

## Terms of Reference

# Midterm Evaluation of Project 6141: Sickle Cell Disease (SCD) - How an Alzheimer medication might save children's lives

## 1. Introduction

### Background on Funding Partner

Fondation Botnar is a Swiss-based foundation established in 2003 whose core purpose is improving the health and wellbeing of children and young people in growing secondary cities around the world. We do this by investing in sustainable solutions, learning with, connecting and catalysing diverse partners.

At Fondation Botnar, we recognize the value of learning in effectively driving towards systemic change, and are committed to cultivating and nurturing learning both within and outside of the organization.

### Background on Implementing Partner (“Grantee”)

With its about 26,000 enrolled students, the University of Zurich (UZH) is Switzerland's largest university. Founded in the year 1833, UZH was Europe's first university to be established by a democratic political system. Today, UZH is not only one of the foremost universities in German-speaking Europe but worldwide. Made up of seven faculties covering some 100 different subject areas, the University offers a wide variety of Bachelor's, Master's and PhD programs. In addition, UZH's continuing education programs offer excellent learning opportunities.

The UZH Foundation (UZHF) seeks donations and requests to achieve its fundamental goal of promoting excellence in scientific education at the UZH. Accordingly, donations accelerate the progress made in research and education, bringing benefits to society at large. Currently, the main focus areas of the UZHF are: digital society initiative, cutting-edge medicine, innovation, and academic career development.

## Project Description

Globally, it is estimated that 300,000 infants are born annually with sickle cell disease. The majority of these births occur in low-resource countries, especially in sub-Saharan Africa where the World Health Organization estimates 70 percent of the world's population of children with SCD live. The majority of children suffer from chronic pain and numerous infections; ultimately, many die before their fifth birthday. A long-term, affordable treatment such as Memantine could contribute to the reduction of the morbidity and mortality of affected children.

The project MEMAGEN, which started in 2018 and in which the Fondation Botnar started its engagement as of January 2019, aims to evaluate a putative low-cost treatment for Sickle Cell Disease (SCD) through the introduction of a Memantine-based therapeutic approach and therefore reduce morbidity and mortality among children. As Memantine is an anti-Alzheimer drug that is off-patent, its (off-label) use might offer an affordable, supportive and long-term solution that would benefit children and adolescents, as deaths from SCD mainly occurs in children under five years, adolescents, and pregnant women. The therapy would consist of a daily dosis of Memantine that most probably will be combined with other anti-SCD drugs such as hydroxyurea. Of note, hydroxyurea - that represents the oldest medication against SCD by inducing expression of fetal haemoglobin (HbF) - is often not well tolerated by individual SCD patients.

Based on the promising first results from a small pilot study at the UZH/USZ (Hegemann et al, 2020, HemaSphere), the project objective is a clinical trial phase IIa/b. The study was originally intended to include 40 young patients in Afula (northern Israel) at the Emek Medical Hospital. The haematologists at this hospital are well experienced with SCD and have already carried out clinical trials with SCD patients in the past. While sample and data collection as well as standard laboratory analysis are performed in Afula, trial coordination, more specialized sample analysis in-depth data processing, statistical analysis and dissemination activities are done in and from Zürich. The primary objective of the MEMAGEN clinical trial is to evaluate safety, tolerability and efficacy of different doses of Memantine when treating adolescent and young SCD patients. Secondary objectives include evaluation of therapeutic potential of memantine and development of criteria to assess responsiveness of different groups of patients to Memantine treatment. The project end is scheduled for 31 December 2021.

The long-term objectives of the project are to introduce this safe and low-cost therapy in all affected countries worldwide, especially focusing on Africa with the goal to reduce SCD-caused morbidity and mortality specially of children, adolescents, and pregenant women.

## Implementation Timing / Current Status

Due to different reasons including the Covid-19 pandemic situation, only 23 patients (12-44 years) have been enrolled of whom 17 (9F, 8M) started treatment, and, until the end of September 2020, a total of 12 patients successfully finished the trial. Notably, 10 out of 12 patients who finished the participation in the trial decided on their own will continuing with the Memantine treatment. Accordingly, follow up has been continued every 2 months with those patients. Concerning the safety and tolerability, first insights were captured after the first patients completed the trial. The analysis of the effects on the quality of life is currently under way, while the first results of the effects on red blood cell properties are promising. Next steps of the trial are:

1. To get more experience for responsiveness of SCD patients to Memantine, to find markers that allow defining the optimal Memantine dosage, and to better understand the long-term effects of this anti-Alzheimer drug in much younger SCD patients. To this end, the tremendous amount of collected (lab-) data has to be analyzed accordingly. In addition, data are awaited on long-term improvement in cognitive function of young patients.
2. To statistical analyse data in-depth as a basis for developing patient stratification protocols allowing best possible therapeutic effect for the individual. This is expected to lead to a better understanding on sex dimorphism detected in the trial, and possible benefits.
3. To continue development of an automated testing technology for monitoring the effects of Memantine .

## 2. Evaluation Objectives and Questions

### Evaluation Objectives and Purpose

1. To support the grantee's reflection on the ways in which the research will contribute to introducing the therapy – if found effective – to regions strongly affected by SCD.
2. Fondation Botnar works with a systemic approach, which assumes that changes does not take place in a linear path, but rather requires a number of different factors to contribute to making the change. The evaluation should support the grantee's reflection on the research through creating an understanding of the projects long-term critical path and context that influences it. Furthermore, Fondation Botnar wishes to understand how its contribution to the research has made a difference in the field of developing effective treatments for sickle cell disease in low-income regions.
3. To learn about the status of the research, and to assess its fairness and equity

Fondation Botnar support the concept of fair partnerships in research based on the principles and Research Fairness Initiative<sup>1</sup> defined by the Swiss Commission for Research Partnerships with Developing Countries (KFPE). It is important for the Foundation that the research it supports is fair and equitable, building lasting partnerships and capacity sustainably. The evaluation should appraise the current status of research fairness in the project for both the foundation as a grant maker and the grantee as a researcher to reflect on and to initiate improvements.

4. To feed into the development of the overall monitoring and evaluation (M&E) and knowledge management system of Fondation Botnar

Fondation Botnar has been developing its strategic learning and evaluation system. The evaluation can contribute to this process by developing indicators and/or guiding questions that could be used in other research projects funded by the Foundation.

## Evaluation Questions

1. How is the project situated in the broader field of developing appropriate, affordable and accessible treatment for sickle cell disease in low-income countries?
  - What role can the Fondation Botnar grant play in in this field?
2. What is the project status with respect to answering the research questions?
  - Which successes or promising results have been attained so far? What are the most important insights the project has generated to date?
3. Which challenges have been met in the course of the project and how have the grantees managed these challenges, to what effects?
  - How has the COVID-19 pandemic influenced the project in its process and outcomes, and how does the grantee manage any project-related issues linked to the pandemic?
4. How has the project been aligned with the Research Fairness Initiative, in particular regarding:
  - Decision-making and responsibilities in the project, i.e. how research partners share their responsibilities in the project to ensure decisions are fair and effective?
  - Project ownership, in particular how research partners share costs and benefits of the research?
  - How can research fairness be optimized in the context of this project?
5. How has the research carried out under the project contributed to providing accessible, appropriate and affordable treatment of sickle cell disease to low-income countries, so as to

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<sup>1</sup> Operationalisation will be based on the KFPE Principles and Research Fairness Initiative Guidelines.

enhance the well-being of children and young people?

- What efforts have been undertaken by the grantee to influence relevant stakeholders, such as pharmaceutical companies, to transfer findings from the research and support adoption of the treatment (if found effective)? What additional efforts should be undertaken and how?
- Which aspects of the project and its theory of change need strengthening or adjusting to enhance chances the treatment – if found effective – is introduced to these contexts and target groups?

During the inception phase, the evaluator can review and develop additional evaluation questions as necessary, in consultation with Fondation Botnar and the implementing partner.

## Alignment with Fondation Botnar Strategic Learning and Evaluation

The project is part of the research portfolio of Fondation Botnar, which aims to support the foundation's objectives by providing scientific evidence in various areas of activity. Fondation Botnar emphasises learning to understand the systems affecting young people's wellbeing and to advance on the path towards the Foundation's vision. Strategic learning agendas guide this approach through learning questions for focused enquiry. The **primary** learning question for this evaluation is:

How can grants for medical trials effectively support the introduction of accessible, appropriate and affordable care for children and youth in low-income countries?

While it is not the primary focus of the evaluation, the learning questions should be taken into consideration.

### 3. Methodology and Paradigm

Medical research processes follow well-established standards. However, the roll-out of new treatments in a wide range of contexts can be a complex process. As the evaluation is expected to provide recommendations for this latter aspect, a theory-based and complexity-responsive approach appears useful. The evaluator is expected to initially review core documentation for the project, refine the evaluation questions as needed, and determine the evaluation approach and methods for data collection and analysis in consultation with the grantee and Fondation Botnar. An approach that triangulates perspectives should be used. The evaluator is expected to foster participation at key moments of the evaluation, seeking the implementation team's advice and of support (i) during the inception phase, when crafting the evaluation instruments, (ii) during the data analysis phase, and (iii) when developing recommendations.

#### Role of the External Evaluator

Fondation Botnar is committed to partnering closely with grantees to enhance learning directly related to implementation and the follow-on phases of the program, be it with or without Fondation Botnar support. The External Evaluator implementing the contract must be able to situate themselves as a partner with the recipient organization for maximum transparency and utility of the evaluation findings for program improvement. Also, the evaluator is invited to provide recommendations for future evaluation processes.

For midterm evaluations, the primary focus of the exercise should be on program improvement to leverage results. The consulting evaluator is expected to work in tandem with the Project Lead based in Switzerland and with the Israeli Partners to understand the research process and its prospective use. The contracting evaluator is expected to collaborate closely with the implementor to:

- A) Reach a shared understanding of the evaluation objectives and questions, and develop the evaluation approach and process accordingly
- B) unpack or develop the broader theory of change for the project and potential future steps towards introducing the treatment
- C) consult regularly with the project team to boost both the validity of findings and the relevance of results and recommendations, also taking into account the grantee's internal communication needs
- D) recommend adjustments to project's measurement framework as needed so as to effectively inform future steps
- E) facilitate a validation workshop or consultation (online) so as to discuss initial findings and recommendations with the implementor and Fondation Botnar.

## 4. Evaluation logistics

### Scope and Field Visits

The evaluation is expected to take place between December 2020 and March 2021. Its overall budget must not exceed CHF 20.000. In view of current restrictions and risks linked to the COVID-19 pandemic, the evaluation will be carried out via online platforms, such as videoconference and (optional) visual collaboration platforms.

### Ethical Considerations

The evaluator is expected to comply with evaluation ethics, as set out in the OECD/DAC Quality Standards for Development Evaluation (<http://www.oecd.org/dac/evaluation/qualitystandards.pdf>) throughout the evaluation process. If any interviews with research subjects (patients in Afula who participate in the trial) are carried out, ethical standards for medical research apply. The research in Israel has obtained ethical approval by the relevant boards in Israel and Switzerland.

## Proposed Timeline and deliverables

Evaluation activities will start upon execution of the consultancy contract and conclude no later than March **2021**. The Final Report including the respective slide deck should be submitted no later than **31.03.2021**.

Work Packages/Action	Responsible	Timeline
Selection of evaluator	Fondation Botnar/Grantee	end of November 2020
Kick-off/inception meeting	Evaluator	early Dec 2020
Submission of inception report	Evaluator	early January 2021
Evaluation research and analysis, including validation workshop	Evaluator/Grantee	January– February 2021
Submission of draft evaluation report	Evaluator	23 February 2021
Feedback on draft evaluation report	Fondation Botnar/Grantee	10 March 2021
Closing workshop	Evaluator	18 March 2021
Submission of Final Report	Evaluator	31 March 2021

## Inception and dissemination consultations

At a minimum, the consultant will plan and facilitate two consultation events/moments in consultation with the implementor. The minimum set of activities are specified as follows:

- \* Inception meeting or workshop (on-line or in a hybrid format) with representatives of Fondation Botnar and of the implementing organisations in Zurich and Afula
- \* Validation workshop (on-line or in a hybrid format) with the implementing organisations, to verify and deepen findings, reflect on future steps and gather inputs for recommendations .

## Deliverables

The deliverables are specified below:

- \* Inception report of up to 10 pages (plus annexes) including:
  - Understanding of the evaluation purpose and scope (– i.e. what is in and out of scope)
  - Proposed adjustments to evaluation objectives and questions as appropriate
  - Tentative work-plan and schedule for the overall evaluation process, specifying involved



stakeholders' roles and moments for communication between the specific stakeholders

- Draft instruments for data collection and analysis (in annex)
- \* Draft outline of the evaluation report (anticipating up to two rounds of feedback)
- \* Full draft evaluation report of up to 30 pages including a three-page executive summary
- \* Closing Workshop
  - Discuss Learnings
  - Reflect on the evaluation process
- \* Final evaluation report (after one round of feedback) accompanied by a short briefing slide deck

## 5. Evaluator Requirements

### Evaluator requirements

#### Evaluation experience

- \* Theory-based evaluation or theory of change development
- \* Touch points with or knowledge of research fairness approaches (Research Fairness Initiative RFI/ KPFE Principles)

#### Contextual experience and linguistic capability

- \* Excellent written and spoken English
- \* Familiarity with medical trials
- \* Knowledge in the field of developing and introducing low-cost medical treatment affecting children and youth in the “Global South”
- \* Experience in conducting interviews, group discussions and workshops via online platforms

#### References

*Applicants are requested to include examples of evaluations that are broadly representative of the evaluator's or the evaluation team's capability vis-à-vis this call.*

### Expression of Interest

The expression of interest should be no longer than **2 pages** consisting of:

- \* Introduction of the evaluator or evaluation team including relevant experience and skills
- \* Short proposal of the methodological approach
- \* Rough day-rate

An annex can include further documentation such as CVs, reports and publications or other relevant documentation. The 2-pager, however, will be the basis for decision-making.

### Deadline

Interested experts are requested to send their expression of interest in PDF format by 16 November 2021 at 11 am Central European Standard Time, to [dsuhr@fondationbotnar.org](mailto:dsuhr@fondationbotnar.org) and [m.raab@posteo.de](mailto:m.raab@posteo.de).