanut/cowpea ready-to-use food	Peanut/milk ready-to-use food	Fortified millet porridge	Micro-nutrient fortificant	Recommended Daily Allowance for 4-8 year-old children[b]
Vitamin A, μg	3	10	0	189	400
Vitamin C, mg	0.2	14	0	17.3	25
Vitamin D, μg	0	0	0	3.2	15
Vitamin E, mg	2.0	1.6	2.7	4.1	7
Vitamin K, μg	0.2	0.40	1	5.2	55
Thiamin, mg	0.2	0.19	0.41	0.28	0.6
Riboflavin, mg	0.32	0.51	0.07	0.50	0.6
Niacin, mg	7.0	5.3	6.0	3.0	8
Vitamin B6, mg	0.2	0.23	0.37	0.43	0.6
Folate, μg	143	148	42	58.7	200
Vitamin B12, μg	0	1.0	0	0.59	1.2
Pantothenic acid, mg	0.7	0.52	1.3	0.32	2
Biotin, μg	32	25	0	12.6	12
Calcium, mg	31	309	14	32.4	1000
Copper, μg	134	163	535	216	440
Iodine, μg	0	0	0	20	90
Iron, mg	2.5	1.6	3.9	1.8	10
Selenium, μg	9.3	6.7	33	2.7	30
Zinc, mg	2.1	1.5	2.6	2.0	5.0

6.3 Adherence monitoring

Two volunteers at each of the 6 participating schools will be designated as responsible for distribution and documentation of receipt of the correct intervention (randomization color/group matched to distributed color/food) each school day. If a child is present and receives their intervention food, such will be noted on attendance sheets provided by the study team for this purpose over the study's final 10 weeks. There will be no efforts to find children who are not attending school.

7 Outcomes

7.1 Primary outcomes

The 4 primary outcomes are scores on the dimensional change card sort (DCCS), flanker inhibitory control and attention (FICA), pattern comparison processing speed (PCPS), and list sorting working memory (LSWM) tests at the end of the school year over which the trial proceeds. Scores will be compared between PM-RUF vs. FP and PC-RUF vs. FP using ordinal logistic regression, including covariates baseline participant age and baseline score on the cognitive test being compared. Further detail on the 4 outcomes and their scoring is offered below:

1. DCCS: two target pictures are presented that vary along 2 dimensions: shape and color. The participant is asked to match a new picture (test picture) based on 1 of the 2 dimensions, and the test picture then appears; the participant then selects one of the two target pictures based on the test picture and dimension requested. The computed score (max of 10) is composed of accuracy and speed components (max of 5 points each).

    1a. The accuracy score is calculated by scaling the proportion of correct answers to 5. For example, a participant who gets 32/40 trials correct would have an accuracy score of 4. For participants < 8 years of age, they first take 10 trials that (1) test a single dimension repeatedly for 5 trials, and then (2) switch to the other dimension for 5 trials. If they score ≥ 9/10, they are allowed to proceed to the next 30 trials, which mix dimensions. For participants ≥ 8 years of age, they automatically begin testing on the 30 mixed dimension trials, skipping the first 10. These "decisions" are made automatically by the tablet after input of participant age. Only participants with accuracy scores > 80% are eligible for speed scores.

    1b. The speed score is calculated automatically by the tablet using the NIH Toolbox software. This is made possible by use of a "home base," which is a printed circle with iPad positioning markers provided by the test publisher. The home base is positioned in front of the iPad. Participants are asked to keep their dominant hand index finger on the home base at the start of testing and to return it there between each test. The test administrators are instructed to attend to this element and provide reminders to test-takers if they are not returning their index finger to the home base. For calculation of reaction time (speed score), briefly, this is computed using only correct trials with reaction times greater than 100 ms and no larger than 3 SDs from the participant's mean. A log base 10 transformation is applied and the scores are then re-scaled such that higher scores correspond to faster reaction times.

2. FICA: A series of fishes (trials 1-20) and then arrows (trials 21-40) are shown on a screen. The fishes and arrows can point leftward or rightward. The participant is asked to correctly identify the direction that the central fish/arrow is pointing regardless of which

direction the flanking fishes/arrows are pointing. The flanking fishes/arrows can either be congruent or incongruent with the direction of the central fish/arrow. The computed score (max of 10) is composed of accuracy and speed components (max of 5 points each).

