Subsidy programme Finding a Cure

Version 3

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1 Mission of the Brain Foundation Netherlands

The Brain Foundation Netherlands is dedicated to doing everything for healthy brains for everyone. That is our goal. For over 30 years we have been finding links between different types of brain disorders, because whatever you learn about one disorder can be significant for another one. To realise our goal, we work together with scientists, healthcare professionals, lay experts, patients and the public. Together we can find solutions to keep the brain healthy, treat brain disorders better, and help people with a brain disorder to participate in society. The Brain Foundation Netherlands has elaborated these goals in its impact agenda.

1.1 Impact agenda

Prevention
Prevention is better than cure. A healthy lifestyle can lower the risk of a brain disorder and delay the consequences of ageing and brain diseases. Together with professionals the Brain Foundation Netherlands is working on initiatives to stimulate sustainable healthy brain behaviour in terms of sleep and exercise.

- Sleep: by improving their sleep behaviour, people improve the quality of their sleep
- Exercise: by exercising more

Cure
More than 4 million people in the Netherlands suffer from a brain disorder. Most of the diseases do not have a solution. Together with professionals the Brain Foundation Netherlands is committed to researching and finding innovations that lead to treatments that cure, stop or delay brain disorders or improve the quality of life for people with a brain disorder.

- Finding a cure: delay, stop or cure brain disorders
- Quality of life: considerably improve symptoms and limitations that greatly impact daily life
- More applicable results from research: develop human measurement models and optimally use data

Participation
We support people to get the most out of their life. We are promoting a society that embraces mental diversity and bans stigmas. Together with professionals the Brain Foundation Netherlands works on initiatives to ensure that people with a brain disorder can actually participate in work, exercise and leisure activities.

- Work: more people with a brain disorder find and/or retain suitable work
- Exercise: more people with a brain disorder participate in regular sport and exercise activities
- Leisure activities: more people with a brain disorder participate in the same activities as people without a brain disorder

2 Aim of the subsidy programme

This subsidy programme falls under the *Cure* pillar of the Brain Foundation Netherlands's impact agenda under the theme *Finding a Cure.* It focuses on the development and improvement of treatments that delay, stop or even cure brain disorders. The target group's need and implementation of the results in the healthcare practice are the main points of attention.
The treatments that will ultimately be developed can be pharmacological, technological or psychological in nature and affect the disease process directly. This means that the proposed treatment changes how the disorder develops over time (in this subsidy programme we call them 'disease-modifying' treatments). This differs from symptomatic treatments that ameliorate the symptoms of a disorder, but do not address the underlying cause. The latter type of treatment will not be considered for a subsidy in this programme.

Rare brain disorders
The Brain Foundation Netherlands feels it is important that there is a treatment for every brain disorder that slows, stops or even cures it, regardless of whether the brain disorder is common or rare. That is why we encourage applicants who are working on the development of a therapy for a rare disorder to submit a subsidy application.

Improved accessibility of the brain
In addition, the accessibility of the brain presents a challenge for developing an effective disease-modifying treatment for many brain disorders. We also encourage applicants working on improving the accessibility for a more effective treatment to submit a subsidy application.

2.1 Criteria

The subsidy application must meet the following criteria. These criteria are divided into relevance and substantive criteria. The criteria are elaborated in section 2.2, and the appendices contain several examples of research projects.

2.1.1 Relevance criteria

1) Needs-driven. The aim is to meet a need of the target group. The need guides the research.
2) Application-oriented. Results of the project are facilitated to get a step closer to application in the healthcare practice.

2.1.2 Substantive criteria

3) Brain disorders. It concerns one or more neurological or psychiatric brain disorders.
4) Disease modification. It concerns developing treatment options that can delay, stop or even cure brain disorders and/or improving them further. For this, there is an identified target point for which scientific evidence has been demonstrated.
5) Development stage. It concerns preclinical, translational or clinical research.
6) People-oriented. The research preferably targets patients, patient materials, or models, data or systems derived from them.
7)

2.2 Clarification of the criteria

2.2.1 Relevance criteria

(1) Needs-driven: the subsidy application is based on one of the target group's needs. The chosen need guides the research.

If there is a patient and/or next of kin association that has already published a knowledge agenda with research priorities, wishes, do's and don'ts – methodically collected from their members – then the target group's need can become clear from the description of how the project idea clearly ties in with it, but in the absence of a link, the need can be judged as absent.

The target group is involved in the preparation of the subsidy application and during the conduct of the study.
Target group is defined as lay experts ((ex)-patients and/or their loved ones).
When preparing the subsidy application, this target group is involved in two aspects: (1) when coming up with the project idea and (2) later in the project application concerning the feasibility of the study. Other conditions apply, depending on the stage that the study is in.

Project idea

- For both clinical and preclinical research, patient and/or next of kin associations are sought (both whether they exist and what kind of association are to be clarified), partly to discover if they have published a relevant knowledge agenda. If one exists (not always the case), then how this information has been incorporated in the project idea must be clarified.
- For *clinical research* the project must have reached at least level 3 of the participation ladder (see fig. 1). At least three patients/loved ones (the primary target group) have been asked for advice to determine the need and arrive at the core of the problem. The proposed project idea has been explained to and tested with the target group. The involved patients/loved ones are lay experts. When gathering advice the researchers listen to solicited and unsolicited advice from the target group. Researchers must justify to the advisors and the Brain Foundation Netherlands why they followed this advice or not and what their rationale was for doing so. This form must be signed for agreement by all of the lay experts and submitted as a separate document with the project idea form.
- For *preclinical research* the project must have reached at least level 2 of the participation ladder (see fig. 1). The primary target group has already been approached about their need and what the problem is. The proposed project idea builds on the result, and it has been explained to the target group what this involves and what it means for them. During a consultation, several patients/loved ones are involved. For example, a presentation is given to the members of a patient organisation. Proof of this must be supplied as an attachment along with the project idea form when submitting.

Advising & Consulting
The similarity between advising and consulting is that both activities involve actively soliciting input from the target group. The difference between these two activities is that with "advising," one is obliged to provide feedback to the advisors on what has/haven't been adopted and the reasons for this. All of this is recorded in the report. With consulting, feedback to the target group is not mandatory, but we highly recommend it.

Project application

- For clinical research, lay experts are involved and requested for advice about the feasibility of the study for the participants. This could cover the tolerance level of the

participants, compensation for participation, the inclusion criteria, the recruitment of the participants, the communication with the participants, and ethical issues.
- For preclinical research, lay experts are involved if the research concerns human subjects (e.g. sampling tissue for examination in the lab). They are asked for advice about the feasibility of the study for the participants.

For more information:
Material for discussion, tips to give target groups a voice in projects (zonmw.nl)
Designing patient participation (participatiekompas.nl)
Conducting inclusive research: suggestions, tips and advice (pharos.nl)
Inclusive co-creation: how do you work together with the people concerned? (pharos.nl)

(2) Application-oriented: the project has been designed in such a way that the results achieved can advance their ultimate application in the healthcare practice a step further. Relevant parties are involved for successful continuation. This is elaborated in the detailed application.

Multidisciplinary collaboration
Multidisciplinary collaboration is essential. Various conditions have been imposed on this collaboration, depending on the stage the research is already in.
- Clinical researchers can involve both preclinical partners and relevant partners further along in the healthcare chain, according to what is needed to bring the results closer to application in the healthcare practice.
- Preclinical researchers are expected to collaborate with clinical researchers. A bridge must be created between preclinical and clinical research, with knowledge from the practice being used in the lab and knowledge from the lab gaining access to the practice. That is why a clinical researcher is involved as a co-applicant.

Involving other stakeholders
Along with lay experts, other relevant parties can be involved if they contribute to the advancement of the results. They are asked for advice in the development phase to aid the essential preparations for the next steps. This could be healthcare professionals from different centres, clinicians, healthcare insurers, regulatory experts or business developers.

Implementation and valorisation are the starting points here, with the focus lying on creating societal and/or economic added value. Societal valorisation means implementation strategies to ensure a patient is given the optimal treatment in healthcare, for example. Economic valorisation confirms that the follow-up research does actually have a chance of succeeding in creating new products and services that are relevant for the patient and the healthcare practice.

If you expect that the research results are likely to have a market application in the future, we strongly advise you to approach the Knowledge transfer office/Technology transfer office (KTO/TTO) of your organisation early on. In case of a collaboration with companies and/or large consortia, their advice is important to take the right steps promptly regarding Intellectual Property. IP agreements are made in advance. For an overview of KTO's & TTO's, see this link. It is strongly recommended to involve an implementation expert or valorisation expert in the application.

To augment the feasibility of a project, the Brain Foundation Netherlands has made the creation of a users' committee mandatory for all projects; this is a group of different experts meeting to provide input for the project, monitor the progress of the project, discuss any problems arising, and make plans for the follow-up. A users' committee aims to promote the chance of transfer and possible application of the project results. Relevant experts are added to the users' committee to provide advice. The detailed application must contain the composition of the users' committee when submitted.

- For clinical subsidy applications, it is mandatory to include at least two lay experts in the users' committee.

Participation ladder

1. *Informing:* researchers explain to the target group what they intend to research and what this means for the target group;
2. *Consulting:* researchers obtain experiential knowledge from the target group but are not obliged to use this information and do not have to clarify this;
3. *Advising:* researchers listen to the solicited and unsolicited advice from the target group. Researchers are obliged to justify to the advisors and the Brain Foundation Netherlands why they have incorporated this advice (or not) and the accompanying rationale;
4. *Co-producing:* the target group contributes ideas to the development of the research and collaborates on the conduct of the study;
5. *Deciding together:* the target group is part of the project team and helps decide on the content of the study. The target group also bears responsibility for the project.

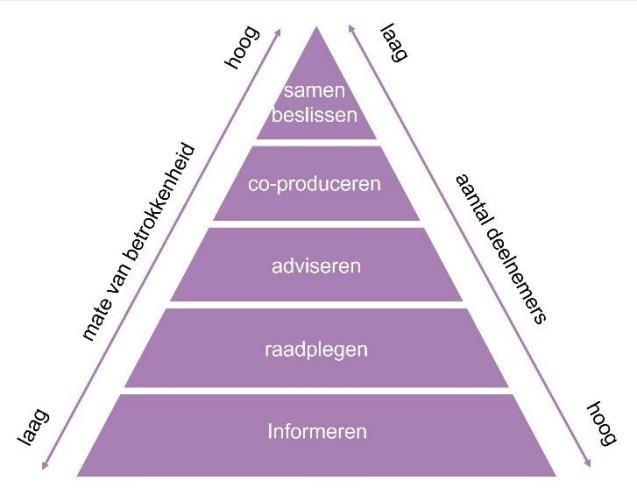

Figure 1: the participation ladder. The extent to which the target groups are involved in the development of the research proposal, the conduct of the study, the evaluation, dissemination and implementation of the research results.

2.2.2 Substantive criteria

1) Brain disorders
   - The Brain Foundation Netherlands focusses exclusively on the brain: that part of the central nervous system located inside the skull. This is defined as including the meninges, pituitary and pineal glands.
   - The spinal cord and the eyes are not included, nor is the skull itself. Neurological disorders with a primary cause in the spinal cord or peripheral nervous system and

muscle disorders (primarily) fall outside the scope of the Brain Foundation Netherlands.
- We advise you to contact us early on if you are not sure whether the disorder on which your project idea is based falls within the scope of the Brain Foundation Netherlands.

2) Disease modification
- The aim is to work towards a disease-modifying treatment.
- These are treatments that tackle the cause or the course of the disorder instead of its manifestations. This means delaying, stopping, promoting recovery from or curing brain disorders. The following does not include treating symptoms without intervening in the underlying condition and without altering the course of the disease.
- The underlying biological, psychological or physiological focus of the ultimate treatment is identified. This means there is plausible scientific support for it. This rationale can be clearly explained and demonstrated.

3) Development stage
- This is a subsidy application for research in the preclinical, translational or clinical phase.
- Support must be offered for why this type of research is still necessary for realising a disease-modifying treatment.
- Fundamental research is not within the scope of this subsidy program. The main difference between fundamental research and preclinical research is that fundamental research aims to generate new knowledge and understanding of a certain phenomenon, while preclinical research focuses on testing potential treatments before they are tested on humans. Some examples include in vitro studies, animal studies, pharmacological studies, toxicological studies, safety studies, and biocompatibility studies.

4) People-oriented
- The research preferably concerns patients, patient materials, or models, data or systems derived from them.
- If animal experimental research forms part of the subsidy application, there must be an especially strong clarification of its link to the human situation and contribution to the objective of this subsidy programme. This type of research is only accepted if it is an essential step in the development of a treatment option.

3 Guidelines for applicants

3.1 Who can apply?

Subsidies are not bound to one particular person but are granted to knowledge institutions. Several applicants may submit a proposal together. The following conditions must be met:

- The coordinator should have a permanent position at a Dutch knowledge institution. Dutch knowledge institutions are defined by the Brain Foundation Netherlands as universities, academic hospitals and universities of applied science based in the Netherlands.
- Co-applicants do not have to meet this condition and could, for example, work in a healthcare institution or company or join as a layperson.
- Only one time can be applied as a coordinator, a second time can be applied as co-applicant. In total two times can be applied as co-applicant.
- It must involve a multidisciplinary collaboration. All relevant parties for the project are involved.
- Participating companies cannot receive a subsidy, except for material expenses.
- Applications previously rejected by the Brain Foundation Netherlands may not be submitted again without revision. Resubmitted plans must have been substantially modified on the basis of the feedback from the earlier rejection. Project ideas may be resubmitted, but it must be clear that substantial improvements have been made.

3.2 Budget

The budget to be requested for each project lies between €300,000 and €600,000. The applicants themselves determine the amount they will be requesting. The submitted plans must reflect the requested budget.
When there are more eligible project applications than available financial means, the Brain Foundation Netherlands can consider together with the applicants to initiate fund-raising actions to obtain more funding. No guarantees can be given for this.

3.3 Budget plan

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

These costs can be divided into the following posts:

- personnel;
- personal bench fee;
- material, equipment, consumables (specified);
- implementation costs (specified).

Personnel

It is possible to use the subsidy to pay both scientific and non-scientific staff. This can include support personnel like technical/ support staff, or healthcare personnel who contribute directly to the conduct of the study.

Regarding the personnel costs, a compensation is made available on the basis of this agreement for the duration of the study to appoint researchers and/or support personnel. When calculating the salary costs for scientific personnel, they will be assumed to be based on the agreements made in the Scientific Research Funding Agreement 2008 arranged with the Universities of the Netherlands (UvN) and the addendum of ZonMw for UMCs. A distinction is made between UvN institutions (e.g. universities) and NFU institutions (e.g. UMCs).

The following functions apply to UvN institutions: Doctoral candidate, Senior scientific employee, Non-scientific personnel MBO (basic vocational), Non-scientific personnel HBO (advanced vocational) and Non-scientific personnel Academic.

- Salary table ZonMw – UvN 2022
  Berekening G posten met sal peil 01-07-2022 v2.xlsx (zonmw.nl)

The following functions apply to NFU institutions: Doctoral candidate, PostDoc, (Physician)researcher, Non-scientific employee MBO (basic vocational), Non-scientific personnel HBO (advanced vocational) and Non-scientific personnel Academic.

- Salary table ZonMw – NFU 2022

(if newer salary scales are available, they may be applied)

Regarding the compensation of other functions, it is assumed to be based on the salary component of the actual level on the salary scale, if the necessity of the appointment for the project is clearly justified in the project application and supported by the reviewers. These personnel costs include:

- The actual salary costs per year of the personnel directly involved in implementing the project; for each function specify the salary scale, the level on the salary scale and the number of working hours factor, and calculate 12 times the gross monthly salary;
- A 40% surcharge on the salary costs to cover additional personnel costs. The surcharge discounts the following: social security contributions, year-end bonus, 13th month, holiday pay, tide-over allowance, disease risk, advertisement costs and other recruitment costs, commuting costs, parental leave and benefits, costs of other leave, training costs, support personnel matters, bonuses, business trips within the country, death benefit, social activities, removal and installation costs, reimbursement of disease costs and so-called end-of-project costs.

The rule applicable for all functions if the level on the salary scale of the employee in question is still undecided is that the salary costs will be calculated based on the middle of the scale. If the level on the salary scale is known, that is taken for the calculation.

The project budget plan should take into account an annual increase in the salaries with a maximum of one increase in level and a correction for inflation of 5% per year. When settling accounts, the actual costs incurred will be taken into account, and consideration given to the maximum subsidy amount available. We can discuss any significant deviations due to the unpredictable effect of inflation.

Personal bench fee
For doctoral candidates (assuming a 4-year posting) and senior scientific staff (assuming a 2-year posting), a personal bench fee of € 5,000 for the whole research period is provided. If the duration of the posting is shorter than 4 or 2 years, respectively, the bench fee will be awarded proportionally.

The bench fee is intended for doctorate costs and conference visits (including foreign ones). The bench fee is intended for the person carrying out the project, but is provided to the project leader. The person implementing the project is thus entitled to it. What the bench fee is used for should be discussed by the project leader and the project implementer. For doctoral candidates compensation for the thesis printing costs is included in the bench fee. This means that doctoral candidates working on this type of project cannot apply for separate compensation for thesis printing costs. However, the bench fee can go towards any use designated by the project leader-project implementer.

Material, Equipment, Consumables (specified)
The material costs are reimbursed according to the amounts reserved in the subsidy grant. This concerns only the direct material costs that had been requested and approved. The costs for the infrastructure (accommodation, office automation) and overhead are not reimbursed.

Implementation costs (specified)
You should reserve part of the budget for the additional requirements that we set when implementing the project (the rule of thumb for this is a maximum of 5%). These costs should be proportional.
This concerns:

- MEC/CCD (see Positive decision of MEC/CDD section)
- implementation/securing results;
- involving lay experts and the associated expenses reimbursement;
- meetings of one (or more) users' committee(s);
- consulting regulators.

What is not reimbursed?

- requests to purchase equipment will not be honoured;
- travel and accommodation expenses for conferences;
- training costs.

Positive decision of MEC/CCD
Certain projects require a positive decision from a competent medical-ethics committee (MEC) or a project licence from the Central Authority for Scientific Procedures on Animals (CCD). Questions about this can be found in the project application form. It is sensible for applicants to check whether they require a positive decision. According to our subsidy stipulations, a project that requires one may not start including study subjects or laboratory animals without it. To request the MEC-declaration or a CCD-licence, you can budget a maximum of € 2500. This request must be supported by the applicable fees. No costs can be included for a re-evaluation, you must pay those yourself.

More information about the MEC is available from the Central Committee on Research Involving Human Subjects (CCMO). Information about licences for animal testing can be found on the CCD website.

3.4 Co-financing

Posts that do not fall within the budget requested from the Brain Foundation Netherlands, but are essential for the project, are stated as 'Financing other' in the budget plan. We ask you to add a written confirmation from the co-financier of contributions from co-financiers (in-kind/in cash) to the appropriate budget plan post. Co-financing is not mandatory if the budget plan does not require it.

Co-financing can come from one of the collaboration partners or corporate funding. Co-financing can also be arranged by partnering with other funds or ZonMW, for example. The associated condition is that the Brain Foundation Netherlands remains the principal financier and approves the co-financing. Financiers with goals that conflict with those of the Brain Foundation Netherlands or detract from the image of the Brain Foundation Netherlands are excluded.

If a subsidy or other financial contribution is requested from third parties for the same activities, the coordinator must state this in the project application, along with the status of the evaluation of the project application or request.

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

NB: substantial changes to the originally submitted plan and budget plan or not informing the Brain Foundation Netherlands promptly can lead to the award (preliminary) being re-evaluated.

4. Procedure

4.1 Webinar

We are organising a webinar to provide more information about this subsidy programme, in which the round will be explained and questions can be asked. For the date and time of the webinar, you can consult the website of the Hersenstichting or subscribe to the subsidy newsletter to stay informed.

4.2 Project idea

For this call for subsidy applications, a pre-selection will be made using a pre-registration form for the submission of project ideas (see pre-registration of project idea at the bottom of the webpage). These project ideas will be presented to the evaluation committee, consisting of members of the Science and Innovation Advisory Council (AWI) and members of the Advisory Council of Lay experts (AvE).

The aim of the project idea step is to select the most relevant, suitable and promising ideas. Submitted project ideas must meet the set criteria and conditions.

Members of the AWI and the AvE of the Brain Foundation Netherlands evaluate the project ideas for relevance and whether they meet the set conditions for project applications. The applicants with the most promising project ideas are invited to submit a project application through our digital evaluation system.

4.3 Project application

Project applications are assessed by at least two external (international) content reviewers for quality, feasibility and relevance and by lay experts for their relevance and usefulness for the target group. The lay experts fill in a lay experts form that is written in generally understandable Dutch. The applicant can formulate a rebuttal to the reviewers' and lay experts' comments. All comments and the rebuttal will be submitted to the AWI and the AvE for their recommendation.

During this writing period, the Brain Foundation offers the EATRIS mentorship program.

EATRIS mentorship program
EATRIS is a European non-profit organization that focuses on improving and optimizing the preclinical and early clinical development of drugs, vaccines, and diagnostics, and overcoming barriers to health innovation.

During the project proposal writing process, EATRIS organizes digital sessions in which grant applicants receive personal advice from experts on which activities can be undertaken in the project to increase the chances that patients will ultimately benefit from the results achieved. This includes, for example, regulatory and IP strategies.

Participation in the mentorship program is mandatory. The Brain Foundation provides this advice to the research groups to increase the chances of results finding their way to the patient. In the project proposal, the grant applicant describes the advice and which steps the grant applicant has taken based on the advice.

4.4 Awarding

Based on the advice of the external reviewers and lay experts and the rebuttal, the AWI and the AvE will produce a final recommendation for the Board of the Brain Foundation Netherlands. The Board will then make a decision.

No appeal is permitted against the outcome in this procedure.

4.5 Timeline

Project ideas can be submitted all year round at:
aanvraag [at] hersenstichting.nl. A selection takes place twice a year, and the selected applicants are invited to submit a detailed project application. Please visit the website for the dates.

5. Appendices

5.1 Examples of research projects

Example 1
SCA7 a showcase for personalised RNA therapy development in the Netherlands

SCA7 is an extremely rare, untreatable neurological disorder. The disease leads to progressive immobility, loss of independence and premature death. The risk that this disorder will be passed on to children is 50%. The brain damage with SCA7 occurs primarily in the cerebellum and brainstem, but other parts of the brain and the eyes are affected. The cause of this brain damage is an error in the ataxine-7 protein. The altered ataxine-7 protein damages nerve cells, among other actions.

This project examines a new treatment that focuses primarily on the brain with the aim to prevent the production of the harmful ataxine-7 protein. This can limit the brain damage or even prevent it. The researchers want to realise this by preventing the production of the harmful ataxine-7 protein, by binding an 'antisense oligonucleotide' (AON) to the ataxine-7 RNA. RNA is the messenger molecule that ensures that the genetic code in the DNA is translated into a protein. The AON alters the messenger molecule so the harmful part of the ataxine-7 protein is no longer produced. This stops the disease progression.

In this project the first development steps are taken, which are essential to test this treatment in patients. In the lab they are going to test the different AONs on human cells cultured from the urine of patients. The natural course of the brain disorder in patients will also be charted.

Example 2
SMArtphone-based monitoring and modification of cognitions against Recurring Depression (SMARD)

The recurrence of depressive episodes (relapse) is a major problem suffered by 50-75% of people with a depression. Recurrences cause a lot of suffering, loss of social roles, loss 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. The recurrence of depressive episodes is a progressive disease course. By preventing recurrences, the progressive course is delayed.

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 sooner (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.

Example 3
Complement Inhibition: attacking inflammation after a traumatic brain injury

After a traumatic brain injury, the brain undergoes an inflammatory reaction in the first few days after the accident. This inflammation in the brain tissue leads to further damage and is difficult to treat. The pressure in the brain builds up because the inflammatory reaction leads to swelling. This swelling is associated with an invasion of immune cells in the brain, which disrupts the activity of support cells in the brain and leads to nerve cells dying off. The consequences of this neuroinflammation are often dramatic for the patient in the short and long term. Research has shown that the complement system, an innate part of the immune system, plays a critical role in the regulation of the inflammatory reaction.

Complement inhibition in the brain can be achieved by administering an inhibitor in the blood. In this project, the researchers want to realise complement inhibition by administering Cinryze in a randomised clinical trial. They expect that this treatment with Cinryze will inhibit the inflammation of the brain. They are using a complement inhibitor for this purpose that has already been approved as a medicine for another disease. Much is already known about this substance, and thus we can clearly weigh the risks of using this substance against the expected positive effects. This is a repurposing trial.

By inhibiting the inflammatory reaction, the disease mechanism is being affected and thus the course of the disease changed.