October 2021

Research programme ME/CFS

ZonMw

Programme text

Research programme ME/CFS

October 2021

ZonMw

Colophon

ZonMw stimulates health research and care innovation. Progress requires research and development. ZonMw funds health research and also facilitates the use of the knowledge developed so that care and health improve.

ZonMw's principal commissioners are the Dutch Ministry of Health, Welfare and Sport (VWS) and Netherlands Organisation for Scientific Research (NWO)

For more information about the ME/CFS programme, please contact the secretariat via email mecvs@zonmw.nl or phone +31 70 515 0382.

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Summary

The myalgic encephalomyelitis/chronic fatigue syndrome(ME/CFS) programme encourages the (further) development, use, embedding and utilisation of knowledge about ME/CFS. The aim is to improve the health and societal position of ME/CFS patients. By doing this, the programme realises the ME/CFS research agenda that was formulated by ZonMw in 2020. For this research agenda, interested parties drew up a list of research subjects and expressed the desire to build up a research infrastructure for ME/CFS in the Netherlands.

In the ME/CFS programme, projects and subjects from the ME/CFS research agenda will be funded within the programme lines 'Biomedical research' and 'Improving practice'. Through these programme lines, the programme wants to achieve three objectives:

1. Generating biomedical knowledge about the aetiology of ME/CFS; the diagnosis ME/CFS (and possible meaningful subcategories) and the treatment of ME/CFS;
2. Stimulating the use of the developed knowledge in practice;
3. Developing a sustainable knowledge infrastructure for ME/CFS with the aim of improving the collaboration between knowledge institutes, patients and practice.

An important part of the programme will be the building up of a Dutch ME/CFS biobank and patient registration. The individual studies in the programme will feed this biobank and patient registration. For the inclusion of patients in these studies, use must be made of a set of criteria for ME/CFS. However, different sets of criteria exist for ME/CFS, which each describe ME/CFS in a slightly different way. As a result, an important point of attention during the assessment of projects in the programme will be which set(s) of criteria the studies use, and why. Within the programme, a lot of attention will also be paid to how the data from different projects will be uniformly and unequivocally brought together in the biobank and patient registration. ZonMw will develop activities to stimulate this so-called 'harmonisation' of data and materials.

Collaboration is vital for the success of the programme. This concerns collaboration between the different research disciplines involved in ME/CFS, such as immunology, microbiology, neurology, cell biology, genetics, (epi)genetics and cardiology. It also concerns international collaboration because outside of the Netherlands, research lines into ME/CFS have been developed that Dutch research must connect with. In addition, this concerns collaboration between various professional groups such as researchers, healthcare practitioners, policymakers and education as well. They must jointly make use of the knowledge that the research programme produces and also draw up follow-up questions for new research into ME/CFS. Ultimately, it concerns the collaboration with patients. Patients will be enabled in various ways to contribute to the programme and the research. Only through this broad collaboration can the programme achieve impact; a genuinely improved situation for ME/CFS patients.

The research programme ME/CFS has a budget of 28.5 million euros and a duration of 10 years. It is therefore a long-term programme in a new and rapidly developing research field. Consequently, the programme needs to be kept flexible. This means that projects will not only be monitored in the standard manner but that after 5 years, there will be a large interim evaluation of the entire programme. In this way, the interim evaluation will provide the opportunity to adjust the programme in good time, based on all of the signals that reach ZonMw. All of the adjustments will be submitted to the commissioning body of the programme, the Ministry of Health, Welfare and Sport.

1 Introduction

1.1 Impetus

On 29 October 2013, 'Groep ME-DenHaag' submitted the citizen initiative 'Recognise ME' to the Dutch House of Representatives. In the petition, the 56,000 signatories called for more biomedical research into the causes of the disease myalgic encephalomyelitis (ME). They noted that ME was not adequately diagnosed and treated, and that it was incorrectly classified as a psychosomatic disorder. In response to the petition, the Health Council of the Netherlands was asked to investigate the current state of scientific knowledge concerning ME. The report was published on 19 March 2018.[1]

In scientific practice, the name of the disease is frequently abbreviated as 'ME/CFS'. As insight into the pathophysiology of the disease is missing, the Health Council of the Netherlands advised adopting this name too. The Council was inclined to believe that various diseases may be covered by this umbrella term. That being the case, it advised to invest in research into ME/CFS by means of a long-term and substantial research programme. In line with this advice, the Minister for Medical Care and Sport requested ZonMw to develop a ME/CFS research agenda for which future biomedical research subjects are formulated. This research agenda was presented to the Minister in December 2020 and served as the next step towards establishing a research programme in this area. The programme proposal presented in this document is an elaboration of the research agenda ME/CFS into a research programme.

1.2 Commission

On 25 May 2021, ZonMw received the request from the directorate Public Health of the Ministry of Health, Welfare and Sport to elaborate a proposal for a research programme into ME/CFS (see commissioning letter, Annex A). The request was for a biomedical research programme with a duration of 10 years that covers fundamental, epidemiological and clinical research. The commission also requested attention for the dissemination of new and existing knowledge about ME/CFS, initiating collaboration between researchers, healthcare practitioners, patients and patient representatives, communication about the programme and the creation of support for it. These needs are satisfied in a separate programme line for Improving practice. ZonMw will contribute to the building up and maintenance of a sustainable knowledge infrastructure via this programme. Patients and their representatives will make a constructive contribution to this.

1.3 Realisation and programme outline

The ZonMw ME/CFS research agenda provided the golden thread for shaping the programme proposal. The terminology from the programme proposal corresponds as much as possible with the text from this research agenda. To translate the ME/CFS research agenda into a programme proposal, ZonMw obtained both internal and external expertise in areas such as data management and patient cohorts, internationalisation and patient participation. The programme proposal was also submitted to several experts within and outside of ZonMw, including the intended members of the programme committee ME/CFS and the intended members of the guidance committee ME/CFS. This current programme proposal was realised on the basis of this information.

The programme proposal first of all presents the aim (Chapter 2) and content (Chapter 3) of the programme ME/CFS. Next, the field in which the programme operates is described (Chapter 4). After that, the organisation of the programme is detailed in the chapters Knowledge use and implementation (Chapter 5), Management and organisation (Chapter 6), Monitoring and evaluation (Chapter 7) and Budget (Chapter 8).

[1] Health Council of the Netherlands; ME/CFS. The Hague: Health Council of the Netherlands, 2018; publication number 2018/07.

2 Aim and structure of the programme

2.1 Mission, basic premises, objectives, results

Mission
The mission of the programme ME/CFS is to improve the health and societal position of ME/CFS patients by means of (further) developing, embedding and using scientific knowledge.

Basic premises
Important basic premises of the programme are:
- The programme must (further) develop biomedical knowledge in the Netherlands that connects with the knowledge development that is already taking place internationally;
- Experiential experts and organisations from the field possess a lot of important experiential knowledge for the development of new biomedical knowledge about ME/CFS;
- International, transdisciplinary collaboration is important for the development of the knowledge infrastructure for research into ME/CFS in the Netherlands;
- Knowledge (including underlying data) must be accessible for a broad public, i.e. researchers, patients, policymakers and people from the field; nationally and internationally;
- Right from the start of the programme, interested parties must be encouraged to realise activities that facilitate the use of knowledge that already exists or is developed in the programme.

