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Comparison of a novel ready-to-use supplementary food (RUSF) with whey permeate to standard peanut/soy RUSF for the treatment of moderate acute malnutrition in rural Malawian children: a randomized, double-blinded, clinical effectiveness trial

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Final report

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1. Title of the project

"Comparison of a novel ready-to-use supplementary food (RUSF) with whey permeate to standard peanut/soy RUSF for the treatment of moderate acute malnutrition in rural Malawian children: a randomized, double-blinded, clinical ef-fectiveness trial"

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4. Sources of funding

Danish Dairy Research Foundation
Arla Foods Ingredients Group P/S
US Dairy Export Council.

5. Project period

Project period with DDRF funding: October 2012

Revised, if necessary:

Total project period, if sub-project within a larger project: October 2014

Revised, if necessary:

6. Project summary

Aim: The utility of dairy ingredients in supplementary foods used in the treatment of childhood moderate acute malnutrition (MAM) remains unsettled. We evaluated the effectiveness of a peanut-based ready-to-use supplementary food (RUSF) with soy protein compared with a novel RUSF containing dairy ingredients in the form of whey permeate and whey protein concentrate in the treatment of children with MAM.

Design: We conducted a prospective, randomized, double-blinded clinical effectiveness trial involving rural Malawian and Mozambican children 6-59 months old with MAM treated with approximately 75 kcal/kg/d of either soy RUSF or a novel whey RUSF treatment for up to 12 weeks.

Results: The proportion of children that recovered from MAM was significantly higher in the group that received whey RUSF (960 of 1144; 83.9%), compared to soy RUSF (874 of 1086; 80.5%; $P < 0.04$; risk difference 3.4%, 95% CI: 0.3%, 6.6%). Children who consumed whey RUSF also demonstrated better growth parameters, with a higher mean mid-upper arm circumference (MUAC) at the time of discharge ($P < 0.009$), greater MUAC gain during the course of treatment ($P < 0.003$), higher mean weight-for-height Z-score at discharge ($P < 0.008$), and greater weight gain ($P < 0.05$). No significant differences were identified in length gain or time to recovery between the two groups.

Conclusion: This study highlights the importance of milk protein in the treatment of MAM, as the use of a novel whey RUSF resulted in higher recovery rates and improved growth than soy RUSF, even though the whey RUSF supplement provided less total protein and energy than the soy RUSF.

7. Project aim

Children with MAM may benefit from a new RUSF because of the whey proteins and minerals contained therein, and a clinical trial is the proper method by which to test this hypothesis.

Objectives:

Broad: To provide MoH and international agencies with another alternative to the standard treatments for MAM.

Specific: To test the effectiveness of two supplementary foods, whey RUSF and soy RUSF, in the treatment of MAM in 6-59 month old children in a 12-week home-based supplementary feeding program.

8. Background for the project

Several supplementary foods, including peanut paste-based ready-to-use supplementary foods (RUSF), have been developed for the treatment of moderate acute malnutrition (MAM) [1-4]. Previous studies prove different types of RUSF are successful in treating MAM [4, 5]; however, the quality and quantity of protein that produces the best outcomes is still debated. While it is well known that dairy protein is both important for growth [6], evidence regarding its impact specifically in the treatment of MAM is needed.

Studies suggest that dairy protein, as opposed to plant-based protein, increases lean body mass, increases linear growth, and improves recovery outcomes in undernourished populations [7-9]. The biological explanation for these improved outcomes is yet to be fully understood. Many researchers hypothesize the differences could be due to various components in milk including bioactive peptides, growth stimulating factors, a high concentration of branched chain amino acids (BCAAs), and lactose [10-13]. At its most basic level, milk consists of two factions: whey and casein. While a recent study showing that casein, not whey, stimulates insulin-stimulating growth factor-1 (IGF-1) [14], several other beneficial functions of whey are related to muscle restoration, bone growth, immune function, and intestinal integrity.

However, evidence supporting the use of whey in supplementary foods for malnourished children is limited [15]. There is a need to determine if whey protein can replace soy protein (the more commonly used protein in supplementary foods) in a more cost-effective manner than milk, while still providing many of the proposed benefits of milk. In this prospective, double-blinded, randomized controlled clinical effectiveness trial, we compare two RUSF products (a whey RUSF versus a soy RUSF) in the treatment of MAM to test the hypothesis that the proportion of children who recover will differ by no more than 3%.