2a. The accuracy score is calculated by scaling the proportion of correct answers to 5, the same as is done for DCCS. Participants < 8 years of age first undergo 20 fish trials. If they score ≥ 18/20, they are allowed to proceed to the 20 arrow trials. Participants ≥ 8 years automatically start on the 20 arrow trials, thereby skipping the fish trials. This is done automatically by the tablet program after participant age is indicated. Only participants who score > 80% for accuracy are eligible for speed scores.

2b. Speed scores are calculated by the same method ass is used for DCCS.

3. PCPS: Two images are displayed and the participant is asked to answer whether or not the two images are the same. Participants are given 85 seconds to answer as many questions correctly as possible. The score is obtained by subtracting the number of inaccurate responses from the number of accurate responses. The maximum score is 130.

4. LSWM: Pictures of animals and/or foods are displayed for 4 seconds and then withdrawn. The participant is asked to recall as many animals/foods shown as possible, ordered from smallest to largest size. There are two tests. In the first test, the participant is shown foods or animals and asked to recall along that single dimension. In the second test, both foods and animals are shown, and the participant is asked to recall them separately, still from smallest to largest. The NIH Toolbox tablet program version was not used because some of the foods and animals were not recognizable to participants on pilot testing. Thus, new, familiar images of culturally identifiable foods and animals were loaded into the tablet and used, and the assessors manually tabulated participant scores. The assessors manually tabulated the score because the participants answered verbally. The score was computed as the number of correct items recalled in order from smallest to largest across the 2 trials.

7.2 Secondary outcomes

1. Composite median ranking of 4 primary outcome scores. The composite ranking will be generated by ranking each participant's score within each test, calculating the median of each participant's ranks, and ranking these medians.

This rank- and median-based composite was chosen because the primary outcomes are not interval-scaled and were unlikely to distribute normally. While the NIH Toolbox does auto-generate age-adjusted z-scores which can be combined, we *a priori* did not think comparison to US-derived normative scores would be valuable, in part because of the novelty of computer-based testing in the study cohort.

2. Change in height-for-age z-score (HAZ) from baseline to endline, calculated by subtracting the baseline HAZ from the endline HAZ. Z-scores will be computed using WHO Anthro 3.2.
3. Change in body mass index z-score (BAZ) from baseline to endline, calculated by subtracting the baseline BAZ from the endline BAZ.
4. Change in fat-free mass (FFM), as determined by bioelectrical impedance, calculated by subtracting baseline FFM from the endline FFM.
5. Change in mid-upper arm circumference (MUAC), calculated by subtracting baseline MUAC from endline MUAC.
6. Speed sub-scores on DCCS and FICA. The NIH Toolbox program automatically computes a speed score for these 2 tests, while PCPS and LSWM do not have such scores. Speed sub-scores are scaled to a maximum of 5.
7. Accuracy sub-scores on DCCS and FICA. This is proportion of prompts answered correctly, scaled to 5.
8. Sub-group analyses based on age (< 9 or ≥ 9 years) and sex (male or female) across the 4 primary outcomes and the composite median ranking.
   9 years is expected to be near the median participant age.
9. Rate of attendance over the final 10 weeks of the trial, calculated as percent of days attended / total possible days.
10. Days enrolled, calculated by subtracting date of enrollment from date of final testing
11. Possible days of attendance / intervention receipt during trial (school days), from date of randomization to date of endline testing
12. Sensitivity analysis wherein DCCS and FICA accuracy and composite scores are computed using the NIH Toolbox scoring guideline for accuracy scoring and compared to results of the method used in this protocol

7.3 Post-hoc outcomes

Per-protocol analysis based on attendance rates. DCCS, FICA, PCPS, LSWM, and composite median ranking compared between PM-RUF or PC-RUF vs. FP among those with attendance rates greater than 50%, 75%, and 90%.

7.4 Outcome relevance

The domains tested between DCCS, FICA, PCPS, and LSWM compose key elements of cognitive development.

7.4.1 DCCS, FICA: Executive function can be described as cognitive control or self-regulation and is involved in "top-down modulations of goal-directed activity."[12] Development of executive function is key for inhibition of inappropriate, and success on appropriate, actions. Executive function is regarded as key for academic success in children via multiple mechanisms, including self-motivation, self-regulation of learning, and through emotional regulation.[13] Recent research has demonstrated evidence of a functional

dependency between executive function development and social interaction in young children.[14]

7.4.2 LSWM: Working memory is often regarded as a component of executive function but is also studied on its own. Working memory in childhood is a predictor of school achievement and later cognitive development.[15,16] Evidence suggests that working memory can be improved through childhood interventions.[17,18] Processing speed has been shown to be a key component of working memory.

