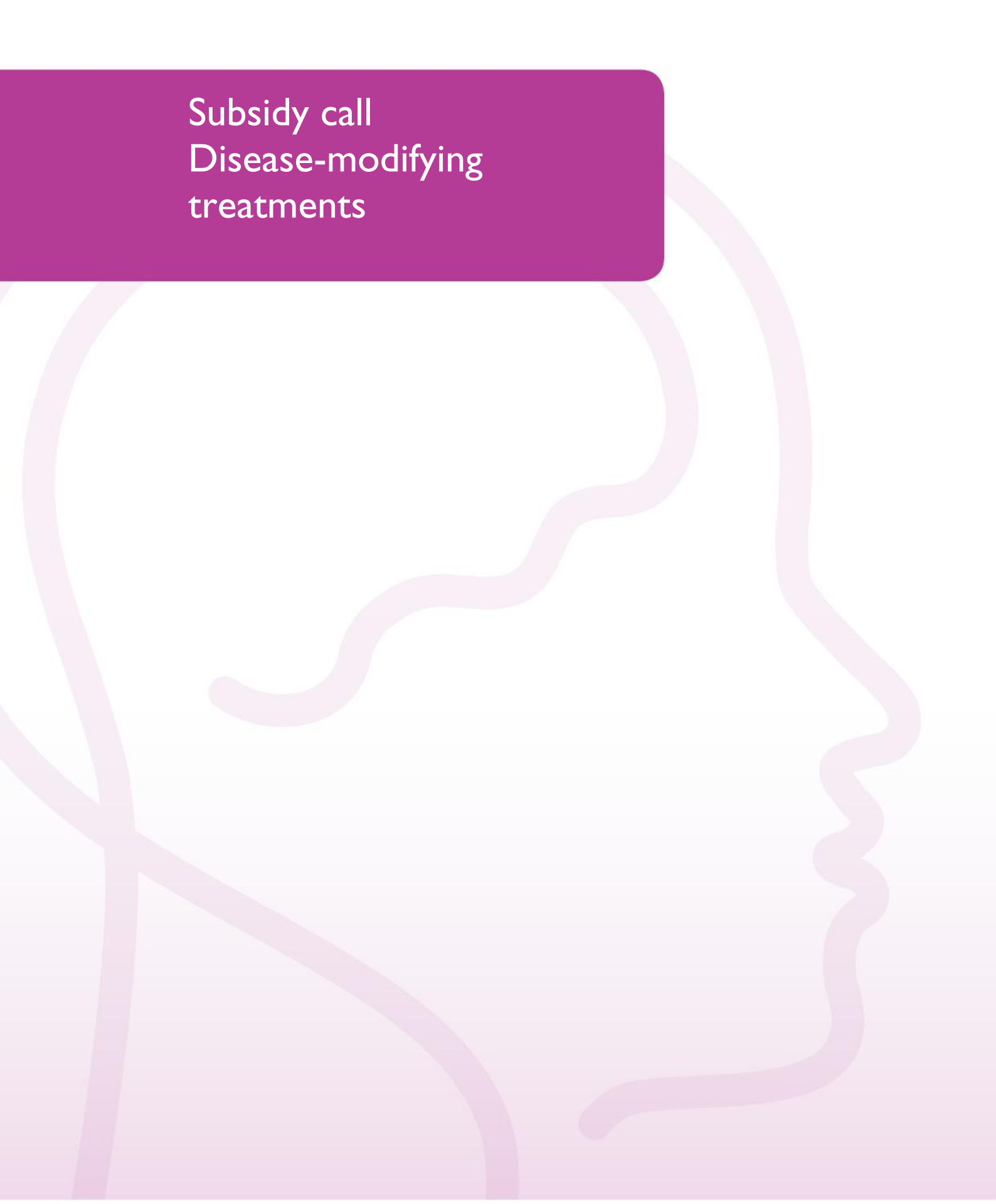
Subsidy call Disease-modifying treatments



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1 Introduction

1.1 Mission and goals of the Netherlands Brain Foundation

There are hundreds of different brain disorders, but you have just one brain. Every day the chance grows that your life will be physically, mentally or socially affected by a brain disorder. We must not let that happen.