9. Sub-activities in the entire project period

Year	2012		2013				2014				2015			
Quarter	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Acceptability Testing	X													
Local Approval and Set-Up		X												
Clinical Trial			X	X	X	X	X	X	X	X				
Enrollment and Treatment			X	X	X	X	X	X	X	X				
Data Entry			X	X	X	X	X	X	X	X				
Statistical Analysis									X	X	X	X		
Cost-Effectiveness Analysis													X	
Write-up and Publication											X	X	X	X

Acceptability Testing

Prior to the randomized clinical trial, acceptability testing of the novel whey RUSF formula was conducted following a protocol modeled on that of Phuka et al. [16]. The purpose was to determine the taste acceptability and physical tolerance of the new RUSF formula. Children 6-59 months without severe acute malnutrition (SAM) were identified at one of the nutrition clinics used for the main clinical trial and randomly assigned to one of the two RUSF interventions at doses ranging from 6 teaspoons (30 mL) for a 5 kg child to 15 teaspoons (74 mL) for a child over 10 kg. Feeding was directly observed at the site and the time it took for the child to consume the entire serving of food was measured, as well as the amount of food remaining if not completely consumed. Caregivers were asked to esti-

mate the supplement's palatability and overall likability on a 5-point hedonic scale that graphically illustrated a series of human faces with varying degrees of smile or discontent. Caretakers were then provided the food to continue daily feeding at home and returned on the fourth day to report again on the child's tolerance of the food and any adverse reactions, including diarrhea.

Local Approval and Set-Up

The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee and Washington University's Human Research Protection Office. Permission to conduct the study from each site's District Health Officer and/or District Nutritionist was also obtained.

Clinical Trial

The trial itself was a randomized, double-blinded, controlled clinical effectiveness trial in which participants were randomized to receive one of two supplementary foods and assessed for recovery from MAM. The primary outcome was recovery from MAM, defined as achieving a MUAC of 12.5 cm without bipedal edema within 12 weeks of therapy. If children did not recover, they were categorized as having continued MAM, developing SAM (MUAC < 11.5 cm and/or bipedal edema), dying, or defaulting (failing to return for three consecutive visits). Secondary outcomes consisted of changes in MUAC, weight, and length; time to recovery; and any adverse events.

A minimum sample size of 1073 children in each group was sought to detect an improved recovery rate in the novel whey RUSF group of 88%, compared to an expected recovery rate of 84% in the soy RUSF group [17-19], assuming 95% sensitivity, 80% power, and an incomplete follow-up rate of 10% [20].

Random allocation was performed by caregivers drawing opaque envelopes that contained one of two coded papers corresponding to either whey RUSF or soy RUSF. This code was accessible only to the food distribution personnel, who do not assess participant outcomes, determine eligibility, or analyze data. The two RUSF formulations had similar color, taste, smell, and packaging. If there were two study participants from the same household, both children received the same type of food to reduce the likelihood of confusing the assigned interventions.

Enrollment and Treatment

Children were evaluated for acute malnutrition by nutrition research assistants and senior pediatric research nurses, trained and supervised by the senior investigators. MUAC was measured with a standard insertion tape to the nearest 0.1 cm (TALC, Harpenden, UK). Weight was measured using an electronic scale to the nearest 5 g (seca 334, Hamburg, Germany). Length was measured to the nearest 0.1 cm using a rigid length board (seca 417, Hamburg, Germany). Children were also evaluated for kwashiorkor by assessing for bilateral pitting edema. The caregivers of children who met enrollment criteria were asked to give verbal and written consent for participation in the study prior to randomization.

Once enrolled, a two-week supply of either soy RUSF or whey RUSF at a dose of approximately 75 kcal/kg/d was provided along with nutrition counseling and instructions for proper feeding of the RUSF. Caretakers were instructed to feed the RUSF only to the enrolled child, to provide additional complementary foods, and to ration the allotted food to last until the next fortnightly distribution. Children were scheduled for follow-up appointments on a fortnightly basis. At each subsequent visit, anthropometric measurements were repeated and caretakers reported on the child's clinical symptoms. If the child remained moderately malnourished, additional RUSF was provided. Children that became severely malnour-

ished during the course of the treatment were treated as outpatients with ready-to-use therapeutic food (RUTF) [21] or, if necessary, an inpatient nutritional rehabilitation center.

Data Entry

All data were double-entered into an Access (Microsoft Corp., Redmond WA) database and compared to original paper charts to resolve any discrepancies. Anthropometric indices were based on the World Health Organization's 2006 Child Growth Standards [22], calculated using the WHO Anthro software (WHO, Geneva).