Objectives
The objectives of the programme are:
- Generating biomedical knowledge about the development of ME/CFS, the diagnosis ME/CFS (and possible significant subcategories) in the treatment of ME/CFS;
- Stimulating the use of the knowledge developed in practice;
- Developing a sustainable and dynamic ME/CFS knowledge infrastructure with the aim of improving the collaboration between knowledge institutes and everyday practice.

Results
With the programme we expect to deliver the following results:
- Biomedical knowledge about the development of ME/CFS, the diagnosis ME/CFS and the treatment of ME/CFS. This knowledge connects with international developments and is realised in collaboration with patients;
- Patients, researchers, policymakers, healthcare practitioners, teachers in secondary and higher education and other interested parties in everyday practice have familiarised themselves with the knowledge developed and, where possible, implement this in their daily working methods;
- A knowledge infrastructure has arisen concerning ME/CFS, in which researchers sustainably collaborate across national borders in a transdisciplinary manner. This knowledge infrastructure also includes policy, education and treatment practice.

2.2 Target group

2.2.1 Ultimate target group

Until we possess more knowledge about the causes of ME/CFS, it remains difficult to precisely define the target group of the research programme. In clinical practice, there is no gold standard to describe the ME/CFS population. With each definition, patients are unintentionally and incorrectly included or excluded from the population that you would like to investigate or treat. In addition, new insights into (the pathophysiology of) ME/CFS could arise during the research programme, with corresponding new definitions of ME/CFS. Therefore, a final delimitation of the target group for the entire programme based on current definitions is not possible at present, although rough delimitations can be indicated.

The main objective of all research in the ME/CFS research programme is to improve the quality of life and/or societal position of existing and future ME/CFS patients. ME/CFS has a complex pattern of symptoms and fatigue symptoms are just one aspect of this. The programme will investigate ME/CFS in all of its complexity. For that reason, the programme will not fund research into chronic fatigue in and of itself or research that is aimed at chronic fatigue as a consequence of illnesses or disorders other than ME/CFS. Forms of fatigue that are independent of ME/CFS can only be investigated within the research programme insofar as this research is carried out in relation to ME/CFS.

2.2.2 Sets of criteria for ME/CFS

For the individual studies in the programme, strictly defining the research population could be very important indeed because a comparison of research groups is only possible if those groups are well-defined. For this purpose, researchers could make use of various sets of criteria for ME/CFS that have been compiled in recent years based on descriptions of symptoms. These sets of criteria cover (partly) overlapping groups of patients, whereby the one set can result in a more limited ME/CFS population than the other (see Figure 1). Frequently used sets of criteria are:

- The criteria for CFS of the American Centers for Disease Control and Prevention (CDC) from 1994,[2]
- The Canadian Consensus Criteria (CCC) for ME/CFS from 2003,[3]
- The International Consensus Criteria (ICC) for ME from 2011,[4]
- The criteria for ME/CFS (SEID) of the American Institute of Medicine (IOM) from 2015.[5]

When choosing which of the various criteria sets to use, the specificity, in particular, plays an important role. For example, the Health Council of the Netherlands advised to stop using the Oxford criteria[6] because these define a group that is too broad and heterogeneous. In the literature, 'post-exertional malaise' (PEM)[7] is described as a characteristic symptom of ME/CFS. In consequence, PEM has been set as a condition in more recent sets of criteria for ME/CFS, such as the CCC, ICC and IOM. The CDC today no longer uses its own 1994 criteria in which PEM was not a condition, but uses the IOM criteria from 2015 instead. However, the IOM criteria were developed as a practical instrument in a clinical setting and cover a somewhat broader group of patients. The ICC builds further upon the CCC and reaches the narrowest definition of the ME/CFS population. Although the ICC is highly specific, it uses its own slightly different definition of PEM, which seems to encompass a slightly different group of patients than other definitions.

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[2] Fukuda K, Straus SE, Hickie I et al.; The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Study Group. Ann Intern Med 1994; 121: 953 – 9.

[3] Carruthers BM, Jain AK, De Meirleir KL et al.; Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Clinical Working Case Definition, diagnostic and treatment protocols. J Chronic Fatigue Syndr 2003; 11: 7 – 115.

[4] Carruthers BM, van de Sande MI, De Meirleir KL et al.; Myalgic encephalomyelitis: international consensus criteria. J Intern Med 2011; 270: 327 – 38.

[5] Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine; Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. The National Academies Collection: Reports funded by National Institutes of Health. Washington (DC): National Academies Press (US) 2015.

[6] Sharpe MC, Archard LC, Banatvala JE et al; A report–chronic fatigue syndrome: guidelines for research. J R Soc Med 1991; 84: 118 – 21.

[7] The definition of PEM is also under discussion and varies between sets of criteria. in the advisory report of the Health Council of the Netherlands, PEM is described as an exacerbation of symptoms following a physical or mental exertion that previously did not give rise to problems. The type, intensity and duration of the symptoms of post-exertional malaise can vary and that also applies to the time interval that elapses between the exertion and the exacerbation of the symptoms. The exacerbation of the symptoms is not proportional to the amount of exertion.

In choosing a definition for ME/CFS, alignment with the current state of science is also an important consideration. Research proposals within the biomedical research programme ME/CFS must therefore make sure that they keep proper pace with the (recent) scientific literature and the definitions of ME/CFS it offers.

The activities that took place within the trajectory of realising the research agenda ME/CFS provide insight into the use of sets of criteria for ME/CFS in ongoing research. In the conducted survey, biomedical researchers seemed to have a preference for the use of the Canadian Consensus Criteria (CCC). During the programme day, the speakers who talked about their research into the development of ME/CFS, stated that they used the International Consensus Criteria (ICC) in their current research. The work sessions revealed, for example, that the UK ME/CFS Biobank (UKMEB) makes use of the CDC 1994 criteria, the CCC, as well as the IOM criteria.

