HUMANITARIAN INNOVATION FUND

Development and Implementation Phase Grant Final Report

Organisation Name	Action Contre La Faim – France

Project Title	OPTIDIAG: Improvements in the diagnosis of child undernutrition through the assessment of emerging biomarkers of deprived metabolic status and vulnerability
Partner(s)	– Duke University Medical Center (USA) – University of Ghent (Belgium) – AgroParisTech University (France) – University College of London (UK)
Problem Addressed / Thematic Focus	The project aimed to increase the sensitivity and specificity of diagnostic measures for children suffering from Severe Acute Malnutrition (SAM) and identify children who are at highest risk for life-threatening acute and chronic complications. Weight for Height Z-score (WHZ) and Mid-Upper Arm Circumference (MUAC) have been acknowledged as criteria for the diagnosis of severe acute malnutrition and the targeting of humanitarian nutrition programmes. However, in the absence of a gold standard to understand their respective diagnosis performances and limits, the statement of their inconsistencies is triggering the urgent need for relevant and practical diagnosis tools to improve the accuracy of SAM diagnosis in humanitarian settings.[1]
Location	Burkina Faso (Gourma district) Bangladesh (Cox Bazar) Liberia (Montserrado County)
Start Date	HIF Grant contract: 14 / 11 / 2015

[1] Shortly before the start of the project, we have published a retrospective analysis of anthropometric surveys which confirmed possible explanations of the diagnosis discrepancy between MUAC and WHZ due to confounders such as age, sex, stunting and body proportions (Roberfroid 2015). The need for OptiDiag studies was further reinforced by a recent study highlighting the extent of the discrepancy and investigating possible reasons through the analysis of the most important surveys dataset ever compiled (Grellety 2016). The authors of this last study clearly called for more research on the pathophysiology and functional severity of the cases diagnosed by the different types of anthropometric deficits.

End Date	30 / 04 / 2018 (extension approved)
Total Funding	From HIF: GBP 169 486 (cost extension approved) Cofounding from ECHO ERC: GBP 69 623
Total Spent	From HIF: 169 486

Reporting Period	14/11/2015 – 30/04/2018 (28.5 months)
Type of Innovation	Development of an innovative point-of-care assay for leptin and assessment of the added value of leptin measurements as well as bioelectric-impedance measurements for the classification of the severity of SAM
Project Impact Summary	Piloting the rapid leptin assay technology in Liberia showed that there are still challenges to solve in the lab before the innovative leptin assay can be considered as a suitable solution for leptin measurements in the field. In the meanwhile, we have successfully implemented the cohort studies aimed at assessing the added value of leptin and other emerging biomarkers of deprived metabolic status and vulnerability for the identification and management of children with SAM, in three different countries, which was the other objective of our proposal. Although most of the analysis is still to be performed, preliminary results show that these studies will provide the unique and long awaited evidence regarding the heterogeneity of the risks associated with different sub-categories of SAM cases and regarding the best strategies to identify most at-risk children who should be considered as priority targets. This will in particular address the research needs surrounding the current SAM MUAC-only programming debate.

PROJECT ACTIVITIES AND OUTPUTS

*Please go to **Appendix 1** and attach the final workplan, showing all work that was actually completed.*

1. With reference to the final workplan, what have been the key achievements of the project?

The objectives of our project were to field test rapid and portable Point-Of-Care immunoassays for leptin, as well as other emerging biomarkers of deprived metabolic status and vulnerability, such as

bioelectrical impedance, and to assess their value in the identification and management of SAM children.

The key achievements of the project are:

1) The development of a methodology for rapid and portable POC immunoassays for leptin at Duke University. This has been recently summarized and validated through a high-level scientific article (Joh D et al. 2017; published in PNAS).

2) Field testing of the rapid and portable POC immunoassays for leptin in august 2017 in Liberia. Of note, at this stage, field testing of the rapid assays, although successfully conducted and providing the proof of concept that a leptin signal can be obtained with such a device in SAM children, has helped us identifying a set of important issues requiring more development work for the POCT technology, before it is ready for another field test. Communication around this pilot experience has been released through the ELRHA blog as well as through Duke University related media.