Statistical Analysis

Rates of MUAC and length gain were calculated in mm/d over the duration of each participant's time in the study. Weight gain was calculated in g/kg/day for both the duration of the study as well as from enrollment to the second follow-up visit (or first visit for those in whom only one visit was recorded). Intention-to-treat analyses were used and all tests were two-sided. Dichotomous outcomes were compared with either Fisher's exact test or the chi-squared test; the Student t-test was used for comparing continuous variables. P-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed in Excel 2013 (Microsoft Corp., Redmond WA) and Prism version 6.05 (GraphPad Software, La Jolla CA).

Cost-Effectiveness Analysis

Costs to produce both types of RUSF were collected in order to compare the cost-effectiveness between Whey and Soy RUSF. Costing information was collected on all food materials, import/duties, packaging, factory/production, and product testing. All price quotes were gathered in 2015 USD, with Malawian Kwacha converted to USD at 1 MWK = 0.00183 USD (using the conversation rate as of 20 August 2015).

Write-up and Publication

Final results were written and accepted for publication in the *American Journal of Clinical Nutrition*.

10. Project results

Acceptability Testing

To balance the conflicting demands of providing sufficient quantities of protein to meet the minimum World Health Organization (WHO) protein recommendations for supplementary foods [23] while developing a novel RUSF that is affordable for widespread usage, a combination of 4.9% WPC80 and 18.7% whey permeate (Arla Foods Ingredients Group P/S, Aarhus, Denmark) was used in the whey RUSF. Peanut paste, sugar, palm oil, soy oil, emulsifier, and a customized micronutrient premix constituted the balance of the whey RUSF. The soy RUSF recipe used has previously been shown effective in treating children with MAM [18, 19] and served as the control RUSF. This soy RUSF included extruded soy flour, peanut paste, sugar, palm oil, soy oil, a micronutrient premix, and dicalcium phosphate or calcium carbonate (Roche, Mumbai, India). The soy RUSF contains no animal-source proteins (**Table 1**).

Table 1. Ingredient composition of the two study foods, as a percentage of total weight[1]

Ingredient	Soy RUSF	Whey RUSF
Peanut paste	26.9	29.4
Sugar	25.7	24.4
Extruded soy flour	24.0	-
Whey permeate	-	18.7
Whey protein concentrate (WPC80)	-	4.9
Palm oil	10.0	10.0
Soy oil	7.3	7.6
Micronutrient mixture	4.6	3.5
Mono- and diglycerides as an emulsifier	1.5	1.5

[1] RUSF, ready-to-use supplementary food.

A total of 60 children aged 6-51 months were enrolled in the acceptability trial; all but one returned for the follow-up questionnaire. The average times for children to consume the two RUSF foods were similar at the initial visit. Both foods were deemed to be highly acceptable based on the hedonic scale ratings and comments from the caregivers. One child in the soy RUSF group and 2 children in the whey RUSF group had a new onset of diarrhea after starting RUSF, all lasting 1-2 days.

Clinical Trial

A total of 2259 children were originally enrolled in the study; 29 were excluded due to enrollment errors, leaving 1086 for final analysis in the soy RUSF group and 1144 in the whey RUSF group. Demographic, anthropometric, clinical, social, and dietary intake characteristics were similar in the two groups, with the exception of a slightly higher rate of HIV-positive mothers in the soy RUSF group.

The percentage of children with MAM that successfully recovered, defined as MUAC ≥ 12.5 cm without peripheral edema within 12 weeks of treatment, was higher in the whey RUSF group at 83.9% compared to the soy RUSF group at 80.5% ($P < 0.04$; RR= 1.043, 95% CI: 1.003, 1.084) (**Table 4** and **Figure 2**). The risk difference for recovery for the whey RUSF group compared to soy RUSF was 3.4% (95% CI: 0.3%, 6.6%). The proportion of children who developed SAM during the course of treatment was similar in both groups: 11.8% in the soy RUSF group and 10.2% in the whey RUSF group ($P = 0.27$). The proportion of children who remained moderately malnourished despite 12 weeks of treatment and the number who defaulted were also similar between the two groups.

Children of mothers known to be HIV-positive recovered 78.3% of the time, compared to 82.8% among children of mothers known to be HIV-negative ($P = 0.11$). In the whey RUSF group, 80.4% of children with HIV-positive mothers recovered, compared to 76.5% in the soy RUSF group ($P = 0.51$). Logistic regression modeling using backward elimination did not show maternal HIV status to be a significant factor in recovery, but the type of RUSF administered continued to be a significant factor in recovery ($P < 0.03$).