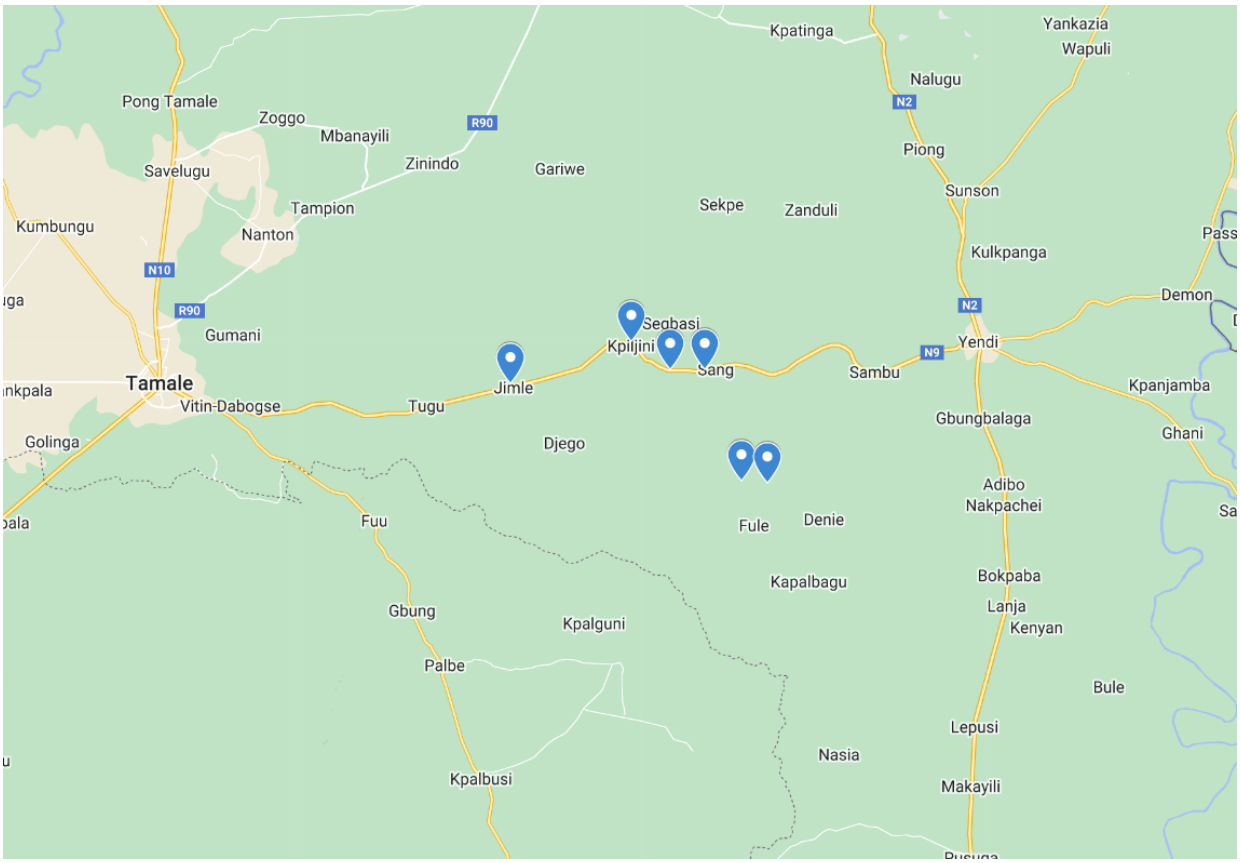
7.4.3 PCPS: Greater processing speed is associated with age-related improvements in performance on tasks including memory, reading, arithmetic, and reasoning.[19,20] Measures of processing speed have been shown to predict preschool mental development.[21] Processing speed has been found to be sensitive to cerebral insults.

8 Participant timeline

8.1 Schedule of enrollment

The study will be conducted in Mion District in the Northern Region of Ghana, about 50 miles east of Tamale. The district has a population of approximately 90,000 people and is served by a small system of primary schools that are sponsored by local community organizations, churches, mosques, or village councils. Each school serves a unique geographical location. The district hires teachers for each of the 7 levels or classrooms at each school: kindergarten, primary-1 (P-1), primary-2 (P-2), and so forth, through primary-6 (P-6).