3) Successful implementation of three parallel cohort studies in three different countries to assess the value of leptin for the identification and management of SAM children. Through these studies, we collected a number of highly relevant indicators and samples, in order to describe more precisely the nutritional and health status of the children currently diagnosed as SAM as per the existing anthropometric criteria. This includes bioelectric impedance parameters, which have been added to the study protocol thanks to a cost extension granted by HIF last year.

Data collection is now almost complete (it is still on going for a remaining few weeks in Burkina Faso).

At the end of the contract, we have achieved almost all data collection, analysed all serum samples from two sites (out of three), and we are on the right tracks to enter into a new phase of results dissemination, with further activities to ensure the uptake of the knowledge generated through this project.

INNOVATION OUTCOMES

Whether this innovative project was successful, not successful, or a mix of both, the HIF would like you to report as much detail as possible, so that success can be built on and failures can be learned from. By 'success' we mean that the innovation has achieved the planned positive impact/outcome, or that it has performed better than the current process, product or system.

2. Has the project demonstrated the success of the innovation? *(Please choose only one answer.)*

☐ Completely successful
☒ Significantly successful
☐ Partially successful
☐ Completely unsuccessful

2b. Please select the successes that your project have achieved:
(You may choose more than one)

☒ There is real evidence that the project achieved the planned outcome(s)
☐ There were perceived contributions or improvements to the planned outcome(s)
☒ Learning was achieved within the project cycle
☐ 'Lessons learned' were gathered and circulated to humanitarian stakeholders and actors
☒ The completion of this project has led to another innovation

☐ Other *(please comment)* _____

_____

2c. Please select the challenges your project has encountered:
(You may choose more than one)

☒ The project did not complete its planned activities
☐ There is no real evidence that the project achieved the planned outcome(s)
☐ There were few perceived contributions or improvements to the planned outcome(s)
☐ Learning was not achieved within the project cycle
☐ 'Lessons learned' were not circulated to humanitarian stakeholders and actors
☒ Other *(please comment)* _At the pilot stage, it appeared that the innovative rapid leptin assay was not yet ready for its intended use in harsh field contexts, and needed more technical development to be considered as a suitable solution for leptin measurements in the contexts where they are most needed to improve SAM diagnosis. _____

2d. If there is any evidence for the successful performance of the innovation, please describe it further:

In order to assess the value of leptin and other emerging biomarkers for the identification and management of SAM children, we have successfully implemented three cohort studies in three different countries

After successful completion of preparatory steps (including legal and ethical approval, staff recruitment and training, biomedical procurement, Standard Operating Procedures definition and piloting), we progressively recruited and followed SAM children and we finally achieved the sample size and composition of the cohorts in each SAM diagnosis category (a third of low MUAC only SAM children, a third of low WHZ only and a third of children with both criteria at the same time) in our three different cohorts in Montrovia (Liberia), Fada N'Gourma (Burkina Faso) and Ukhia Upazilla (Bangladesh). The balance between different types of SAM cases has been achieved through the implementation of relevant screening and recruitment procedures.

Data collection on anthropometry, biomarkers, and treatment outcomes, as well as on household risk factors of nutritional status, with a focus on admission, two weeks and 8 weeks of treatment, was implemented in each site according to standard protocols, which have received a global ethical approval and a specific legal and ethical approval in each country. For a summary of the studies, please refer to https://clinicaltrials.gov/ct2/show/NCT03400930.

Although most of the data management and analysis work still needs to be performed, analyses of circulating leptin levels in samples from Liberia and Bangladesh have already been performed, at Duke University, thus displaying very promising preliminary results, which confirm the benefit of leptin measurements to complement the existing anthropometric proxy indicators of SAM. According to the first analyses of leptin, performed on serum samples sent from Liberia and Bangladesh, it appears that leptin:

1. increases sharply from admission to 2weeks. Then does not significantly change between 2 weeks and 8 weeks.

2. significantly differs depending on admission category, with lowest leptin levels found in children combining both SAM definition criteria and highest leptin levels found in low MUAC-only children.