Table 4. Outcomes of children treated for MAM during 12-week study period[1]

	Soy RUSF (n = 1086)	Whey RUSF (n = 1144)	*P* value[2]
Recovered [*n* (%)]	874 (80.5)	960 (83.9)	0.039
Time to recovery (d)	30.4 ± 20.1[3]	29.3 ± 19.0	0.22
Did not recover [*n* (%)]	212 (19.5)	184 (16.1)	0.039
Developed SAM [*n* (%)]	128 (11.7)	117 (10.2)	0.27
Remained moderately malnourished [*n* (%)]	52 (4.8)	49 (4.3)	0.64
Default [*n* (%)]	28 (2.6)	16 (1.4)	0.064
Died [*n* (%)]	4 (0.37)	2 (0.17)	0.44
MUAC at final visit (cm)	12.59 ± 0.56	12.66 ± 0.53	0.0088
MUAC gain (mm/d)	0.22 ± 0.28	0.26 ± 0.27	0.0025
WHZ at final visit	-1.18 ± 0.90	-1.08 ± 0.86	0.0077
WHZ change to final visit	0.70 ± 0.66	0.77 ± 0.62	0.012
Weight gain to final visit (g/kg/d)	2.79 ± 2.16	2.95 ± 2.04	0.11
Weight gain to 2nd follow-up visit[4] (g/kg/d)	2.65 ± 2.30	2.88 ± 2.18	0.042
Length gain to final visit (mm/d)	0.29 ± 0.29	0.30 ± 0.28	0.18

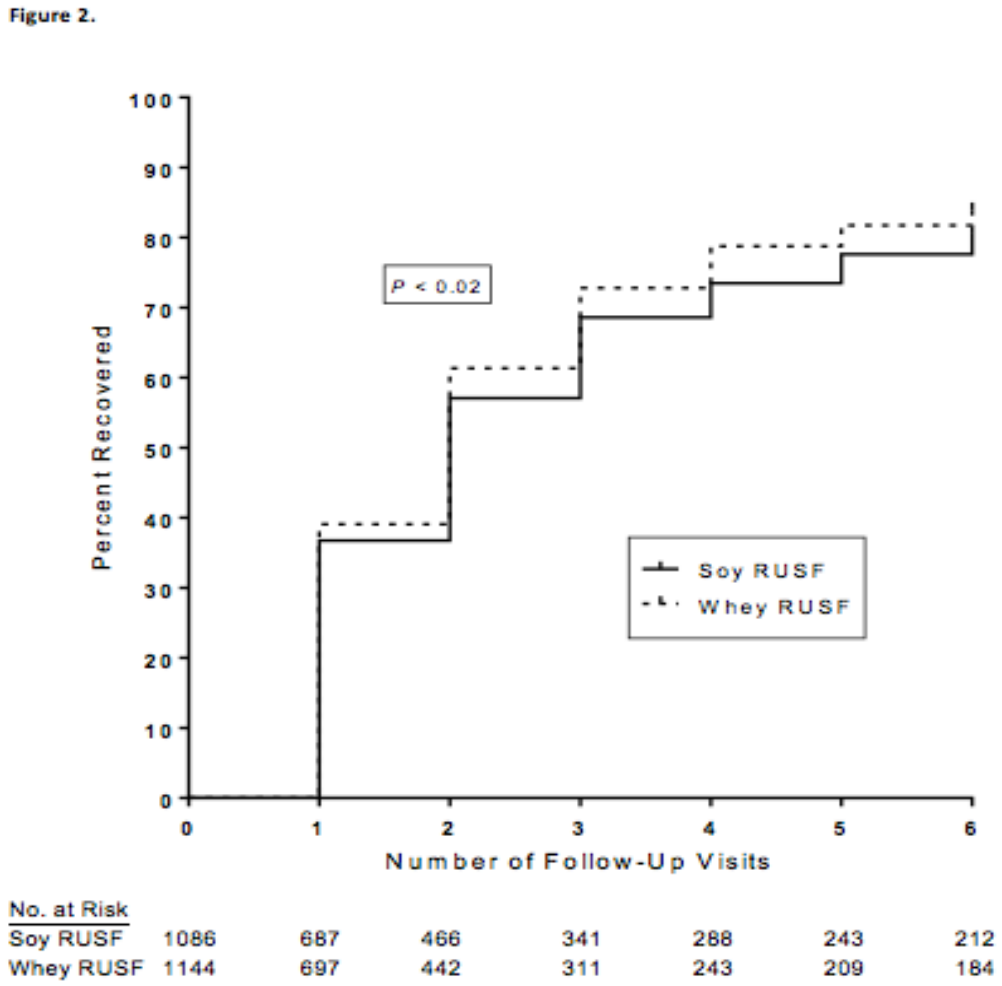
[1] HAZ, height-for-age Z-score; MAM, moderate acute malnutrition; MUAC, mid-upper-arm circumference; RUSF, ready-to-use supplementary food; SAM, severe acute malnutrition; WHZ, weight-for-height Z-score.
[2] *P* values derived from Fisher's exact test or Chi-square test for categorical values and t-tests for continuous variables.
[3] Mean ± SD (all such values).
[4] Or 1st follow-up visit for those with only 1 follow-up.