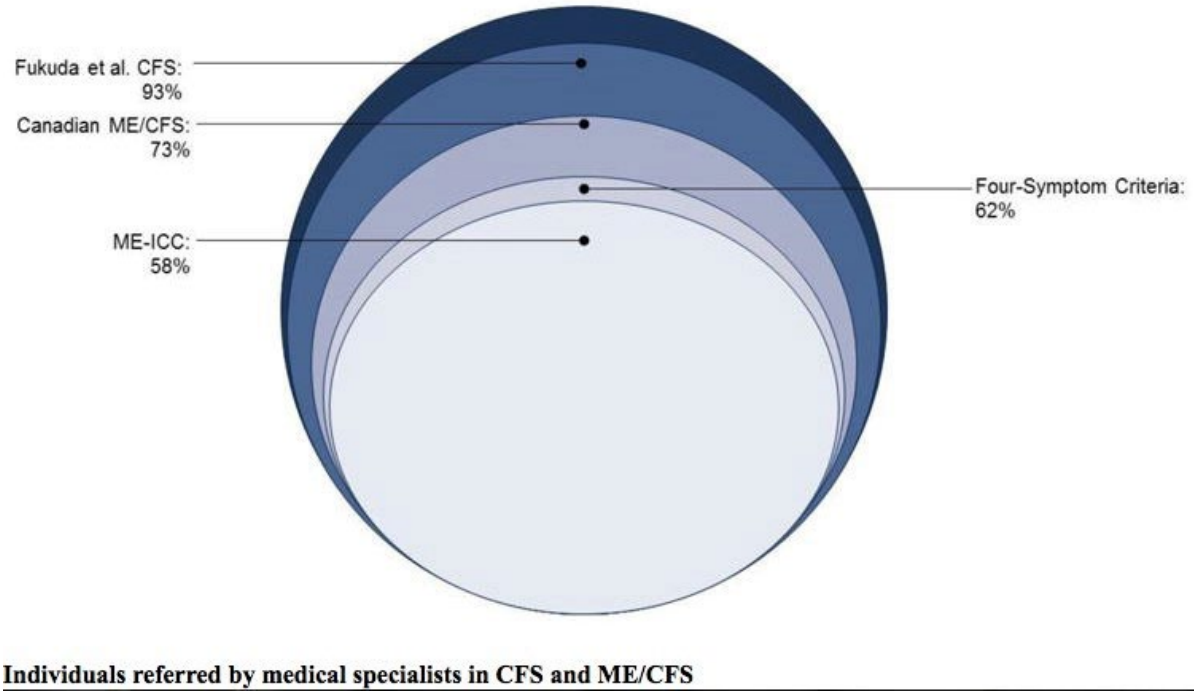


Figure 1: Comparison of different sets of criteria for ME/CFS according to number of patients.
The 2011 International Consensus Criteria for ME (ME-ICC) form the most recent and stringent description of ME/CFS; patients that satisfy these criteria can currently be regarded as the core of the ME/CFS population. Besides the ICC, there are sets of criteria for ME/CFS with decreasing specificity that cover a larger population, such as the Canadian Consensus Criteria ('Canadian', 2003) and the Four-Symptom Criteria (not described in the text). The IOM criteria for ME/CFS (SEID) are missing in the figure, but these also cover a larger population than the ICC. At the outer limit of definitions of the population, patients are found that only satisfy the criteria from the Centers for Disease Control and Prevention from 1994 ('Fukuda'). This figure provides a comparison of the numbers of ME/CFS patients and therefore does not make a substantive comparison between the types of patients that fall under the different sets of criteria.

Source: Jason L A, Kot B, Sunnquist M, Brown A, Evans M, Jantke R, Williams Y, Furst J, Vernon SD; Chronic fatigue syndrome and myalgic encephalomyelitis: towards an empirical case definition. Health Psychology and Behavioral

2.2.3 Use of sets of criteria in the programme

To recap: debates about the sensitivity and specificity of different sets of criteria for ME/CFS make it difficult to choose a specific set. The fact that researchers use different definitions of ME/CFS throughout the literature makes it difficult to compare research results and build up knowledge about ME/CFS through such a comparison. So how should researchers within the biomedical research programme ME/CFS define their research populations?

Researchers should at least be aware of the pros and cons of using the various sets of criteria. The Health Council of the Netherlands makes no concrete recommendations about which sets of criteria should be used in research into the aetiology and treatment of ME/CFS. The steering group of the research agenda states that the ICC could, at this point in time, be a good starting point in many such studies. The Health Council of the Netherlands advises that research into a better substantiation of the diagnosis ME/CFS – and possible sub-diagnoses – should include all characteristics that figure as diagnostic criteria in the various definitions of ME/CFS. The steering group of the ME/CFS research agenda has endorsed this advice. It is important that research proposals always make their definition of ME/CFS explicit and show how this relates to existing definitions, patient groups and hypotheses about the pathophysiology of ME/CFS.

2.2.4 Intermediate target groups

The programme's ultimate objective is to improve the lives of ME/CFS patients and, in that sense, it focuses on ME/CFS patients. To achieve this objective, the programme also focuses on intermediate target groups, such as researchers, healthcare practitioners, policymakers and teachers in secondary and higher education. All of these interested parties of the research programme are relevant for building up a knowledge infrastructure around ME/CFS. The programme therefore focuses on them as well, and on improving the collaboration between them. The programme stimulates and facilitates researchers in starting and carrying out research into ME/CFS. Healthcare practitioners must be able to contribute their own knowledge questions to the programme and should ultimately be able to use the knowledge developed within the programme. We will only be able to genuinely improve the situation of patients if the intermediary target groups are effectively engaged in the programme too.

2.3 Patient participation

Patient participation helps to advance healthcare research. By collaborating with patients and their relatives, the research connects better with everyday practice. As a consequence, ZonMw encourages patient participation in all of its programmes and studies. During the writing of the ME/CFS research agenda and the further trajectory in the run-up to the research programme, patients proved to be an important source of knowledge about ME/CFS. They also made a valuable network of contacts with (foreign) researchers available to the trajectory. ZonMw will continue this collaboration during the research programme.

The research programme will enable patients to participate and to contribute ideas to the ME/CFS research programme in several ways:

1. **Participation at programme level**
   Participation in the guidance committee of the research programme and, linked to that, a rotating participation in the programme committee ME/CFS. In Chapter 6, the working methods of the guidance committee and programme committee are described in greater detail. During the assessment of research proposals, patients and their representatives can be supported by ZonMw.

2. **Participation at project level**
   The supervision by patients of projects awarded funding. The participation of a patient or patient representative in the project team or the supervisory committee of a project proposal is a condition for funding. This condition will be further elaborated in the calls for proposals texts.
4. **Collective patient participation**
   ZonMw is currently developing a new form of patient participation which can possibly be deployed within the ME/CFS programme. This concerns obtaining a better insight into the wishes and interests of patients by collectively acquiring and systematically organising experiential knowledge. Collective, systematic experiential knowledge can be used within research but can also be relevant for ZonMw or other programme stakeholders. For example, ZonMw can use this knowledge to better match its programmes to the needs of patients. The possibilities for collective patient participation in the ME/CFS research programme must be further investigated during the course of the programme. The acquisition and systematic organising of collective experiential knowledge could, for example, be placed under the responsibility of an ME/CFS knowledge centre. This knowledge centre will be established in the programme line Improving practice (for a description, please see Section 2.4.2).