The study will be coordinated with the Mion Educational Service, the local government agency managing the primary educational system. The educational service identified 6 potential schools in which the project could offer school meals (map shown below). There were no other school feeding programs currently ongoing or in planning stages at any of the included schools. In Ghana, the school year is divided into 3 terms, each lasting about 14 weeks: September to December, January to April, and May to August. The project worked in close cooperation with the Education Service in planning. All students attending the participating schools will receive the daily meal at about 10:15 AM.



A community meeting will be held in each of the towns and villages selected for participation. The meetings will be open to anyone wishing to attend. During them, the procedures of school feeding will be explained, the foods will be available to be sampled, and the rules of participation elucidated. At the conclusion of this meeting, parents will come with the children's birth certificates and will have the opportunity to offer informed consent for the specified, eligible children.

The study was approved by the Ghana Health Service research and ethics board and the Washington University Human Research Protection Office.

The names, birthdates and parent names of these consented children will be entered into the 5 iPad tablets as participant identifiers.

Neurocognitive testing will commence within a week of the community meetings. At the initiation of testing, care will be taken to accurately link the appropriate child with the data entered into the tablet, including cross-identification with teachers and siblings. Each child's facial image will be photographed by the tablet and linked to this information. At every subsequent testing interaction, facial recognition will be used identify each participant. This will reduce confusion that might be arise from similar names of children, something common in Moslem culture in Ghana, as well as children not knowing their birthdates.

A provision will be made to consent and enroll any students who were not identified at the community meetings after verifying with the school headmasters that these were indeed students and their parents or guardians undergoing the consent process.

8.2 Intervention schedule

The intervention will be distributed to each participant each day of school attendance following completion of baseline cognitive testing. The intervention will continue until the end of the school year.

8.3 Assessment schedule

The table below summarizes the schedule for study assessments.

Measure	First 6 weeks of school year	Last 10 weeks of school year	Last 3 weeks of school year
Demographic questionnaire	X		
Attendance assessment*		X	
4 NIH cognitive tests	X		X
Anthropometry	X		X

* Correct child – intervention pairing will be confirmed every day of the study, and daily documentation of attendance will be done over the final 10 weeks.

9 Sample size

The study plans to enroll 880 participants, anticipating that 15% will drop out during the school year, which would provide >80% power to detect an odds ratio (OR) for a higher score of 1.6 at a two-sided α of 0.05. This calculation was based on the use of ordinal logistic regression applied to simulated datasets because data were not available to estimate the primary outcome distributions in rural Ghanaian children and the scores consisted of ordered numbers that were not interval-scaled. Further details on the simulation-based power analysis approach and its results can be found in the statistical analysis plan.

10 Recruitment

This will be done through the aforementioned community meetings as well as teachers and headmasters at each local school.

11 Allocation

Following eligibility assessment and consent, participants will be randomized when their parent or guardian selects a small opaque envelope enclosing a colored piece of paper from a larger opaque envelope. This larger envelope will contain 24 such identical small envelopes, 8 per study group, wherein one color corresponds to each study group. There will be no stratification. A study team member who will remain masked to the code for color – intervention group will produce the smaller and large envelopes used for randomization.

12 Masking

Participants will not be masked. A study coordinator responsible for study food production and delivery to participating schools will be unmasked but will not take part in outcomes assessment or data analysis. Two volunteer school employees at each school will be trained as feeding supervisors and will be responsible for disbursement of study foods and tracking their receipt, and thus will not be masked. All outcome assessors will be masked. The allocation key linking colors to food groups will be kept locked and inaccessible to outcome assessors and the investigators responsible for statistical analysis until after analyses arere completed.

Children who experience adverse events will be unmasked to the study lead, Dr. Mark Manary, by the unmasked study coordinator.

13 Data collection, management, and analysis

13.1 Demographics

Data collected will include parent/guardian age and relation to child, whether the child's parents are alive and in the home in which the child resides, number of children in home, household water source, radio ownership, computer ownership, motorbike ownership, and roof material. These data will be doubly entered into a locked Microsoft Access database.

13.2 Anthropometric measurements

Participant height, weight, mid-upper arm circumference, and fat free mass will be measured with scales, height boards, measurement tapes, and a bioelectrical impedance analyzer, respectively. WHO Anthro will be used to compute age-adjusted z-scores. These data will be doubly entered into a locked Microsoft Access database.

13.3 NIH Cognition Toolbox testing

The NIH Toolbox tablet-based program automatically collects data on the tests, including number of trials undertaken, number of correct responses, and reaction time (speed) scores.