Although the average MUAC at enrollment was similar between the two groups, the average MUAC at final measurement in the whey RUSF group was greater than in the soy RUSF group ($P < 0.009$). Given that the time to recovery was similar between the two groups, the average daily MUAC gain was also thus greater in the whey RUSF group ($P < 0.003$). The whey RUSF group also demonstrated a greater rate of weight gain over the first 2-4 weeks of therapy ($P < 0.05$), higher WHZ at final measurement ($P < 0.008$), and greater improvements in WHZ than the soy RUSF group ($P < 0.02$).

Given the relatively short follow-up period of the study, no significant difference in the average length gain between the two groups was identified. No significant adverse events that could be attributed to the intervention foods were identified in either treatment group.

The cost to produce soy RUSF was $2.78 per 1 kg and $3.13 for whey RUSF. (Both are less expensive than RUTF, which cost $4.82). This includes costs of all raw materials – both locally purchased in Malawi and imported from overseas – as well as shipping costs, import taxes, product testing, and production costs. For a typical child weighing 7 kg, the total amount of RUSF provided until recovery is just over 3 kg, for a cost difference of the RUSF of approximately $1.49 per child treated, or $1.36 per child who recovers.

Figure 2. Kaplan-Meier curves for time to recovery[1] in children with MAM receiving either Soy RUSF or Whey RUSF[2]



Conclusion

This study provides the first specific evidence to support the value of whey ingredients in RUSF to treat MAM. While prior studies have shown positive correlations between the consumption of dairy protein and improved outcomes in undernourished populations [24-26], it was unclear as to whether those findings were due specifically to the type of protein in the food or simply the total amount of protein [27]. Despite the Whey RUSF providing 33% less total protein and nearly 8% less total energy, outcomes were better in children receiving whey RUSF than those receiving soy RUSF.

11. Deviations

There were not major deviations from the original proposal.

12. The relevance of the results, including relevance for the dairy industry

In this randomized, double-blinded controlled clinical trial, we demonstrate that replacing extruded soy flour with whey permeate and WPC80 in a proven RUSF recipe improves nutritional recovery and anthropometry when treating children in sub-Saharan Africa with MAM.

This result is consistent with previous studies demonstrating the superior performance of dairy protein in the treatment of acute malnutrition. When treating children for SAM, substituting soy for dry skim milk in RUTF resulted in lower recovery rates and poorer growth outcomes in a similar population of Malawian children [26]. However, substituting WPC for dry skim milk in a novel RUTF recipe produced recovery rates similar to the standard formulation [28]. For children with MAM, a soy/whey RUSF led to a similar recovery rate as soy RUSF [19]; yet those treated with the soy/whey RUSF were more likely to remain well-nourished during a 12-month follow-up period [29, 30].

Whey is known for its high quality amino acid (AA) profile when compared to plant-sourced proteins. Whey protein is an excellent source for branched-chain amino acids [31], which are metabolized by muscle and counteract lean tissue breakdown [28] – a critical step in the recovery from acute malnutrition. Whey supplementation has also been shown to increase fasting insulin and facilitate the retention of absorbed AAs [14, 31, 32].

Other factors may explain the improved outcomes observed in the whey RUSF group, including the presence of bioactive peptides such as α-lactalbumin, β-lactoglobulin, serum proteins, lactoferrin, and immunoglobulins [32, 33]. These compounds have important biological functions related to growth and immune system support, such as iron binding, tissue repair, and resistance to infections [32, 34]. Any of these substances which support the immune system may contribute to whey RUSF's superior recovery rate, considering malnourished children's increased susceptibility to infections [35].