Brain disorders are the biggest health problem currently and for the foreseeable future. They will affect us all sooner or later. That is why we are not focussing on one disease, but investing widely in ground-breaking solutions that will help prevent and cure all brain disorders.

The Netherlands Brain Foundation is dedicated to doing everything for healthy brains, to save and restore as many lives as possible. We aim to accomplish this through lowering the mortality and disease burden due to brain disorders, and we feel it is important that people with a brain disorder are identified and recognized.

Our mission has been translated into two primary goals:

- **Lower mortality and burden of disease from brain disorders**
  Brain disorders have an enormous impact on people's lives. By preventing brain disorders or ensuring that the disease develops at a later age, more slowly or is even stopped, people live longer. If symptoms are alleviated and people can function better, the disease will be considered less serious.

- **People with a brain disorder are identified and recognised**
  Brain disorders too often go unrecognised: by the patients, their environment, caregivers and society. This situation has to change. People with a brain disorder must get the right care at the right time so they can continue fulfilling their meaningful role in society.

These two goals for 2030 have been translated into five concrete result areas. Two of them target identification and recognition, and the other three focus on reducing the mortality and burden of disease due to brain disorders:

1. More treatments that delay or stop brain disorders
2. More interventions that alleviate symptoms or improve functioning
3. More people know how to reduce the risk of brain disorders

1.2 Background and starting point

This subsidy call focuses specifically on result area 1, which **aims to stop and delay brain disorders**. We want to achieve the following:

> ***A visible increase in the number of treatments which have been shown to delay or stop a brain disorder in people (2024). This also means an increase in the number of patients receiving a treatment that delays or stops the disorder (2030).***

To realise lower mortality and burden of disease due to brain disorders, more treatments are necessary that influence the disease process so it can be delayed or stopped and people can live a good-quality life for longer. For many brain disorders, these treatments do not yet exist. The Netherlands Brain Foundation intends to focus its investments on those disorders with a good chance that the treatment will delay or stop them.

For this result area, we are looking primarily for research and development projects and collaboration with private parties which aim to bring treatments closer to the patient. To achieve real results, we focus on projects that examine the efficacy of treatments in humans. Because these treatments must slow or stop specific brain disorders, we call them disease-modifying treatments. These treatments are pharmacological, technological or psychological in nature and influence the disease process. We are also interested in 're-purposing'. This term means that we examine whether an existing disease-modifying treatment for a specific disorder also has an effect on another brain disorder. This concerns instruments and treatments that stop the disease or ensure that the patient's condition does not worsen or decline, or slows this process, in the short and long term. It is also important to prevent or delay the restrictions caused by the disease.

1.3 Aim of this call

This call targets research that will lead to treatments that will contribute in the future to slowing or stopping brain disorders. This research must meet the following 7 key criteria:

1. It concerns neurological and/or psychiatric brain disorders in both the clinical/ symptomatic and pre-symptomatic phases.
2. The research targets health gains for the patient.
3. The research concerns a new therapeutic treatment that is not yet available in clinical practice.
4. The therapeutic treatment is disease-modifying in nature (aims to delay, stop or repair/heal the brain disorder).
5. There is a likely starting point (biological, physiological or psychological) for the new treatment for which plausible scientific support exists based on replicated (pilot) studies.
6. The research falls within a further demarcated phase of translational research, with the focus lying on first in human clinical studies that aim to achieve a human proof-of-concept through to efficacy studies in patients.
7. The research is preferably multidisciplinary: all disciplines needed for this research, this technology and disorder are directly involved.

2 Guidelines for applicants

2.1 Clarification of the key criteria

The subsidy call is demarcated by six points. The object of the study must fulfil the first six key criteria. If relevant or possible, studies that also fulfil key criterion 7 will take priority.