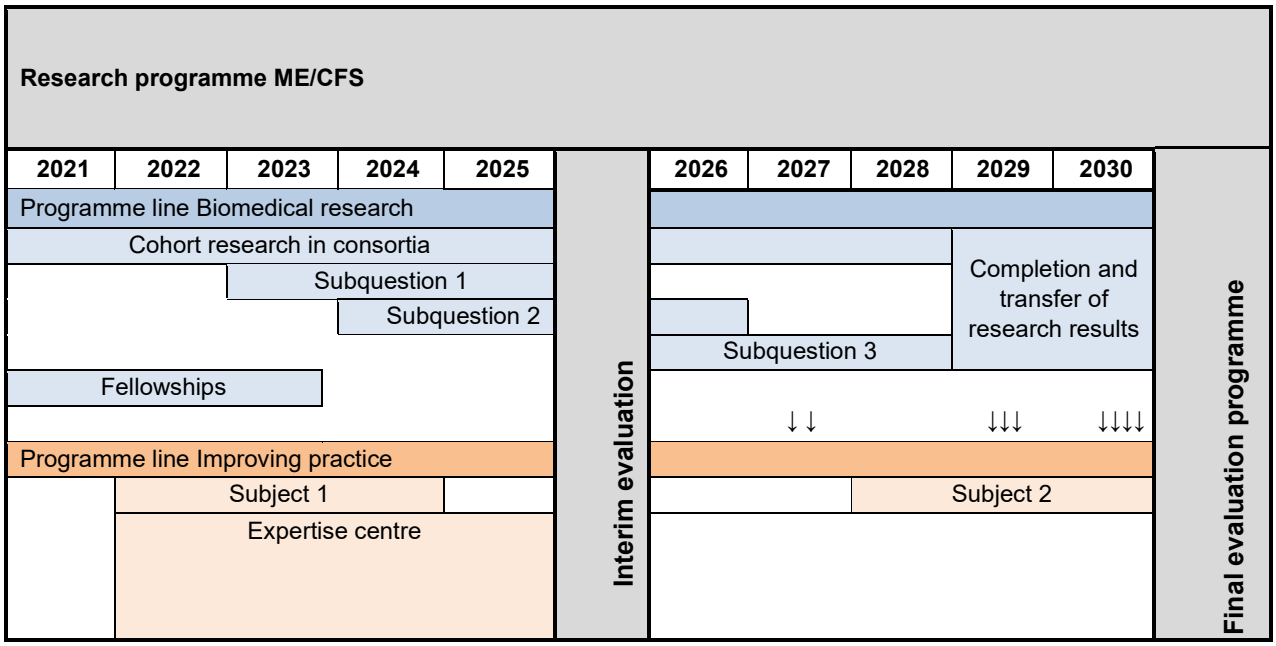
2.4 Structure of the programme

Two substantive programme lines have been formulated to realise the programme's objectives: the programme line Biomedical research and the programme line Improving practice (Figure 2). These programme lines are explained in Sections 2.4.1 and 2.4.2, respectively.

In terms of budget, the main emphasis of the programme is on the programme line Biomedical research. The phasing of the programme lines is not synchronised. The emphasis on the programme line Improving practice could increase somewhat during the course of the programme based on the results from the programme line Biomedical research. Exchange between both programme lines will be stimulated and facilitated by ZonMw, for example through the organisation of project leaders' meetings.

Within the Netherlands, little research is taking place into ME/CFS. The ME/CFS research programme wants to change that by setting up a research infrastructure for ME/CFS. In doing this, it is imperative to offer (young) researchers perspective by providing funding for long-term research projects. However, as the ME/CFS research field is rapidly developing, there needs to be the possibility to adjust the programme during its course too. That being the case, the programme will carry out an interim evaluation after 5 years (see also Section 7.2).

Figure 2: Programme structure



2.4.1 Programme line Biomedical research

The programme line Biomedical research focuses on the first and most prominent part of the programme commission, and builds further upon the recommendation from the Health Council of the Netherlands for a ZonMw research programme. It develops biomedical knowledge about the aetiology, diagnosis and treatment of ME/CFS. Within this programme line, a limited number of large consortium proposals will be funded at the start of the programme. The collaboration between different disciplines in these consortia serves to investigate ME/CFS as a multisystem disease. The consortia will formulate questions around subjects for fundamental, epidemiological and clinical research. These questions are described in the next chapter (Section 3.1). Besides different academic centres, these consortia should include non-academic partners, such as peripheral treatment clinics or patient organisations. The collaboration with non-academic partners can facilitate the inclusion of patients within the various studies. ZonMw encourages alignment between the consortia concerning the inclusion of patients. That way, the consortia can jointly work on building and characterising a homogenous Dutch ME/CFS biobank and patient registration.

During the funding rounds in subsequent years, (follow-up) questions will be set to investigate ME/CFS in greater detail (subquestions 1-3 in Figure 2). The programme committee will shape these calls for proposals during the course of the programme based on the latest knowledge concerning ME/CFS. These subquestions concern, for example, monodisciplinary research, population research, replication research, the elaboration of specific techniques, or questions that emerge from the large consortia studies that have already started. The studies in these funding rounds will be stimulated to connect with current research in the programme to facilitate the integration of the Dutch research field.

The Health Council of the Netherlands states that compared to other countries, the Netherlands needs to catch up on research in the field of ME/CFS. Therefore, the possibility has been created to enlist foreign expertise within the programme line Biomedical research. An important aspect of this is awarding fellowships for research in collaboration with the NWO Rubicon programme. Via these fellowships, researchers will make contact with foreign institutes where research into ME/CFS seems to offer perspectives, and also has a relevant scope. Examples are ME/CFS research centres in the United States, Canada, Australia, Sweden, Germany and the United Kingdom. The fellowships can be used, for example, to acquire research methodologies or to facilitate replication research.

Undertaking activities that transfer this knowledge or facilitate the use of this knowledge is an integral aspect of each of the projects within the programme line Biomedical research.

2.4.2 Programme line Improving practice

The programme line improving practice will work on the remaining part of the programme commission: improving the treatment practice by disseminating and utilising existing and new knowledge about the diagnosis and treatment of ME/CFS. The programme line Improving practice is far smaller in size than the programme line Biomedical research, but hopes to be able to realise improvements in the lives of ME/CFS patients in a shorter period than is possible with biomedical research. The programme committee will further elaborate upon the subtopics that will be worked on in the various funding rounds of this programme line (Subjects 1 and 2 in Figure 2).

One aspect of the programme line Improving practice is developing a knowledge centre ME/CFS. This knowledge centre can fulfil several functions: independently bringing together knowledge, issuing advice towards research, policy, patients and healthcare professionals, being a platform for contact between interested parties, systematically storing experiential knowledge, recruiting patients for research, etc. An interesting example of a knowledge centre for ME/CFS is the expertise centre ‘Q-support’ established on behalf of the Ministry of Health, Welfare and Sport. In this several, but not all, of the aforementioned functions of a knowledge centre have been accommodated in the field of the disease Q fever. The programme committee ME/CFS will decide which objectives the ME/CFS knowledge centre must serve and what the knowledge centre will be commissioned with.

3 Content of the programme

3.1 Research subjects

The research subjects of the Biomedical research programme ME/CFS are formulated in the ZonMw Research Agenda ME/CFS.[8] The ME/CFS research programme has been divided into a programme line Biomedical research and a programme line Improving practice.