The prebiotic effects of lactose found in whey permeate may also contribute to recovery. Feeding large amounts of lactose has shown to stimulate bifidobacteria and lactobacilli and increase short-chain fatty acids (SCFAs) in weaning piglets [36, 37]. Increased lactose consumption has also been shown to increase intestinal and body weight in turkeys [38]. It is possible that lactase activity is reduced in malnourished children due to their compromised intestinal barriers [39] and that this secondary lactose deficiency causes undigested lactose to be fermented into SCFAs which improve colonic microbiome composition [31].

Although our study may indirectly support a prebiotic effect of lactose, others have had mixed results with prebiotics. A randomized trial in Malawi examining the addition of a different type of prebiotic to RUTF did not improve recovery rates from SAM [40]. A study in Bangladesh demonstrated the microbial composition in malnourished children only improved for one month after initial recovery with therapeutic food containing milk (and thus some lactose) [41].

Another factor in recovery may be the higher content of the anti-nutrient phytic acid in soy RUSF (more than double that found in whey RUSF), which inhibits protein digestibility and mineral absorption [34].

Whey RUSF performed better than soy RUSF, even with lower total energy and protein content, highlighting the benefits of dairy-based food. Many nutrition and

public health experts have recommended the increased use of dairy products to improve the quality of supplemental foods used in the treatment of MAM [42]. However, the use of animal-sourced protein is generally more expensive than plant-based protein. For a typical child weighing 7 kg, the total amount of RUSF provided until recovery is just over 3 kg, for a cost difference of the RUSF of approximately $1.49 per child treated, or $1.36 per child who recovers. In the larger context of the operational costs of a supplementary feeding program that includes staff, anthropometric equipment, logistical support, and facilities, this additional cost is quite minimal for the significantly higher recovery rate achieved. While some have questioned whether the benefits of including dairy protein are worth the additional expense [27], this study provides evidence that their inclusion leads to improved outcomes in children with MAM with only a marginal increase in cost

13. Communication and knowledge sharing about the project

Papers in international journals:

Stobaugh, H.C.,et al., *Including whey protein and whey permeate in ready-to-use supplementary food improves recovery rates in children with moderate acute malnutrition: a randomized, double-blind, clinical trial.* Am J Clin Nutr, 2016, 103(3): p. 926-33.

Easily read papers:

Student theses:

Heather Stobaugh, PhD Candidate at Tufts University. This research will be incorporated into the doctoral candidate's final Doctoral Thesis: "Evidence-Based Interventions for Improved and Sustained Recovery from Moderate Acute Malnutrition." Anticipated to be completed by March 2017.

Oral presentations at scientific conferences, symposiums etc.:

Heather Stobaugh to present summary findings as panelist at conference entitled, "Dairy: An Engine for Economic Growth, *The First 1,000 Days*", hosted by the Dairy for Global Nutrition c/o U.S. Dairy Export Council (USDEC) and the United Dairymen of Idaho, on October 10-11, 2016 in Boise, Idaho.

Oral presentations at meetings:

Power point and oral presentation or preliminary results communicated to Arla Foods in November 2014.

Other:

Poster presentation at the Consortium of Universities for Global Health (CUGH) 2016 Conference, held in San Francisco, CA from April 9 to 11, 2016.

14. Contribution to master and Ph.D. education

Heather Stobaugh, MS, MPH
Doctoral Candidate at Friedman School of Nutrition Science and Policy
Tufts University

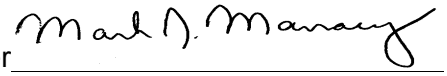
This study will contribute to Ms. Stobaugh's final Doctoral Thesis.

15. New contacts/projects

Project Peanut Butter is exploring new ways to use whey permeate in food aid products.

16. Signature and date

The project is formally finalised when the project manager and DDRF-representative (e.g. steering committee leader) have signed this final report.

Date: 26-Apr-16 Signature, Project manager 

Date: _____Signature, DDRF-representative:_____

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This study will contribute to Ms. Stobaugh's final Doctoral Thesis.

15. New contacts/projects

Project Peanut Butter is exploring new ways to use whey permeate in food aid products.

16. Signature and date

The project is formally finalised when the project manager and DDRF-representative (e.g. steering committee leader) have signed this final report.

Date: 26-Apr-16 Signature, Project manager Mark D. Manary

Date: 30.5.16 Signature, DDRF-representative: