Completion Assessment Executive Summary

VALID RUTF
December 2021

Investee	VALID Nutrition
Main implementation country	Malawi
Additional implementation countries	None
Funding amount agreed	US$230,000
Funding amount disbursed	US$230,000
Co-funding	None
Investment Date	December 2015
Expected PYI at year 10 (ex-ante)	Not scored

Innovation

The innovation was an improved and more cost-effective Ready-to-use Therapeutic Food (RUTF) for the treatment of Severe Acute Malnutrition (SAM). The context is as follows.

Even as Wasting (Acute Malnutrition) affects an estimated 150 million children under five years old annually, the standard treatment, Ready-to-use Therapeutic Food, has undergone no innovation over the last two decades.

Moreover, only 10 to -25 percent of those children can access treatment**.** The most cost-effective treatment model is Community Management of Acute Malnutrition (CMAM), but nearly half of the program cost, on average, is the cost of the food, so lower cost RUTF would increase coverage within existing budgets.

The standard RUTF product is made from peanuts and milk and since its development, the market for this product has remained quite stagnant. Nutriset, the original product developer, remains the dominant supplier, both directly to communities as well as through franchisees. While the global price of RUTFs has come down roughly 23 percent from 2007-2018, the market efficiencies for the standard model are thought to be fully exploited, with milk powder acknowledged as the sticking point. Milk powder, a large share of the ingredient costs, is not locally produced in most of the developing world and is expensive to import.

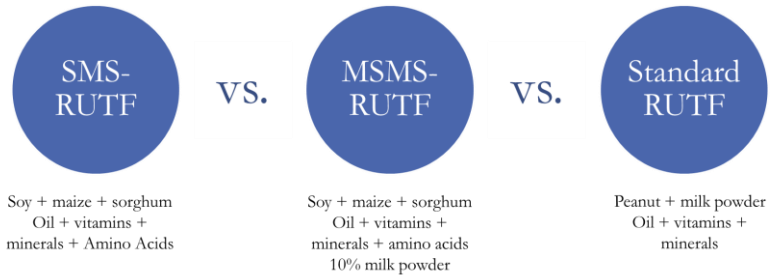
The founder of VALID Nutrition was the pioneer of the CMAM approach and instrumental in its adoption and promotion by the World Health Organization in 2007. VALID devoted over a decade of research and development toward the goal of a lower-cost product that works as well – if not better – than the standard peanut-milk recipe. In partnership with the Japanese food company Ajinomoto, VALID developed a plant-based recipe enhanced with amino acids, which Ajinomoto has expertise in fabricating. These amino acids helped compensate for those derived from dairy.

This recipe was promising and if efficacious offered cost savings on several fronts. First, with no milk powder, the recipe eliminates the largest share of ingredient cost in the standard product. Many of the ingredients in the innovation can be sourced locally or with shorter upstream supply chains than peanuts and milk, making local production more cost-effective than the peanut-milk recipe. (The COVID-19 pandemic has also highlighted the importance of local resilience and short supply chains.) The new recipe also uses ingredients with lower environmental footprints of production which, along with the shorter supply chains, also reduces the environmental impact relative to the standard product. Local production and lower environmental impact are priorities for many stakeholders and UNICEF has made formal commitments to source at least 50 percent of RUTF from local producers.

Goal of investment:

GIF invested in VALID Nutrition to produce and test the efficacy of an amino acid-enhanced plant-based RUTF via a clinical trial in Malawi. GIF made a US$230,000 grant in 2015 to increase the trial's sample size and add a third arm (See **Error! Reference source not found.**.)

Figure 1 VALID's three arm clinical trial



Type of investment

Grant

Original investment rationale

The lower cost and local production potential of the SMS-RUTF, compared to dominant market players, presented an opportunity to increase the reach of treatment to save more children's lives. VALID Nutrition's product was identified as having tremendous promise to be as or more efficacious than the peanut-milk recipe, lower cost, and, by being locally produced, becoming a more attractive option for buyers committed to local sourcing or needing to access products faster than importing from overseas.

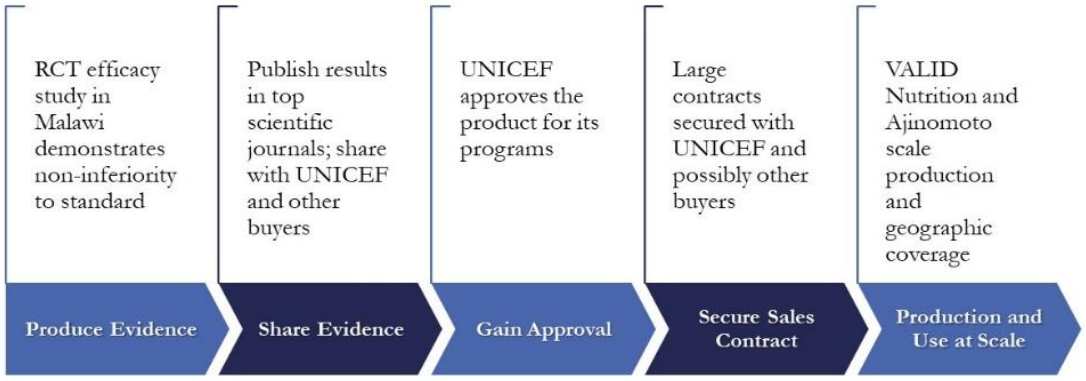
Expected impact

It was expected that the SMS-RUTF product would be shown to be non-inferior to the peanut-milk recipe. The MSMS-RUTF arm was added to address the research question regarding whether some milk is necessary for efficacious treatment or superior in any way to an efficacious plant-based product. If efficacious, VALID Nutrition estimated the SMS-RUTF would cost about 20 percent less than the standard product.

If the efficacy trial yielded positive results, GIF believed VALID would be well positioned (especially as compared to other new market entrants) to secure large contracts from UNICEF, the largest RUTF purchaser. VALID was seen as reasonably well situated to develop the capacity to produce large quantities, including by licensing it. VALID stated that their mission was not only to advance this product but also to disrupt the market by demonstrating the potential for local sourcing and manufacturing as well as for using non-milk based formulas. The imputed theory of change is presented in

Figure 1.

Figure 1 Theory of Change



Results

Performance against objectives at time of investment is presented in the table below.

Objective	Outcome
To add a third arm to their VALID trial to test efficacy of a product with some milk components and improve the analysis associated with this trial.	Achieved. A third arm was successfully added to the trial. The trial was completed, demonstrated efficacy, and resulted in three peer-reviewed publications.
Regulatory approval of the new RUTF product by UNICEF.	Not achieved. Regulatory approval by WHO was not obtained, and this is a prerequisite to UNICEF procurement.

The trial was implemented successfully, and the results were published in three scientific articles in highly reputable journals [Bahwere et al (2017)[1], Sato et al (2018)[2], Akomo et al (2019)[3]] **The trial showed the first plant-based RUTF that is at least as efficacious as the peanut-milk recipe and also better treats anaemia**. Dozens of previous trials of alternative product formulations had been carried out by VALID Nutrition and numerous others, and nearly all had found the alternative products to be inferior to the existing standard in treating SAM. The addition of tailored amino acids made the cereal-legume product as efficacious as one containing milk powder because it compensated for the lack of any animal-source food ingredients by directly incorporating missing amino acids. Furthermore, by comparing all three trial arms, the study yielded a significant finding that the ability to restore body iron stores appears to be inversely proportional to the milk content. This relationship is most likely be explained by other factors present in milk, such as casein, which are known to inhibit iron absorption, since the composition of the SMS-RUTF and MSMS-RUTF were otherwise identical.

[1] https://doi.org/10.3945/ajcn.117.156653

[2] https://doi.org/10.1371/journal.pone.0201686

[3] https://doi.org/10.1186/s12889-019-7170-x

Route to scale and impact

Thus, from a scientific perspective, the investment was successful in rigorously demonstrating the nutritional value of SMS-RUTF. Yet this demonstration did not trigger adoption and widespread use of VALID's product, contrary to the assumptions underlying the theory of change. In retrospect, the investment plan did not adequately address the severe hurdles to securing regulatory approval for a non-dairy based RUTF. Although GIF did subsequently highlight VALID's achievements to DFID (FCDO), the innovator required greater advocacy and, consequently, support was lacking during FAO and WHO review processes bearing on RUTF approval. The context is as follows.

The market and policy environment for RUTF is very complex, in part because it is both a medicine and a food. In 2007, WHO, WFP, UNICEF, UNHCR, and the UN Standing Committee on Nutrition (UNSCN) published a guideline on the management of acute malnutrition known as the 'Joint Statement'[4] that provides the *de facto* regulation of RUTF. The product specifications therein require at least 50 percent of the protein in RUTF to come from dairy sources and that it contains amounts of all other macro- and micronutrients within specified ranges. This 50 percent requirement was a key barrier preventing widespread take-up of VALID's formula.

VALID and GIF thought the pathway to scale would simply require approval from UNICEF, the *de facto* accreditor and principal buyer of RUTF. The grant agreement specified that VALID would receive a bonus payment in the event of "regulatory approval of the new RUTF by UNICEF." In fact, the complex institutional environment was such that WHO and FAO were the relevant regulators.

International nutrition is a unique problem space where policy processes are exceptionally complicated and major changes, such as removing the milk requirement for RUTF, have taken years to come about. UN agencies rely on expert guidance from the science community to provide recommendations for new and revised policies. Expert review groups look at the full body of evidence and in the case of RUTF, there was abundant evidence that the peanut-milk recipe is highly effective, and abundant evidence that all other plant-based products that have been tested, except for the SMS-RUTF, have not been.

In response to the development of non-dairy RUTFs, and recognizing their potential cost advantage, WHO commissioned in 2019 a re-examination and update of the 2007 "Joint Statement" guideline requiring dairy-based proteins. The review[5] undertook a meta-analysis of six trials of non-dairy RUTFs, three of which were conducted by Valid on its formulations. The review concluded that:

> The available evidence was not enough to justify a change in the current recommendation that RUTF should have at least 50% of protein coming from dairy. The efficacy outcomes favoured the standard RUTF, while there were no robust data from producers to demonstrate that reducing the dairy content will reduce the costs and resource requirements of RUTF. The group therefore did not recommend the use of the reduced/no dairy formulations but noted the potential of these alternative formulations if more evidence of efficacy and cost-effectiveness is generated.

VALID considered the process to be flawed. It disputes the conclusion on several grounds[6]. VALID disagrees with basing the conclusion on the pooling of its most recent and successful formula with its prior iterations and with those of unrelated organizations. VALID contests also the criteria against which RUTF formulations were assessed, and the rigor of the cost-effectiveness assessment. VALID strongly

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[4] World Health Organization, 2007. Community-based management of severe acute malnutrition: a joint statement by the World Health Organization, the World Food Programme, the United Nations System Standing Committee on Nutrition and the United Nations Children's Fund. Available here

[5] World Health Organization. (2021). WHO guideline on the dairy protein content in ready-to-use therapeutic foods for treatment of uncomplicated severe acute malnutrition. Available here.

[6] USAID, The Future of Food Assistance for Nutrition: Evidence Summit II, Oct 5-8, 2020. Session recording at https://youtu.be/8AfZXB85bBY

feels that the maintenance of the status quo severely puts at risk the lives of children in developing world and has articulated this at various fora.

A recent survey of 36 RUTF stakeholders on this issue concluded[7]:

> Consensus is building among stakeholders that, due to the cost of producing the original RUTF recipe and the challenges in procuring some of the ingredients locally, there is a need for alternative formulations that could make it easier to scale up treatment and therefore improve coverage. A number of non-peanut 'alternative formulations' are now in development, which may or may not include milk powder. For a small number of these new formulations, study leads claim non-inferior treatment outcomes and even added advantages (e.g., lowering anaemia) over standard, peanut-based RUTF. Others feel such conclusions are premature and that further research is needed. There is currently no consensus on the best way forward to build the evidence base to inform specifications and guidance. Stakeholders interviewed for this work agreed that there is an urgent need for decisions on clear benchmarks around evidence; i.e., what is 'good enough' and what is important in terms of demonstrating product effectiveness.

In sum there is disagreement on whether a blanket policy (the dairy requirement) should be changed based on one (or a limited number) of promising results, and indeed how to evaluate those results. Meanwhile the revised WHO guideline "encourages" use of noncompliant (<50% dairy) RUTF in "research and evaluation settings."

Despite the regulatory barrier to widespread approval and use at the international level, some progress on the pathway to scale continued moving forward on the ground in Malawi in 2018. From January through June 2018, the Ministry of Health worked with World Vision to use the SMS-RUTF in its routine CMAM program in three districts of the country. World Vision saw a dual opportunity to test the new SMS-RUTF and a potential market opportunity for the farmers engaged in their agriculture programs. The published results of the trial (Banda et al 2021)[8] concluded that the SMS-RUTF exceeded SPHERE standards (reference standards for humanitarian operations) in a real-world setting and advocated its use.

Gender considerations

Though Gender outcomes were not an explicit consideration of the grant, CMAM places a central role on mothers in the care process.

Key learnings

For the development community

- There is a need to balance regulatory goals – in this case, to assure the safety and efficacy of RUTF – with a clear path to allow for innovation.

For GIF

- It is important to understand the institutional barriers of innovations, especially for those subject to regulation. Here, GIF diligence failed to fully understand the regulatory context for RUTF. (Note, as this was one of GIF's earliest investments, GIF's diligence processes have been substantially strengthened including developing strength of evidence rubrics to guide internal analysis on scaling pathways amongst other dimensions, and increased consultation with sector-specific experts.)

[7] Mates, E., and Sadler, K. Ready-to-use Therapeutic Food (RUTF) Scoping Study. ENN, June 2020. https://www.ennonline.net/rutfscopingstudy

[8] https://doi.org/10.1177/0379572120968703

- It is important to formulate, to the extent possible, the innovation's ultimate path to scale, and to orient activities during and after the investment period to support that path. At outset, and during implementation, GIF should assess its capacity and ambition to provide advocacy and other support for scale, taking into account resource constraints and the likely efficacy of its efforts.
- For GIF, a typical stylized theory of change is to rigorously show that an innovation is effective, which in turn catalyzes the innovation's adoption. It is important to recognize that a new study is read in the context of prior evidence. When a few new incremental studies contradict a large existing body of evidence or challenge entrenched practices, their demonstration effect is likely to be weak. Additional supporting evidence may be required to bring about change.