These differences between the different SAM diagnosis categories, which are consistent with the expected levels of nutritional needs and risks at admission, considering pre-existing evidence of the clinical significance of leptin and of higher mortality risks in children combining both deficits, disappear after two weeks of treatment.

These preliminary results and the more complete information our studies will soon release, will provide relevant information addressing the research needs surrounding the debate related to MUAC-only programming for SAM management. We believe this will thus lead to another innovation, which will be evidence-based guidance for the targeting and prioritisation of sub-categories of SAM children. The ultimate goal being to increase the sensitivity and specificity of diagnostic measures for children suffering from SAM and to identify children who are at highest risk for life-threatening acute and chronic complications.

3. Please show the components of the project which contributed the most to any *successes*:
(where 1 = most influence 3 = least influence)

Component	*1*	*2*	*3*	*N/A*
Design and placement of the innovation	☐	☐	☒	☒
The methodology or approach to collecting evidence	☒	☐	☐	☐
Context	☐	☒	☐	☐
The availability of resources and capacities (financial, human, technical etc.)	☒	☐	☐	☐
Success in identifying and responding to different project and innovation risks	☐	☒	☐	☐
Strength of relationships and collaborations within the team and with other stakeholders	☒	☐	☐	☐
The process was flexible and responsive to emerging results	☒	☐	☐	☐
Ability to draw on experience and expertise of existing practice, codes and standards	☐	☐	☐	☒
Other:	☐	☐	☐	☐
Other:	☐	☐	☐	☐

4. Please show the components of the project which contributed the most to any unsuccessful elements of the project

Component	*Yes- contributed to failures*
Weaknesses in the design and placement of the innovation	☒
The methodology or approach to collecting evidence	☐
Context	☒
A lack of access to resources and capacities (financial, human, technical etc.)	☐
Difficulty in identifying and responding to different risks	☐
Lack of good relationships and collaboration within the team and with other stakeholders	☐
Having a process that was not flexible or responsive to emerging results	☐
No ability to draw on experience and expertise of existing practice, codes and standards	☐
Other:	☐
Other:	☐

5. What are the top three, key lessons learnt relating to the innovation? *This should relate to the innovation or the sector in which it operates, rather than project implementation.*

1.
Considering the objective related to the development of a POCT leptin assessment tool, a considerable amount of work has been done, which has led to reach important milestones summarized in a high-level scientific publication, what we think is the best possible illustration that a credible evidence has been generated. However, field-testing of the tool allowed us identifying key areas which are still requiring more laboratory development before it can be considered as a functional POCT. Thus we confirm the importance of field-testing as a key step to validate and improve innovative tools before they can be widely disseminated.

2.
Considering the objective of investigation of the added value of leptin measurement, we have, as explained in earlier reports, added the measurement of Body Impedance Analysis (BIA) parameters to the list of alternative indicators of nutritional and health status we are assessing alongside leptin levels and anthropometric diagnosis criteria. We have been successfully incorporating BIA to our studies in our three different study sites. It is crucial that BIA information is also collected in a group of healthy children pair-matched to those in our cohorts for age and sex, in order to fully interpret BIA information, through semi-quantitative BIVA analysis. Overall it is a key lessons-learnt that, in studies aimed at validating the added value of an innovation such as the cohort studies we have implemented, all the information required for a valuable assessment is planned early in the study design (which is not an easy task considering that both the implementation and the assessment of the innovation are, by definition, new to the field.

3.
The studies implemented to assess the added value of the innovative leptin assays will in fine lead us to another innovation, which is a long-awaited evidence-based guidance for a rational targeting of SAM cases, based on the identification of most at-risk subgroups. So it is probably or third key lessons-learnt that working on an innovation is a very good way to find other innovations.

6. Do the final outcomes support the initial rationale for the innovation?

☐ Yes, completely
☒ Yes, significantly
☐ Partially
☐ No, not at all

Please describe further: Although most of the analysis of the data we have collected still needs to be performed, preliminary analysis of leptin levels confirms its negative correlation with the severity of nutritional status, and thus its potential usefulness for classification of SAM children.

7. How has your understanding of the innovation changed through the project period?

One could argue that there has been an increased intensity in the global debate around the discrepancy of the SAM diagnosis by classical anthropometric proxies, and around the choice of MUAC and/or WHZ for diagnosing SAM, with some recent publications putting forward strong pros and cons arguments. Many stakeholders are showing a will to move forward, or are already engaging, into a switch to MUAC-only programming, while this contradicts WHO recommendations, and while this comes with a high potential public health impact. In such a context, we think that the need for improving SAM diagnosis with relevant tools and credible evidence, and thus the need for the innovation we are developing, has never been so high. We thus realized that our studies will greatly inform the debate on the choice of MUAC and/or WHZ for diagnosing SAM, and will greatly contribute to the evidence base for a rational targeting of SAM.

8. Did the innovation lead to any unexpected outcomes or results? How were these identified and managed?

METHODOLOGY

9. Was the methodology successful in producing credible evidence on the performance of the innovation?

☐ Yes, completely
☒ Yes, significantly
☐ Partially
☐ No, not at all

Please describe further:

We have been constantly adapting our methodology during the preparatory phase and during the pilots in order to optimize it. We are now smoothly implementing the OptiDiag cohort studies to assess the added value of leptin measures and, at the same time, we have implemented a field test of the innovation last august.

Considering the evaluation of the added value of leptin measures, our multicentric study design of cohort studies and the balanced recruitment of the three subcategories of anthropometric diagnosis of SAM, together with the addition of bioelectric impedance records and other biomarkers of

nutritional needs and risks, will allow for both confirmation of the good correlation le leptin levels and risk, and useful comparison of the different types of cases to inform policies.

Considering the development of the POCT leptin assessment tool: thanks to the field test of the rapid leptin assays using smartphones visualization devices, in August, in Liberia, we know that more development is required to 1) improve the stability of the assays' chemistry during transport and field conditions; 2) ensure an internal control or to visualize a standard curve on a single chip (in order to make sure to rightly correlate a signal with a leptin concentration) and 3) improve practicalities in the use of the D4 assays to minimize the need for a skilled specialized staff, power, and material (like the need for a special centrifuge depending on power to dry the chips). Colleagues at Duke University are working on these challenges. In particular, they are currently testing a new imaging system, which could solve the issue number 2, and they are investigating a range of technical options to remove unpractical steps (like washing and drying) in the assay.

PARTNERSHIPS AND COLLABORATION

10. How and why did the partnership change during the course of the project?

There was no change in the partnerships over the course of the project, outside the additional collaboration with Jonathan Wells from UCL on the implementation of BIA data collection.

11. Are there plans to continue your partnership, either while scaling up this innovation or on other projects?

- ☒ Yes, with this innovation
- ☐ Yes, with another project
- ☐ Maybe
- ☐ No

Please describe further:

Duke University will keep analysing the last remaining serum samples from Burkina Faso. Besides, since all our academic partners are genuinely interested in the outcomes of the project, they will be actively involved in results analysis, interpretation and dissemination under the format of scientific papers in peer-reviewed journals, or through participations in conferences and uptake workshops.

DISSEMINATION

12. Please describe any steps taken to disseminate the outcomes of the project.
Please include all completed and forthcoming, as well as all planned and unplanned products (for example, research and policy reports, journal articles, video blogs, evaluations).

The first dissemination of the outcomes of the project has been the publication of a scientific article on the development of the D4 POCT technology by our colleagues at Duke University, in PNAS, a prestigious scientific journal.

Then during our field-testing of the D4 assays in Montrovia, a communication specialist has been sent by Duke University and has produced an article on this experience for the University Journal, as well as a blog and a video.

We have been sharing information on the project methodology through an oral communication by project manager/PhD student, at the Research For Nutrition conference organised by ACF in Paris, the 13th of November 2017. The project manager has also been presenting an update of the project to an event organised by ACF research foundation, the 7th of December 2018.

Finally, regular formal or informal interactions have been established with our institutional partners in Liberia and Bangladesh in order to inform them about the advancement of the project.

The results from the cohort studies will be widely disseminated through various means, starting with scientific publications to ensure their peer-review validation, in the coming months.

13. Has the project received any third party coverage during the project (from news media, third party blogs, researchers or academics etc.)?

Yes the project has been covered by Duke University media and blog.

SCALE UP AND DIFFUSION – WHAT NEXT?

14. Is the project or innovation to be replicated or scaled up?

- ☐ Yes, we will scale up in the same or similar context
- ☐ Yes, we will scale up within our organisation (including running more pilots or trials)
- ☐ Yes, we will replicate the innovation/project in another context or country
- ☐ Yes, the innovation/project will be replicated or scaled up by another organisation or stakeholder
- ☐ Yes, other
- ☒ No

If you answered *yes* to question 14, please answer 14b:

14b. What model are you pursuing to scale up or sustain your innovation?

- ☐ Applying for more donor funding
- ☐ Selling the innovation or patent
- ☐ Cost recovery (for example, selling your service or being paid as a consultant to implement the innovation)
- ☐ Innovation to be taken up by organisation or government as standard and included in standard planning and core funding by them
- ☐ Other_____

Please describe further:

The innovative leptin assays are not yet ready to be used in the field, though our studies show it may have a very important added value in field for the discrimination of most at-risk children.

15. If the project or innovation could be replicated or scaled up, please list the three most important issues or actions that will need to be considered:
(where 1 = most important and 3 = least important)

Suggestion/issue	*1*	*2*	*3*
1	☐	☐	☐
2	☐	☐	☐
3	☐	☐	☐

Appendix 1. Final Workplan

Below is a table that is the same as the workplan that you submitted with your original application. There are **three ways** to respond to this section.

1. If there have been no changes at all through the project you may cut and paste your original workplan here.

2. If there have been changes to the project but these changes **were previously reported to the HIF** in an *Agreement Amendment* form, please adjust your original workplan so that these changes are recorded in it here.

3. If there have been changes which were **not previously reported to the HIF**, please **also** fill in Table 2 (which is on the next page). In particular, please make sure to explain any budget various greater than 15% in Table 2.

Please paste your final workplan in here >

Expected Results	Main Planned activities	Implementation period 2-Months time periods														Responsible party / person	Amount			
																	2016		2017...	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14		HIF	Others	HIF	Others
Development of the rapid leptin assay technology and first test	D4 POCT assay development	X	X	X	X	X	X	X	X	X	X	X				Duke University; Daniel Joh, Ashutosh Chilkoti, Michael Freemark	9520			
	Clinical validation of the assays in the USA	X																		
	Training of the Project Manager/PhD at Duke University	X																		
Field test of the rapid assays in Montrovia, Liberia	Preparation of the pilot study									X	X					Duke University/ ACF-France			30 000	
	Implementation of the pilot study											X								
	Pilot study samples analysis and results interpretation											X								
Validation studies, aimed at assessing the value of leptin for the	Contextualization of study protocols and proposal for the ethical committees	X	X	X	X											ACF-France Project Manager PhD			126 146	69 623

identification and management of SAM children.	Program Manager and field staff recruitment			X	X										and research coordinator				
	Preparation for patient enrolment (medical material, questionnaires, etc.)			X	X	X	X	X											
	SAM cohort follow-up in								X	X	X	X	X	X					
	SAM cohort follow-up in Fada N'Gourma, Burkina Faso									X	X	X	X	X	X				
	SAM cohort follow-up in Cox's Bazaar district								X	X	X	X	X	X					
	Bangladeshi cross-sectional survey in Cox's Bazaar district							X											
	Biosamples shipment to Duke University and Germany														X				
Evaluation of the innovation	Serum samples analysis														X	ACF-France/Duke University/Ghent University/ UCL			3820	
	Evaluation of the correlation between leptin levels and anthropometric indicators. Results analysis and interpretation														X				

Table 2: Changes to Workplan

For every change in the final workplan that is different to your original worktable AND that has not already been reported to the HIF, please add a record in this table. Changes can include alterations to the methodology, project process or innovation design, for example.

Change (as referenced in workplan above)	Reason for change	Overall impact of change
1.		
2.		
3.		

4.		