For DCCS, FICA, and PCPS, these data will be uploaded to a Washington University in St. Louis-based, secure, cloud-based data repository, from which they will be downloaded for analysis in St. Louis, MO. The output will be in Microsoft Excel format and will be kept locked and secure. Following data upload, download, and confirmation, tablets will be wiped of stored data. For LSWM, scores will be computed by cognitive testers manually on data sheets and entered into a password-protected Microsoft Excel database, which will be uploaded onto the same cloud-based data repository and downloaded for analysis in St. Louis.

13.4 Attendance

Once feeding commences at a school, the study coordinator, a full-time research team member residing in Mion Distict, will create a feeding list for each school. The list will be demarcated by classroom, as children will present to collect school food as a class. The lists will have checkboxes for each day of the week. As the child receives his/her daily ration, a check will be recorded in the box by the designed distributors of the food at each school. New and updated lists will be created weekly for each school and distributed prior to each school week. This will allow for collection of attendance data.

13.5 Data storage for analysis

All data will be uploaded into R for analysis.

13.6 Plan for data collection with respect to attendance

Endline anthropometric and cognitive tests will be performed on all enrolled children if they attend school within the last 3 weeks of the school year regardless of prior attendance. This will allow the study to be analyzed according to its planned modified intention to treat (mITT) populations, with the modification being that participants must undergo final testing to be included in the analysis, as it requires such testing.

14 Statistical methods

14.1 Significance level

$\alpha = 0.05$ and 95% confidence intervals (CIs) will be applied in the interpretation of statistical significance tests. All reported *P* values will be two-sided. *P* values will be computed for primary outcomes, key secondary outcome median composite ranking, and sub-group interaction effects; otherwise, 95% CIs with point estimates will be provided.

14.2 Correction for multiple comparisons

We will not correct for multiple comparisons, accepting an increased risk for type I error to avoid inflating the type II error in this trial of a low-risk intervention with 4 outcome measures that are expected to be highly correlated, which increases the chance of type II error with multiple-test corrections.[22,23] In the place of *P* value corrections, 95% CIs will be reported throughout, and a composite outcome metric chosen to rely on the fewest assumptions possible (median of ranks) has been chosen to compare food groups.[24]

14.3 Timing of final analysis

Once all endline cognitive tests and anthropometric measurements are completed, the data will be evaluated in a blinded, descriptive manner without separation by study group to assess distribution of scores – histograms/probability density plots and mean/SD, median/IQRs will be produced, including with respect to participant age. Such a step is necessary because likely performance of rural Ghanaian children on the NIH Toolbox tests is not known, and the NIH scoring guideline contains several assumptions about how children will perform, including older children testing at the ceiling for DCCS and FICA. The study team member responsible for statistical analysis will then perform primary and secondary analyses while remaining blinded to study group.

14.4 Analysis sets

All primary and secondary outcomes will be analyzed in a modified intention-to-treat (mITT) population. The single modification (*contra* full intention-to-treat) is that participants must complete endline cognitive testing to be included in outcomes analysis, as the results of such testing are the study's primary outcomes. Thus, those who dropped out of school and did not return for endline testing are excluded from primary and secondary analyses, by necessity.

A post-hoc analysis wherein the 4 primary outcomes and the composite median ranking are compared across PM-RUF vs. FP and PC-RUF vs. FP groups was undertaken based on degree of attendance, which is a metric of adherence, as spot visits revealed that children reliably consumed all study food if they were present at school.

14.5 Descriptive statistics

Categorical variables will be summarized as number (%), while continuous or multiple-ordered variables will be summarized as mean ± SD if their distribution approximates normality or median (IQR) if it is skewed or otherwise diverges from a normal distribution. Cognitive test results will be summarized using both mean ± SD and median (IQR) to provide a fuller picture of their distributions. Based on prior experience, it is expected that change in anthropometrics HAZ, BMI, MUAC, FFM will be normally distributed and thus likely will be presented as mean ± SD.

14.6 Analysis of primary outcomes

DCCS and FICA computed scores, PCPS scores, and LSWM scores will be compared between PM-RUF and FP and between PC-RUF and FP using ordinal logistic regression. The dependent variable will be endline cognitive test score. Independent variables will be randomized food group assignment and the 2 prespecified covariates: participant age and baseline cognitive test score. For example, the regression for DCCS will be:

$$DCCS_{endline} = \text{Food group} + \text{Baseline participant age} + DCCS_{baseline}$$

The fortified porridge group serves as the referent group for primary analyses. Because higher scores on cognitive tests indicate better performance, an odds ratio > 1.0 indicates more favorable results for the PM-RUF or PC-RUF group compared with FP. Results of the primary analysis of the primary outcomes will be presented as an adjusted common odds ratio with associated 95% CIs.

14.7 Analysis of secondary outcomes

As per the statistical analysis plan, composite median rankings, speed and accuracy sub-scores of DCCS and FICA, and assessment for heterogeneity in intervention effect by age and sex will be done using ordinal logistic regression, with covariates baseline participant age and baseline score on the cognitive test / composite median ranking. For subgroup analyses, interaction terms between the subgroup (i.e., age or sex) and food group will be included in regressions, and *P* values for the interaction term will be estimated and reported. For interactions, age will be included as a continuous variable.

Changes in height-for-age z-score, BMI-for-age z-score, MUAC, and FFM will be compared using linear regression. Rate of attendance over the final 10 weeks of trial will be compared using the Wilcoxon rank sum test. A continuity correction will be used to produce 95% CIs around the median of differences between groups.

In a sensitivity analysis, DCCS and FICA accuracy and computed scores, as calculated by the NIH Toolbox scoring guideline, will be compared between PM-RUF vs. FP and PC-RUF vs. FP using ordinal logistic regression, with covariates baseline cognitive score and participant age. ORs with 95% CIs will be shown in comparison to the results obtained using the trial's SAP scoring strategy.

14.8 Post-hoc analyses

The 4 primary outcomes and the composite median ranking will be compared PM-RUF vs. FP and PC-RUF vs. FP according to degree of school attendance over the study's final 10 weeks, as a type of per-protocol analysis. Attendance cut-offs will be ≥ 50%, ≥ 75%, and ≥ 90%. Attendance rate will be introduced as an interaction term with study group into ordinal logistic

regressions to assess for effect modification, with covariates baseline participant age and baseline score.

14.9 Missing data

No missing data will be imputed.

15 Monitoring

15.1 Adverse events

15.1.1 Definitions

Adverse event: Any untoward medical occurrence associated with the use of an intervention or a study procedure, whether or not considered intervention related
Serious adverse event: An adverse event that results in death, a life-threatening experience, prolonged hospitalization, significant or persistent disability
Adverse reaction: An adverse event wherein there is a reason to conclude the study intervention caused the event.
Suspected adverse reaction: An adverse event for which there is a reasonable possibility that the intervention or procedures were the cause.

15.1.2 Monitoring

Parents, guardians, participants, and the two volunteers at each school will be instructed as to potential adverse events, including allergic reactions causing rash, anaphylaxis, or gastrointestinal discomfort such as diarrhea, bloating, gas, nausea, or vomiting. All parties will be instructed to notify the on-site study coordinator as to any occurrence, which will trigger documentation of time of onset, symptoms, and signs of adverse event, whether hospitalization is required, and outcome. The on-site coordinator will notify the study lead, Dr. Mark Manary, of any adverse event immediately, and the participant's engagement will be paused. The unmasked study coordinator will inform Dr. Manary of the participant's randomized group identification. With the study team, Dr. Manary will decide whether the adverse event was likely to be related to the intervention. If the adverse event is deemed a suspected adverse reaction or adverse reaction, the participant will stop receiving the study intervention and their data will be recorded. If the adverse event is deemed unlikely to be related to the intervention, and the parent/guardian/participant elect to remain in the study, they will re-start their intervention. Monitoring will continue for the entire duration of the study. All serious adverse events, adverse reactions, and suspected adverse reactions will be recorded.

16 Ethics and dissemination

16.1 Ethics approvals

The trial will be implemented in accordance with the Declaration of Helsinki. The study was approved by the Ghana Health Service Ethics Review Committee and the Human Research Protection Office of Washington University.

16.2 Consent

A parent or guardian of every participant will give oral and written informed consent. The consent is included in the Appendix of this document. The procedure for consent for the study was determined by the Ghana Health Service Ethics Review Committee which operates under the standard guidance provided by the Helsinki Declaration.

This study was minimal risk and was to be conducted in a rural population in northern Ghana that speaks Dagbani, a dialect that is not written. The population is by-in-large illiterate. Ghana is a nation which has many languages and no dominant ethnic group; the official country language is English. To communicate the essence of participation to the parents, the Ethics Committee instructed us to develop a presentation that a trained Dagbani speaker would present to each parent orally. The presentation would include the key elements of study participation, which are listed below.

1. Participation is voluntary, the child can withdraw at any time.
2. There would be food given daily and how the choice of that food was to be made.
3. There would be a computer tablet based set of games that would be played by the participant at the beginning and end of the study.
4. There would be measurements of the child's body size, weight, length, arm circumference and impedance, at the beginning and end of the study.
5. The parents were provided with a contact phone number and also told that the study representative would be present at the school on certain days.
6. The child's attendance would be recorded when he/ she was given food.
7. There was the opportunity for the caretakers to ask questions.

As proof that such a presentation was made, a consent with 4 signatures were collected, including parent/guardian, principal investigator, community witness, and the individual making the presentation.

In the case of children > 7 yrs, the child also signed an assent document.

16.3 Withdrawal of consent

Participants and their parents or guardians will be able to withdraw their consent to participate at any time during the study without prejudice. Participants and their parents or guardians may elect to have use of their data collected prior to that point withdrawn; if they do not, data recorded up to the point of withdrawal will be included in analysis. Withdrawal of consent prior to baseline data collection will be regarded as a screen-failure and will be recorded.

16.4 Confidentiality

All participants will be assigned a unique study ID for tracking. Participant identities will never be revealed in any manner. The minimum data necessary containing participant identities will be collected. All data collected during the trial will be stored securely in an online database.

16.5 Declaration of interests

The funders will play no part in study design, implementation, analysis, publications, or decisions made therein. The anticipated authors have no conflicts of interest to report; if authors are added, their potential conflicts will be assessed and reported as necessary.

16.6 Dissemination policy

The results of this study will be disseminated via publication in a peer-reviewed journal. It is anticipated that one paper will focus on the cognitive outcomes, while another will focus on the operational aspects of the study, including food production, distribution, acceptability.

17 Appendix

17.1 Informed consent materials

PARTICIPANTS INFORMATION SHEET

Title of Study: Integrating the power of peanuts into school feeding programs in Ghana

Principal Investigators: Prof Mark Manary, Prof. Matilda Steiner-Asiedu and Prof. F.K. Saalia

Address: Dept. Pediatrics, Washington University in St. Louis, MO, USA; Dept. Nutrition and Food Science Dept., University of Ghana, P.O. Box LG 134, Legon, Accra, Ghana

Contact Information : Prof Steiner-Asiedu, phone : 0541260704, email : tillysteiner@gmail.com
Prof F.K. Saalia, phone: 0547802413, email: fsaalia@gmail.com

Background and Purpose of research:
Poor nutritional status in school-aged children has a major impact on a child's future, it not only increases risk for infectious diseases and negative health outcomes, but also the child's physical

abilities or work capacity. Governments, policy makers, and organizations have embraced school feeding programs as a way to ease hunger while increasing school enrolment, attendance and retention. Our research group has extensive experience and success in development of food aid products. Our recent study in Ghana, showed that among healthy school children aged 6-9 years old the use of milk and micronutrient powder in their morning porridge improved the child's thinking and led to an increase of lean body mass. This suggests that school food in Africa may do more than just promote school attendance; it can boost health and school performance.

The purpose of this study is to conduct a clinical trial to determine if consumption of a groundnut-based school food ready-to-use will improve brain function and height/weight in Ghanaian school children aged 5-12 years old.

Nature of research:
This study is conducting a clinical trial to determine if consumption of a groundnut-based school food ready-to-use will improve body size measurements and brain function in Ghanaian school children aged 5-12 years old. Up to 900, 5 to 12 year old children enrolled in classes at 6 selected schools in the Mion District will be randomized to receive one of three school foods, a peanut-based food with milk, same peanut-based food without milk, and a control group composed of commonly available tuber/cereal with added micronutrient powder.

Participants' involvement:
Your child will be provided one of the following three meals: a) Local porridge with a vitamin and mineral sprinkle powder, b) peanut butter/ cowpea mixture or c) peanut butter/ milk mixture. The vitamins and minerals in the foods contain the recommended amounts for your child. Your child will receive this food before school every day for a school year. A study aide at your child's school will take daily attendance and ensure that your child receives the food. The amount food that your child consumed will be recorded daily. You will be asked to complete a questionnaire on behalf of your child.
At the beginning of the project your child will have weight, height, and mid upper arm circumference measured. Measurements of body fat and lean muscles and measurement of brain function will also be conducted. All these assessment methods are not painful or harmful.
The body fat and lean muscle is measured by using a body composition machine, that sends a harmless electrical signal throughout the body and detects the amount of fat based on the speed at which the signal travels. Measurement of brain function will be done using a tablet-based test.

Potential Risks:
There are no known serious health risks associated with the foods or tests used, however, there might be some small risk. No serious side effects are expected from the food if taken by your child but the cost of treating any study food related disease such as allergic reaction to any ingredients will be met by the research project. The foods do contain peanuts; therefore, there is a risk for an allergic reaction due to an unknown peanut allergy. If there is a known peanut allergy, the child will be ineligible to participant in the study. In the rare case of allergy or anaphylactic reaction to the study food, the child will be taken to the local health center and cost

of treatment will be met by the research project. Participation in this study may have some of the side effects listed above. In addition, there is always the risk of developing previously unknown side effects. The investigator is willing to discuss any questions you might have about these risks and discomforts.

Benefits:
There are no specific benefits to your child. All the participants will be given a balanced food supplement that contains all of the nutrients that help support growth and development in children. The researchers will use the information they collect to guide decisions about foods used in future school feeding programs.

Costs:
There is no cost to the participants. The research project will provide all foods and tests.

Compensation:
Students will receive a token of appreciation, a school notebook, workbook and/ or writing instruments.

Confidentiality:
All reasonable measures to protect the confidentiality of your child's records and your child's identity will be taken. The data cards will not be shared with anyone outside of the study staff. After information is collected it will be stored in a computer that does not contain your child's name, just a number that the study staff have given to the child. Data cards will be stored in a locked cabinet when not in use. We may be required to show information to university or government officials (or sponsors), who are responsible for monitoring the safety of this study. Directly identifying information (e.g., names, addresses) will be safeguarded and maintained under controlled conditions. You will not be identified in any reports or publication from this study.

Voluntary participation/withdrawal:
Your child does not have to be in this study if you do not want him/her to do so. If you agree to your child's participation in this study, but later change your mind, he/she may stop at any time. There are no penalties or consequences of any kind if you decide that you do not want him/her to participate.

Outcome and Feedback:
You will be informed of any significant new findings developed during the course of participation in this research that may have a bearing on your (your child's) willingness to continue in the study. The investigator may withdraw you (your child) from this research if circumstances arise (such as non-compliance with the protocol and non-tolerance of a study medication) which warrant doing so.

Feedback to participant:

Individual children or their caretakers will not be told the results of any of the testing or measurements made on the child. A meeting at the end of the project will be held in each community where the study results will be shared.

Funding information:
This study is made possible by the generous support of the American people through the United States Agency for International Development.

Sharing of participants Information/Data:
Your child's personal information will be removed or changed before files are shared with other researchers or results are made public. All data produced through studies funded by Peanut Innovation Lab research activities will be systematically managed, tracked, stored and published.

Provision of Information and Consent for participants
A copy of the Information sheet and Consent form will be given to you after it has been signed or thumb-printed to keep.

Contacts for Additional Information/Clarification/Questions
If you have any questions or concerns regarding this study, if any problems arise, or you are feeling pressured to participate, you may speak with the Principal Investigator Prof. Matilda Steiner-Asiedu (0541260704) or Prof. F.K. Saalia (0547802413)

Your Child's Rights as a Participant
This research has been reviewed and approved by the Ghana Health Service Ethics Review Committee. If you have any questions about your child's rights as a research participant you can contact Nana Abena Apatu, 0503539896, ethics.reseach@ghsmail.org

CONSENT FORM

INTEGRATING THE POWER OF PEANUTS INTO SCHOOL FEEDING PROGRAMS IN GHANA

Participants' statement:

I acknowledge that I have read or have had the purpose and contents of the Participants' Information Sheet read and all questions satisfactorily explained to me in a language I understand (English). I fully understand the contents and any potential implications as well as my right to change my mind (i.e. withdraw from the research) even after I have signed this form.

I voluntarily agree to be part of this research.

Name of Participant……..

Participants' Signature ……..OR Thumb Print……

Date:…….

Interpreter statement:

I interpreted the purpose and contents of the Participants' Information Sheet to the afore named participant to the best of my ability in the Dagbani language to his proper understanding.

All questions, appropriate clarifications sort by the participant and answers were also duly interpreted to his/her satisfaction.

Name of Interpreter…….

Signature…….. OR Thumb Print ……..

Date:……

Statement of witness:

I was present when the purpose and contents of the Participant Information Sheet was read and explained satisfactorily to the participant in the language, he/she understood.

I confirm that he/she was given the opportunity to ask questions/seek clarifications and same were duly answered to his/her satisfaction before voluntarily agreeing to be part of the research.

Name:……

Signature…….. OR Thumb Print ……..

Date:……

Investigator statement and signature

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed.

Researcher's name…….

Signature …….

Date…….

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