Clarification of the key criteria:

1. **It concerns neurological and/or psychiatric brain disorders in both the clinical/ symptomatic and pre-symptomatic phases.**
   - The specialist field of the Netherlands Brain Foundation concerns the brain, the part of the central nervous system located inside the skull.[1]
   - Brain disorders: Clinical diseases, dysfunction, disorders or damage to the brain[2]. Both neurological and psychiatric disorders fall under this.
   - The research in this programme may also concern the treatment of a subclinical or pre-manifest stage of a brain disorder. In that case, it concerns the early treatment of brain disorders, when clinical symptoms have not yet manifested, but the pathology/aetiology is already measurably manifest so it can possibly be delayed, stopped, or reversed. The conditions for involving pre-symptomatic patients in a study within this programme are: 1) there is insight into the causal mechanism and starting points for treatment; 2) biological and/or psychological markers for the disorder are demonstrably present in this early phase; 3) in the later phase these markers manifest as a disease (predictive validity).

2. **The research targets health gains for the patient**
   - The programme's approach is to considerably improve the treatment options for patients with brain disorders in the future and ultimately to realise the greatest possible health gains for patients. Researchers must be able to support the potential health gains to be provided by the treatment.
   - **Lay experts' input is incorporated**: Applicants are expected to actively consult lay experts and users to test how well their ideas match the needs of interested parties and whether they are relevant, feasible and useful. Applicants must indicate how they discussed their proposal with lay experts and incorporated the suggestions in their application.

     Lay experts include:
     - Patients and their informal carers (they can contribute ideas about the feasibility and relevance of a study)

     Users include:
     - Healthcare professionals (from different treatment centres; this increases the chance of successfully promoting further development of the results)

[1] The spine and the eyes are outside this scope, as is the skull itself.
[2] Prevention and clinical research in healthy people that is not directly related to the treatment of brain disorders are outside the scope of this programme.

- Healthcare insurers: What requirements must the proof of the effectiveness of the treatment meet for the new treatment to be considered for reimbursement by healthcare insurers? Make sure that the right outcome measures are included in the study design.

3. The research concerns a *new* therapeutic treatment that is not yet available in clinical practice.

- **New**: This concerns research into *new, innovative* therapeutic treatment strategies and techniques. These are treatments that are not yet available in clinical practice (for the intended patient group)[3].
- **Re-purposing:** The wheel does not have to constantly reinvented, sometimes existing treatments can also offer a possibility for a new group of patients. The condition remains that there must be health gains for the patient and that there is already considerable scientific support based on replicated studies (criteria 2 and 5).
- **Therapeutic treatment:** Different treatment modalities/intervention techniques are possible: the entire range of clinical therapeutic treatments, including pharmacological, molecular, biological/physiological, medical devices, and psychological and remedial therapy treatments fall within this programme[4]. The condition is that it must be a disease-modifying treatment, see key criterion 4.
- **Targetting 'better treatment in the future'**: The results of the studies in this programme (i.e. the intended innovative treatments), if successful, are expected to become available to patients in the middle to long term.

4. The therapeutic treatment is disease-modifying in nature (aims to delay, stop or repair/heal the brain disorder).

- **Disease-modifying treatments:** These are treatments that address the cause or the course of the clinical disorder instead of its challenges; i.e. causal treatments. This refers to delaying, stopping, repairing and healing brain disorders. For example: existing medication for which a supported suspicion exists that it could also have an effect on another group of patients with a brain disorder (re-purposing). Another example is the prevention of relapse after depression, based on known underlying disease mechanisms. This research programme places express emphasis on this type of study. For an elaboration of two examples, see appendix 4.1.

5. There is a likely starting point (biological, physiological or psychological) for the new treatment for which plausible scientific support exists based on replicated (pilot) studies.

- The intention is to understand the underlying pathophysiology and disease mechanisms and identify the underlying biological, physiological or psychological starting point on which the

[3] Research into the underlying mechanisms that must provide new starting points for causal treatments plus the development/establishment of research models to test causal treatments fall outside the scope of this programme.
[4] Interventions for human enhancement, prevention and diagnostics fall outside the scope of this programme.

treatment can be based. This means that there is considerable scientific support for it based on replicated studies. This rationale can be clearly explained and demonstrated.

6. **The research falls within a further demarcated phase of translational research, with the focus lying on *first in human* clinical studies that aim to achieve a human proof-of-concept through to efficacy studies in patients.**
   - **Development stage:** further delimited phase of translational research in which the translation step to humans is made and the target treatment is tested in humans for the first time: the clinical part of the T1 phase through the clinical 'efficacy' part of the T2 phase. (https://ictr.wisc.edu/what-are-the-t0-to-t4-research-classifications/).
   - **Hypothesis-driven research:** the intended studies aim to test the safety and working of the target treatment. The hypothesis is based on substantial scientific support and has clear and relevant outcome measures. Explorative research falls outside the scope of this call.
   - **Outcome measures** are validated, reliable and responsive, i.e. have a standardised scale, and aim to measure and predict the safety and efficacy of the therapeutic treatment for humans.
   - **Proof-of-concept:** the demonstration and realisation of a technology or idea for a new treatment and demonstration of its feasibility to be a new therapeutic treatment for humans using important human disease parameters.

7. **The research is preferably multidisciplinary: all disciplines needed for this research, this technology and disorder are directly involved.**
   - Multidisciplinary collaboration between different relevant disciplines/areas of expertise is a requirement for this programme. All of the disciplines needed for this research, this technology and disorder are directly involved. The Netherlands Brain Foundation also likes to see the involvement of relevant parties for the research such as private partners (including for example biotech or pharmaceutical companies) and care institutions (for example, peripheral hospitals, rehabilitation centres, nursing homes) because they can provide added value for the research. International collaboration is also welcome, but the project must be led by a Dutch institution. It is preferable for the partners to provide part of the co-financing for the project in question (in addition to the part of the subsidy from the Netherlands Brain Foundation).

2.2 Who can apply

This type of subsidy targets a practical aim: the development of new disease-modifying treatments. This type of subsidy is not bound to one particular person, and several applicants may submit a proposal together in the framework of multidisciplinary collaboration[5]. It is also possible to employ personnel with the money from the subsidy. They can be support personnel like technicians or supportive staff, or doctoral students, or postdocs/fellows.
To promote the feasibility and viability of the projects, conditions applying to the applicants have been formulated:

[5] For practical reasons, one main applicant is appointed as the coordinator who communicates with the Netherlands Brain Foundation. The main applicant is the one with final responsibility for the subsidy application.

Conditions for the applicant(s) and the research team:

- The applicants have a doctorate and a position at a Dutch research institution (university of applied sciences, academic university/ UMC) or research institute (RIVM, TNO, KNAW, NWO institute).
- Each person may be involved with at most two applications, but for only one of them as the main applicant. An exception to this rule is formed by project members with a supportive role like statisticians, ethicists, heads of GMP facilities and comparable positions.
- The applicants must be able to clearly demonstrate that they have the relevant experience with the topic and this type of study.
- A multidisciplinary partnership is preferred. All relevant disciplines for this study are involved, clinical and non-clinical researchers working together.
- A clinical study must be conducted in one or more Dutch knowledge or care institution(s).
- Participating companies must not receive a subsidy.
- Applications previously rejected by the Netherlands Brain Foundation may not be submitted again without revision. Resubmitted plans must have been substantially modified on the basis of the feedback from the earlier rejection.

2.3 Budget

In this round a total sum of €1.8 million is available. The budget to be requested for each project is at least €150,000 and at most €600,000. The applicants themselves determine the amount they will be requesting. The submitted plans must reflect the requested budget.

The subsidy covers in principle the researchers' salary and the cost of the research. You should reserve a small portion (suggested target is 5%) of the budget for the implementation and meetings of a users' committee. Finally, a bench fee of at most €5000 can be included for visits to conferences to disseminate the results. Applications for the purchase of equipment will not be honoured.

Budget

The budget provides insight into all income and expenses of the project. It is accompanied by a clarification of each item.

The calculation of the amount of a salary (including overhead expenses) is based on the Scientific Research Funding Agreement 2008 arranged with the VSNU and the addendum of ZonMw for UMCs:

- Salary table ZonMw-NFU 2017: https://www.zonmw.nl/fileadmin/documenten/Corporate/Berekening_G_posten_met_sal_peil_01-08-2017_tbv_NFU.pdf
- Salary table ZonMw-VSNU 2018: https://www.zonmw.nl/fileadmin/zonmw/documenten/Corporate/Subsidies/Berekening_G_posten_met_sal_peil_01-07-2018_def.pdf

Co-financing

Posts that do not fall within the budget requested from the Netherlands Brain Foundation, but are essential for the project, are stated as 'co-financing' in the budget. For cash sums from other financiers we ask you to add a written confirmation from the financier to the relevant budget post.

Co-financing can come from the applicant's own organisation, collaboration partners in academia, government, research organisations or corporate funding. Co-financing can be arranged by partnering with other funds or, for example, ZonMw. There is the condition that the Netherlands Brain Foundation must be the main financier.

If a subsidy or other financial contribution is requested from third parties for the same activities, the main applicant must state this in the application, along with the status of the evaluation of the other application(s).

If other financial sources for the project application are found at a later time, the Netherlands Brain Foundation must be informed of this as soon as possible, and a potential budget adjustment will be discussed.

NB: a substantial amendment of the originally submitted plan and budget or not informing the Netherlands Brain Foundation promptly can lead to the award/preliminary award being re-evaluated.

3 Procedure

3.1 Selection of project submissions

Project ideas (short preliminary application)

For this subsidy call, a pre-selection of project ideas will be done. Project ideas are at most 7 pages (A4) long and present the ideas for projects to the evaluation committee. The aim of the project idea step is selection of the most suitable and most promising ideas. A project idea also offers the possibility of including suggestions for the elaboration of the ideas into a subsidy application, such as recommendations of potential co-financiers and the involvement of users/end users. The project ideas also ensure that the number of subsidy applications to be handled will not be too big in relation to the available means. Submitted project ideas must meet the set conditions.

Members of the Science & Innovation Advisory Council (AWI) of the Netherlands Brain Foundation evaluate whether the project ideas meet the set conditions. The best project ideas will be asked to submit an elaborated subsidy application via our digital evaluation system.

Project applications

Elaborated project ideas (project applications) are evaluated by at least two external (possibly international) reviewers for quality, feasibility and relevance and by a lay expert panel for the relevance and usefulness of the result. Based on the reviewers' comments, a rebuttal can be formulated by the applicant. The result will be submitted for evaluation to the AWI.

Awarding

On the basis of the reviewers' evaluation, the lay experts' evaluation and the rebuttal, the AWI will submit a list of priorities to the MT of the Netherlands Brain Foundation. For an equal score for the various criteria, projects will be selected with a higher ranking in the priority listing based on communicative and fund-raising strength. The director of the Netherlands Brain Foundation takes a decision based on the final recommendation of the AWI.

Timeline

- Deadline for submitting project ideas: 1 April 2019 (12:00 noon)
- Invitation or rejection: 16 April 2019
- Deadline for submitting project application: 28 May 2019
- Awarding decision: mid-September 2019

3.2 Evaluation criteria for project submissions

Criteria for reviewers

Quality

Quality of the research and the researchers

- The project proposal is of good, very good or excellent quality.
- The applicant(s) has/have the right qualifications to complete the project properly.
- The research builds on a sound foundation/ rationale from the literature and experiments.

Relevance

Relevance for the research programme and work field of the Netherlands Brain Foundation

- It fulfils the needs of the target group, and representatives are involved in advising on and writing this application.
- It is expected to have a relevant positive effect (clinical) for the intended target group, and the intervention is expected to have a clear added value compared to the existing interventions.
- It focuses on a large target group or has a considerable positive effect on a small target group.
- It provides for taking the next step / safeguarding / implementing the results.

Feasibility

Feasibility of research and intended subsequent trajectory to clinical practice

- The project is feasible in terms of time, money and other means.
- The applicant and the project are well embedded in the relevant field.
- The implementation plan presents a realistic step-by-step plan of the trajectory from the study to the patient.

Criteria for lay experts

- Usefulness of the result for lay experts
- Involvement of lay experts in formulating the research question and study design.
- Societal and clinical relevance; relevance of the research and the intended intervention for the patient's needs.
- Planned involvement of lay experts in conducting the research.
- Burden of the study for lay experts
- Well-conceived implementation plan.
- The laymen's summary is short and concise and written in easily understood Dutch.

3.3 Conditions for conducting the project

This section contains information about the procedure followed by the Netherlands Brain Foundation when initiating and following up projects after awarding a subsidy.

The subsidy conditions are described in the contract. A draft version of it can be requested. Important aspects to keep in mind are:

- The project must start within 9 months after awarding the subsidy, otherwise the award lapses.
- A research project may only start after a copy of the approval from the Medical-Ethics Review Committee has been received by the Netherlands Brain Foundation. This application must be submitted promptly to the relevant agency.

Milestone planning
The Netherlands Brain Foundation wants project leaders to work with a milestone planning. This document forms the basis for collaboration between the researchers and the Netherlands Brain Foundation. A milestone planning:

- provides an overview for monitoring the progress with the project and the budget, allowing effective adjustment or guidance where necessary;
- gives insight into critical decision moments and interim results during the project, e.g. how different activities are linked;
- gives insight into the end result and the path to be followed by anyone implementing it and the office of the Netherlands Brain Foundation;
- contains significant moments for communication.

Implementation plan
The Netherlands Brain Foundation wants project leaders to work with an implementation plan, because this is a tool for bringing the project results closer to practical implementation. It has prepared a template for this. By working with an implementation plan, the chance of applying the project results is promoted. The Netherlands Brain Foundation does not want the results to be left on a shelf after the end of the research project, and it wants to avoid leaving the practitioner or patient waiting unnecessarily long for good results to be applied because certain processes were not put in motion.

After you have outlined the different target groups, investigate for each one:

- what benefit does implementation have for them?
- what will the implementation cost them?
- what do they need to know, think and do?
- how will you manage to achieve this?

By answering these questions, you can determine what actions are desirable or necessary for which target groups at what moment for a sound implementation of the project results.

Users' committee
The Netherlands Brain Foundation wants project leaders to set up a users' committee to improve the chance of applying the project results. Users are people who can apply the results of a project. They could be patients or informal carers, or professional users such as caregivers or researchers.

The Users' committee will meet several times during the course of the project. The frequency of these meetings will be set before the start of the project. Members of the Users' committee are meant to ensure that the implementation of the results is always kept in mind during the conduct of the project. They may also be asked to encourage the application of the results after the study. The Users' committee has an advisory role, not an evaluating role.

The study cannot be started until the above is recorded in documents which are approved and signed by the director of the Netherlands Brain Foundation and there is a signed version of the contract.

Open science
Research subsidised by the Netherlands Brain Foundation should produce results that are published in international scientific journals. The Netherlands Brain Foundation expects neutral and negative results of effectiveness studies to be published also (or the investigators can at least demonstrate they made efforts to get them published).

Communication
The applicant must be prepared in agreement with the Netherlands Brain Foundation to communicate about the results via other channels and raise funds together for the Netherlands Brain Foundation. The aim is to increase the societal impact by spreading the results, science education (making scientific insights and enthusiasm for science palpable for a broader public), fund-raising, accountability and transparency (explaining to target groups how the money is being spent, and what the intended result is).

4 Appendices

4.1 Examples of research into Disease-Modifying Treatments

Example 1

Complement C5 antibodies to reduce brain damage after a subarachnoid brain haemorrhage

A subarachnoid haemorrhage is a type of bleeding in the brain with a poor prognosis: 1/3 of the patients die, and 1/3 suffer permanent sequelae. Half of the patients are younger than 50 years old. After the haemorrhage an inflammatory reaction develops between the brain membranes. This inflammatory reaction is not the consequence of a bacterial or viral infection, but of blood appearing between the brain membranes. The stronger the inflammatory reaction, the severer the brain damage.

Earlier research with animal models revealed that treatment with certain inflammation inhibitors ('C5 antibodies' or 'eculizumab') led to a >40% reduction in brain damage. The laboratory results are so promising that C5 antibodies are being investigated as a potential new treatment for patients with a subarachnoid haemorrhage. A reduction in brain damage means a better prognosis for the patient and a better quality of life.

Why is this a disease-modifying treatment?

The inflammatory reaction leads to brain damage. By inhibiting the inflammatory reaction, the disease mechanism is addressed and thus the course of the disease is permanently changed.
Eculizumab is an existing medicine for other disorders than subarachnoid haemorrhage, and thus, this is a case of 're-purposing'.

Example 2

SMArtphone-based monitoring and modification of cognitions against Recurring Depression (SMARD)

The recurrence of depressive episodes is a major problem suffered by 50-75% of people with a depression. Recurrences cause a lot of suffering, loss of social roles, lack of productivity and high costs, along with the risk of suicide and a chronic course. The great challenge is to recognise imminent recurrent episodes early on. Patients are often only seen once the depressive episode has fully developed, when the prognosis is more unfavourable. Prevention of the recurrence of depressive episodes is extremely important to avoid these negative consequences.

In this project a new recurrence-prevention programme is being developed. The researchers want to offer a form of cognitive and positive attention training alongside PCT (via a Smartphone app). With a background app (BeHapp), they can monitor to see if they can detect early signals of an imminent recurrence earlier (instead of early warning plans). This is done on an individual basis, compared to a stable period before the symptoms recur. When a relapse is suspected, they explore further whether this is/will become an actual depression using diary measurements (EMA), after which the cognitive and attention training can be initiated again if necessary. With this intervention they want to reduce recurrences by 30% in 1.5 years.

Why is this a disease-modifying treatment?
The recurrence of depressive periods is a progressive disease course. By preventing relapses, the progressive course is delayed.

4.2 Tips for writing for lay experts

When elaborating a project idea, we ask you also to fill in a Dutch application for lay experts (patients and their informal carers). It will be evaluated by a panel of lay experts. It is important to ensure that they understand your project proposal so they can make a proper judgement of its feasibility and relevance. Answer the questions concisely in language that is easy to understand. Here are some useful tips:

- **Use active sentences (subject, finite verb, remainder):** '*We want to investigate/ our research group is going to examine the effect of..'* instead of *'The effect of xxx will be investigated using…'*
- **Use short sentences**: Make the sentences as short as possible. Try to keep to an average sentence length of 10 to 15 words.
- **Avoid inserted phrases: '***The protein plays a prominent role in frontotemporal dementia, and is also involved in Alzheimer's disease'* instead of **'***The protein, that is also involved in Alzheimer's disease, plays a prominent role in frontotemporal dementia.'*
- **Avoid text in parentheses: '***Almost all cases of dementia arising before 65 years of age are caused by hereditary factors'* instead of *'Research has revealed that (almost) all cases of dementia at a young age (<65 years) are caused by hereditary factors.'*
- **Explain medical/scientific terms in laymen's language:** like *'protein'* instead of *'Amyloid-Beta-42'*, *'mental faculties'* instead of '*cognition', 'link'* instead of *'correlation'* and *'has an effect'* instead of *'statistically significant'*.
- **Use visual language or recognisable examples:** *'This process is comparable to a chain letter with which the sender (APP) sends one message to the recipient (tau) through a series of letters (message proteins).'*
- **Do not explain the method or results in too much depth:** *Do not explain how it works exactly in chemical, physical or statistical terms. Explain the method briefly: we do 'this' test to show 'that'*.
- **Finally:** Let someone who is not scientifically trained have a look at the completed application form: do they understand it?

4.3 Tips on recruiting participants for brain research

Hersenonderzoek.nl

Are you looking for patients for a clinical study? Or are you looking for healthy people for an online questionnaire? Hersenonderzoek.nl will bring you in contact with suitable participants for your study. Hersenonderzoek.nl is an online register with more than 15,000 people who have stated that they are interested in participating in brain research. As an academic brain researcher, you can call on its services free of charge. A wide range of studies is welcome: from questionnaires and online tests to intervention studies and observational research with clinical visits. If you would like to learn more, please contact info@hersenonderzoek.nl

Link:
https://hersenonderzoek.nl/voor-onderzoekers/