The programme line **Biomedical research** offers room for research into the following subjects:

Fundamental research
- Research into (chronic) immune activation (for example, after viral infections as well as host-microbe interaction and the intestinal microbiome), immune metabolism and neurological disorders;
- Brain imaging research to investigate disruptions in the functioning of the brain;
- Research into the cellular energy metabolism linked to cell function.

Epidemiological research
- Research aimed at the aetiology of ME/CFS: an (epi)genetic basis for ME/CFS, the influence of environmental factors and research into infectious causes;
- Longitudinal research into the progression of ME/CFS and prognostics studies;
- Research aimed at a better description of ME/CFS, so that a better diagnosis can be made and subgroups and comorbidities can be established.

Clinical research

Greater insight into the cause or biomedical mechanisms of ME/CFS will allow more targeted and innovative therapies to be developed. For benefits in the somewhat shorter term, a start can already be made with:
- The testing of (existing) treatments that alleviate important symptoms;
- The testing of therapies known for other diseases, such as comorbid disorders that frequently occur with ME/CFS;
- Identifyin and testing ME/CFS treatments that are used abroad;
- Research aimed at a better diagnosis, for example physiological tests/exertion tests, biomarkers, serology and genomics.

The results from the programme line Biomedical research will probably only become available in the long term. In its commissioning letter, the Ministry of Health, Welfare and Sport therefore requested that efforts will also be made as part of the ME/CFS research programme to improve the perspective of patients in the short term. This will happen in the programme line Improving practice.

The programme line **Improving practice** offers room for projects aimed at:

- Putting into use (new) biomedical knowledge about ME/CFS in the Dutch healthcare system; for example by Dutch healthcare providers, medical assessors, guideline developers and in secondary and higher education.
- Improving how patients with ME/CFS are regarded and respected in clinics and by society, in line with existing experiential studies among Dutch ME/CFS patients (for this, please see the ZonMw Research Agenda ME/CFS).
- Building up knowledge about life with ME/CFS and/or applying this knowledge to the lives of people with ME/CFS and their relatives.

[8] Research Agenda ME/CFS The Hague: ZonMw, 2020.

3.2 Research infrastructure

The research programme stimulates the development of a Dutch research infrastructure for ME/CFS research. The aspects of biomedical research realised in the programme must strengthen each other and bear fruit internationally. The projects in the programme must exhibit a mutual coherency in which fundamental research, epidemiological research and clinical research become interwoven with each other. The aim is to build up a network in which researchers, care providers and patients structurally collaborate. In this way, cross-fertilisation can take place and new perspectives be put forward. Transdisciplinary collaboration facilitates the integration of research results and theorisation from different, often unrelated disciplines. Transdisciplinary collaboration is consequently highly desirable in the case of ME/CFS and counts as a criterion for the assessment of research proposals.

To facilitate the building up of the research infrastructure, one of the focus areas in establishing the research agenda was the formation of consortia for research into ME/CFS. ZonMw wants to give the programme a head start by first of all funding a limited number of large research consortia in which transdisciplinary research will take place. ZonMw encourages research proposals submitted in a later stage and/or independently of the research consortia formed in the first phase, to connect with existing research consortia.

Partnerships established must also be maintained. The programme therefore provides possibilities for long-term funding and has a strong focus on the effective transfer of research results. The programme wants to provide perspectives for young, highly promising talent as well, with the aim that they focus their research career on ME/CFS. During the process of drawing up the research agenda, this was put forward as an important condition for building up an enduring research infrastructure. Attracting and retaining young talent is therefore a point of attention for all activities within the programme.

3.3 Biobank and patient registration

Also, data collection and the collection of biomaterial are important points of attention during the realisation of the research programme ME/CFS. A uniform approach yields data that are ‘FAIR’. One way of achieving that uniformity and coherency in the research programme is by building up a Dutch ME/CFS biobank and patient registration. This will be fed by the various cohort studies in the research programme. The population in the patient registration must, however, be epidemiologically well-characterised and, where relevant, followed for a number of years. Patients for the research can be recruited by making use of the networks of Dutch ME/CFS patient organisations or collaboration can be sought with one of the Dutch independent treatment clinics for ME/CFS. The individual research cohorts must be large enough to be able to draw statistically significant conclusions about the questions posed in that study, and about possible subgroups as well. Furthermore, the entire biobank and patient registration must be a good reflection of the intended target group (young, old, degree of disease burden, etc.). In the research programme, it is also important to devote attention to the diversity of the Dutch population in the broad sense of the word. In principle, the entire ME/CFS population must be represented in the biobank and patient registration without exclusions: men, women, ethnic groups, or other specific groups must all be included.

During the building up of the biobank and the patient registration, a lot of attention will have to be given to the quality of the patient selection. This quality must be safeguarded by following an established diagnostic protocol and an assessment carried out by expert and experienced clinicians. This might require seeking connection with expertise outside of the Netherlands.

The recruitment of patients via different research projects will lead to a heterogeneous population for which the collected data must be classified according to known sets of criteria for ME/CFS (see also Section 2.2.2). Biomaterials and data (blood, brain scans, cardiovascular data, questionnaires, etc.) must be taken and stored in as standardised a manner as possible in all studies in the programme. In the Netherlands, the Health-RI Biobank Community provides expertise and standards for the storage of biomaterial. Standards for clinical research can also be helpful, such as the Common Data Elements for ME/CFS of the American National Institute of Neurological Disorders and Stroke. Standardisation of data facilitates the alignment of research results with other research carried out within and outside of the Netherlands, and is therefore encouraged by ZonMw. By means of its FAIR data policy, ZonMw is developing activities to facilitate the standardisation and reuse of data in the programme (see also FAIR data and data management ZonMw). One such activity is the development of the national COVID-19 data portal. The ME/CFS programme might connect with this data portal

because of substantive overlaps. The possibilities in this regard will be further elaborated in the programme.

During the building of the patient cohort, specific attention will need to be given to the inclusion of two groups of patients: young people and the seriously ill. The ME/CFS research agenda states that the investigation of young people and adolescents with ME/CFS requires special attention, because ME/CFS appears to develop differently among these groups. Furthermore, the ME/CFS research agenda states that emphasis must be given to investigating severely ill patients as, in general, these have not been investigated up until now. This concerns patients who are housebound or completely bedridden and dependent on care. The limitations of these patients requires a specific approach and logistics. Inclusion of this group will possibly require house visits to be made by research nurses who have been specifically trained for this purpose. The ME/CFS research agenda indicates that much expertise in this area can be obtained from abroad. To increase the feasibility of including young people and the seriously ill, it is important that an approach specifically geared towards them is designed in collaboration with them.

3.4 Population research

Research into the incidence and prevalence of ME/CFS within the Dutch population and research into environmental factors related to the aetiology of ME/CFS can be realised in various ways, for example, by making use of an existing population cohort. It is nevertheless important that ME/CFS is defined and investigated in the correct manner in the population cohort to be used. Due to shifting definitions of ME/CFS, such research will be more appropriate in a later phase of the programme. For the research within an existing population cohort it is expected that additional questionnaires and tests will need to be taken that are selected by ME/CFS researchers.

3.5 Replication research

The advisory report from the Health Council of the Netherlands reveals that, in general, too little research of sufficient quality has been done until now to be able to make clear statements about the causes of ME/CFS. Furthermore, positive research results are more frequently published in science than negative ones. This results in a distorted picture about the state of research. That being the case, the Royal Netherlands Academy of Arts and Sciences advises to publish more negative research results and perform replication research more often.[9]

The Health Council of the Netherlands advises performing replication research more often for ME/CFS as well. Therefore, the ME/CFS research programme not only provides room for original research, but also for replication research, for example on medicinal treatments. This replication research must use the same definition of ME/CFS as the research to be replicated and will therefore probably make use of older definitions of ME/CFS. However, in replication research, older definitions of ME/CFS can also be combined with more recent and specific definitions, which could result in new insights into ME/CFS.

[9] Royal Netherlands Academy for Arts and Sciences; Replication Studies – Improving reproducibility in the empirical sciences. Amsterdam: KNAW, 2018.

4 ME/CFS programme in context

In international research, many biological processes have been correlated with ME/CFS, but according to the advisory report of the Health Council of the Netherlands, no definitive conclusion has been drawn about the aetiology of ME/CFS. The programme ME/CFS must contribute to more clarity in this area. In the research programme, ME/CFS will be investigated as a multisystem disease. Accordingly, the programme has been placed within a broad field of other research and initiatives with which it exhibits common ground. The ME/CFS research programme follows developments in this broad field and responds to the possible forms of synergy. Alignment and collaboration with parties in the field is necessary to provide a relevant and efficient research programme. This collaboration is described below.

4.1 International alignment and collaboration

In its advisory report from 2018, the Health Council of the Netherlands states that, compared to other countries, the Netherlands needs to catch up on research in the field of ME/CFS. Therefore, the programme needs to align properly with **international** developments in research into ME/CFS. Research into ME/CFS is also gaining more prominence globally. The Open Medicine Foundation is a privately funded non-profit organisation that has made USD 30 million available worldwide for scientific research into ME/CFS. At the American National Institutes of Health, three 'Collaborative Research Centers' were funded in 2017 to the tune of USD 35 million over a period of 5 years. In Australia, the United Kingdom and the Scandinavian countries, similar developments are taking place at the national level.

Furthermore, research into ME/CFS appears to be increasingly encouraged at the **European** level. In Horizon 2020, two ME/CFS projects were awarded funding: Help4ME (Horizon 2020/SME) and Euromene (Horizon Cost Action). Within the programme Horizon Europe, a Scoping Study will be set up in the coming years to investigate whether and how Horizon Europe must realise a better competitive position for research into certain disorders (such as ME/CFS).

The programme ME/CFS ties in with these developments and will encourage exchange with foreign research institutes. Connection with two **European research networks**, the European Network on ME/CFS (EUROMENE) and the European ME Research Group (EMERG), seem to be the most important routes initially within Europe. Other obvious options are collaborations with **European biobanks**, such as the ME/CFS Biobank (UKMEB) in the United Kingdom or the ME/CFS patient cohort at the hospital Charité – Universitätsmedizin Berlin.
In addition, the programme will encourage more direct international exchange, amongst other things, via foreign speakers at project leaders meetings and through other activities organised by ZonMw. Within the programme, ZonMw will also reserve a relatively large budget for activities such as congress visits, long and short research internships and fellowships. Funds for these activities will be reserved within projects, but a separate funding round to apply for fellowships will also be established within the programme. Other forms of internationalisation such as co-funding with international funding routes will be investigated during the first two years of the programme and, where desirable, further elaborated upon.

4.2 Alignment and collaboration with other Dutch partners

As end users of the research results, **patients** have an important and encompassing role within the programme ME/CFS. They contribute to the exchange of data between researchers and patients. In addition, patients and patient representatives will advise about the relevance and quality of the projects in the ME/CFS programme. Section 2.3 describes how patient participation within the ME/CFS research programme is further elaborated.

The programme ME/CFS falls under the director of public health of the **Ministry of Health, Welfare and Sport**. The connection of the programme with policy will be ensured during regular consultation with the Ministry and adjustments will be made where necessary. Furthermore, a representative of the Ministry is an observer in the ME/CFS programme committee.

The **National Health Care Institute** (Zorginstituut Nederland) has placed the development of an ME/CFS guideline on the multi-annual agenda for quality instruments 2021. As part of the programme

line Improving practice, the ZonMw programme secretariat will maintain contact with the National Health Care Institute.

ZonMw will involve **healthcare practitioners** in the research programme. Relevant groups will be actively approached. This is necessary to facilitate the recruitment of patients for research and to establish a Dutch ME/CFS patient cohort. In doing this, ZonMw will create an enduring knowledge infrastructure for ME/CFS. Healthcare practitioners also have an important role to play in the dissemination of specific (research) results. For this, ZonMw will call upon the associations of medical professionals, for example, general practitioners, neurologists, internists, cardiologists and/or company doctors to strengthen the impact of the results from the programme. Finally, healthcare practitioners are important users of the new knowledge that the research programme will generate.

From the perspective of establishing a Dutch ME/CFS **biobank** and **patient registration**, ZonMw has contact with organisations that have expertise in these areas. First of all, with Health-RI: the Dutch initiative for the integration of Dutch health data within a single infrastructure. The Health-RI partners also include initiatives specifically aimed at biobanks: BBMRI and Parelsnoer. The Lyme biobank and patient registration of the NLe (Netherlands Lyme expertise centre) are relevant at a substantive level. In addition, the recently published research agenda Q fever[10] states the ambition to realise a national database with well-documented datasets of about 500 CQK patients. This also provides collaboration opportunities for the ME/CFS research programme.

ZonMw maintains contact with partners in the field of **policy** and **education**. For example, new knowledge about ME/CFS could give cause to adapt existing (medical) curricula. Or new knowledge could require health insurers or medical assessors to modify their policy. ZonMw will therefore actively inform these partners about the (research) results. It is also possible that projects focusing on education or medical assessment will be funded in the programme line Improving practice.

The dissemination of research results has an important place in the programme line Practice improvement. New developments will make it necessary to connect with other partners and interested parties. ZonMw will monitor and respond to these developments.

4.3 Alignment and collaboration within ZonMw

ZonMw has several programme-overarching themes, such as diversity, eHealth and ICT in care, innovation in care, participation and positive health. The ME/CFS programme regularly exchanges information about these policy themes with other ZonMw programmes. Furthermore, the ME/CFS programme will actively give shape to its position within the ZonMw knowledge programming by means of collaboration and demarcation. This will prevent overlap, accelerate the transmission of knowledge in the knowledge chain and strengthen the impact of research for practice and policy. In contact with other parties, the ME/CFS programme will work together with other programmes and will align its approach. Due to substantive common ground, collaboration with the following programmes is particularly relevant.

In the **COVID-19** programme, ZonMw is working on current and future possibilities to use research and knowledge to contribute to solutions for the COVID-19 pandemic and the effects of this on society. Since the start of the COVID-19 pandemic, there has been increasing attention for residual symptoms after a COVID-19 infection. There is an overlap between the (residual) symptoms pattern after a COVID-19 infection (the so-called PASC) and ME/CFS. It is not yet clear whether this overlap has a biomedical basis. To ensure a clear demarcation, the ME/CFS programme will not fund any research into ‘PASC’ in and of itself. Nevertheless, it seems advisable that the ME/CFS programme seeks connection with the COVID-19 programme, for example in the form of harmonising data and materials and encouraging knowledge exchange. That way, research data can be properly compared and any possible overlap between the two diseases can be investigated properly.

Research into Lyme’s disease is taking place as part of the **Infectious Disease Control** programme. Patient organisations, researchers, policymakers, companies and healthcare practitioners drew up an action plan for Lyme’s disease in 2016. The action plan contains research subjects and other activities

[10] Q-support; Onderzoeksagenda Q-koorts en de langetermijneffecten: Q-koorts vermoeidheidssyndroom (QVS) en chronische Q-koorts (CQK) [Research agenda Q fever and the long-term effects. Q fever fatigue syndrome (QFS) and chronic Q fever (CQF)]. Q-support, 2021.

in the area of basic knowledge (including knowledge about the *Borrelia* infection), diagnostics, treatment and prevention. One of the outcomes of the action plan is a Dutch Lyme disease biobank and patient registration. Related to this is the now completed **Q fever** programme. The aim of the Q fever programme was to make a short-term contribution to preventing and combating Q fever, improving the diagnostics and improving the treatment. Research into Lyme disease and Q fever share a similar societal dynamic as the research into ME/CFS. The ME/CFS programme therefore seeks collaboration with the programmes focussed on Lyme disease and Q fever about subjects such as patient participation, the (societal) utilisation of research results and common causal factors.

In 2019, the Association of Dutch Health Foundations and ZonMw commissioned Maastricht University to draw up a **Knowledge Synthesis Chronic Fatigue**. This knowledge synthesis summarises the scientific knowledge about fatigue as a disease-overarching symptom and concludes that this symptom receives too little attention in scientific research. Research into chronic fatigue must be given a place within the ZonMw programming in light of the ageing population in the Netherlands, where a growing number of people are expected to develop one or more chronic diseases. Eventually, it will be examined whether collaboration between the ME/CFS programme and this possible new programme is relevant. A condition for this will be that the idiosyncratic character of fatigue in the case of ME/CFS will be kept in sight.

Within ZonMw, there are several **practice programmes** aimed at helping people with a chronic disease or disability to participate in society. In these programmes, the importance of participating in society is also translated into the actual design of the programme. This allows new ZonMw methodologies to be developed that also enable people with a disability to participate, for example, at the level of assessing project proposals. The incorporation of patient participation in the ME/CFS programme has been inspired by examples from these other programmes, and collaboration with these other programmes will also be sought in carrying out the ME/CFS programme.

The ME/CFS programme, as a disease-specific programme, shares much common ground with the diversity of subjects considered in ZonMw's disease-overarching programmes. The programme line Biomedical research has a connection with programmes and studies within the programme clusters **Fundamental Research**, **Efficacy Research** and **Translational Research**. The programme line Improving practice has a connection with the programme cluster **Quality of Care,** for instance. Collaboration with programmes in these programme clusters can, amongst other things, assume the form of exchanging policy instruments to encourage the transmission and use of research, making use of each other's networks and the development of forms of co-funding.

5 Knowledge use & implementation

5.1 The knowledge cycle of ME/CFS research

New knowledge about ME/CFS must be developed to bring about a positive change for the patient. Subsequently, it is important that this new knowledge is also used in practice, policy, education and (follow-up) research. This way, a knowledge cycle arises: from the development of (fundamental) research questions, the realisation of the research and the transmission of research results into new, more applied research questions, through to the utilisation of the applied research results in practice. In turn, the latter will lead to the formulation of new research questions.

A condition for utilising knowledge is that the knowledge developed in the programme connects with the needs of the parties interested in the programme. This requires a good collaboration between all interested parties. The first steps towards this broad collaboration were made in the process prior to the research programme: during the writing of the ME/CFS research agenda. In this process, as many interested parties from research into ME/CFS as possible were involved in formulating relevant research projects. To establish a knowledge infrastructure for ME/CFS in the Netherlands, ZonMw wants to continue this way of collaborating in the ME/CFS research programme. In this, research institutes and medical centres will broadly collaborate with patients, education, policy and practice.

Via the two programme lines Biomedical research and Improving practice the ME/CFS programme will exert an influence on all steps in the knowledge cycle and will encourage the utilisation of knowledge for each step. Utilisation of knowledge can assume different forms in the various steps of the knowledge cycle. In the case of fundamental biomedical research, utilisation of knowledge should mainly be seen as the transmission of knowledge to new (and possibly more applied and/or clinical) research and innovation of the research practice. This is the focus of the activities that can stimulate the utilisation of knowledge within the ME/CFS programme. Particular attention will be paid to encouraging and transmitting research results that have a major (societal) effect.

With respect to more applied research, the results from the research projects must be utilised by relevant professional groups: parties in healthcare, education and policy, as well as patients. The programme line Improving practice will fund projects that focus on the explicit utilisation of new and already published knowledge and with that improve (healthcare) practice. The ME/CFS knowledge centre to be established is an important aspect of that.

The ME/CFS research programme encourages applicants to think at an early stage about implementation: the transmission, dissemination, utilisation, embedding and exploitation of their results. For example, all consortia must involve a Knowledge Transfer Office from their own institute in the design and realisation of their research. ZonMw communication and implementation employees can support project leaders with further advice. To support the utilisation of knowledge in all steps of the knowledge cycle, ZonMw will also develop communication and implementation activities during the course of the programme. Various resources are available, such as the ZonMw website, the ZonMw newsletters, project leaders' meetings, or other meetings and the intended knowledge centre ME/CFS. During the first year of the programme, ZonMw will elaborate these activities into a communication and implementation plan. The communication and implementation plan to be written will be based on the basic premises and objectives stated below.

5.2 Basic premises and objectives

Basic premises for communication and implementation activities within the programme are:

- Patients and their representatives, organisations from the field and other interested parties are involved in all phases of the programme and demonstrably involved in each project within the programme;
- Data and knowledge developed must be accessible for a wide public: for experts and non-experts, nationally and internationally;
- Applicants and parties from the field will be encouraged at an early stage to realise activities that facilitate the transmission, spread, implementation and embedding of the knowledge developed.

Objectives of the communication and implementation activities from the programme are:

- Optimal transmission, spread, implementation and embedding of the knowledge developed; both substantive knowledge about ME/CFS as well as knowledge about research and knowledge utilisation (for example, with respect to innovative research designs);
- Wider awareness of the ME/CFS research programme among interested parties; this will encourage new research and improve the practice;
- Closer collaboration in the subject ME/CFS between the interested parties from the programme: between policy, education, research and practice – nationally as well as internationally.

5.3 Open Science

The subject 'Open Science' deserves special attention with respect to the impact of the ME/CFS programme. Open Science is a key policy of ZonMw and concerns making knowledge produced accessible for science, the economy and society (see Open Science ZonMw). Open Science has several facets, such as Open Access publication, FAIR data management, recognising and rewarding talent differently and Citizen Science. The ME/CFS programme adheres to the Open Science policy in practice.

First of all, Open Access publication is mandatory for all projects in the programme. Secondly, the principles of FAIR data management are applied in the composition of the Dutch ME/CFS patient registry and biobank and in other projects funded. For this, the ME/CFS programme might collaborate with the COVID-19 data portal currently being established. ZonMw will also actively assist applicants with the harmonisation of data from the different ME/CFS studies; FAIR data management will be an important point for attention. Thirdly, within the ME/CFS programme, it is important not just to recognise and reward researchers on the basis of bibliometric information. ME/CFS is an emerging research field in which applicants should be valued, in particular, for putting in extra efforts to build up the field, such as investing in education about ME/CFS. This appreciation will be translated into the conditions for specific funding rounds. Finally, it is quite possible that the limitations of many ME/CFS patients will require innovative research designs. So-called 'Citizen Science' projects enable people with disabilities, as is the case for ME/CFS, for example, to participate in all phases of the research. The programme will encourage innovations in the area of research design. These innovations must make it possible for people who are difficult to reach due to the limitations of their chronic illness to nevertheless participate in the programme.

6 Management and organisation

ZonMw works as an intermediary organisation on improving health and healthcare by encouraging and funding research, development and implementation. In doing so, ZonMw assumes an independent position between policy, practice and research. The programme committees play a key role in the programmatic approach of ZonMw.

6.1 Role and task description programme committee

For the programme, a committee will be appointed that has between 10 and 14 members consisting of patient representatives, members from society (drawn from representatives from a number of relevant sectors/organisations), scientific members (who come from the research field) and an independent chair. These committee members will assess the proposals without any instructions or consultation. The members will be appointed for a period of 5 years, in a personal capacity and based on a specific expertise. After a period of about 3 years, a committee member with valorisation expertise will be added to the committee.

An observer from the Ministry of Health, Welfare and Sport will also be present at the meetings of the programme committee. The programme committee will advise the ZonMw board about the scientific quality and societal relevance of the research proposals. The programme committee is also responsible for the substantive supervision of the programme and monitoring the projects in progress. Broadly speaking, the commission of the programme committee is as follows:

1. assuming responsibility for the content of the programme throughout the duration of the programme;
2. assuming responsibility for the programming, assessment and ranking of projects. To accomplish this, an effective and transparent assessment procedure will be used. In this procedure, project proposals will be assessed for their scientific quality, their relevance for practice, and their relevance for patients and their relatives;
3. providing a contribution to the communication about and use of the results from the project and programme and creating conditions for the utilisation of those results;
4. monitoring the progress of the programme and its projects;
5. evaluating the programme (or having the programme evaluated) both during its course and after its completion. This evaluation concerns the programme's content, methods, procedures, and results as equally the timetable and finances.

ZonMw highly values objectivity in its decision-making and that the assessment procedures it realises are both transparent and meticulous. One condition for objectivity and transparency is that actual or apparent conflicts of interest are prevented. On that account, ZonMw adheres to a code of conduct (see: Code of Conduct for Dealing with Personal Interests). It is the responsibility of the ZonMw office to apply the code appropriately. To avoid every form of a conflict of interest, ZonMw has authorised the chair and secretary of the programme committee not to send documents to any committee member who could be directly or indirectly involved in a proposal and would in consequence acquire a knowledge advantage.

6.2 Role and task description guidance committee

The programme committee will be supported by a guidance committee made up of patient representatives and the chair of the programme committee. The guidance committee will advise about the programme strategy and will issue to the programme committee an assessment of both the (scientific) quality and the relevance of project proposals. Accordingly, the assessment of the guidance committee is binding, for it ranks equal to the assessment of the scientific referees in the funding procedure. For its assessment, the programme committee must clearly consider both the assessment of the referees and the assessment of the guidance committee.

Two members of the guidance committee will also be part of the programme committee and therefore convey the input from the entire guidance committee to the programme committee. For guidance committee members, participation in the programme committee is a rotating position linked to the calls for proposals under consideration. As the chair of the programme committee is also the chair of the guidance committee, he/she safeguards the continuity between what is discussed in the guidance committee and what is discussed in the programme committee.

6.3 Procedure

ZonMw uses standard procedures and criteria as much as possible for all programmes. A description of these will be given in the brochure 'Procedures ZonMw' (see Procedure ZonMw). The following sections describe the general and programme-specific procedures and criteria. These criteria form the basis, and specific criteria can be added to this in the calls for proposals to be published.

6.3.1 General procedure for a grant application

A project idea is an abridged application that is mainly assessed for relevance and a minimal assessment for quality is carried out. The use of a project idea phase is optional within ZonMw procedures. In most cases, a project idea phase will indeed be part of the ME/CFS programme, but this can be deviated from within specific calls.

The assessment of research proposals takes place in the following 12 steps, for which steps 2 to 5 are only completed in funding rounds with a project idea phase:

1. **Announcement call for proposals**
   ZonMw will announce the open round on its website, in its online relations magazine Mediator (and possibly in professional journals) and will invite interested parties to register a research proposal;

2. **Submission project idea**
   Applicants submit a short research proposal;
3. **Assessment project idea**
   Guidance committee and programme committee assess mainly the relevance of the project idea for the programme, and perform a minimal assessment of quality;
4. **Invitation or rejection project idea**
   Applicants will receive an advice not to submit a proposal or an advice to submit a full project proposal, possibly accompanied by points of attention formulated by the programme committee;
5. **Announcement call for proposals by invitation only**
   Funding round is reopened for applicants who have received an invitation to submit a full proposal in stage 4;
6. **Submission full proposal**
   Applicants submit a detailed research proposal;
7. **Referees' assessment**
   ZonMw submits each project proposal received to at least two external, independent referees who assess the quality and relevance. In the ME/CFS programme, this will often be foreign referees. These referees will be selected for different areas of expertise;
8. **Rebuttal**
   The applicant will be given the opportunity to respond in writing to the anonymised assessments of the referees;
9. **Assessment guidance committee**
   Based on the referees' assessments and the written rebuttal from the project applicants, the guidance committee will preferably formulate a single, joint advice about the quality and relevance of the project proposal.
10. **Assessment programme committee**
    The programme committee will reach a final assessment about the quality and relevance of the proposal based on the anonymised assessments of the referees, the applicant's rebuttal and the advice from the guidance committee, which weighs heavily as part of the assessment;
11. **Ranking**
    The programme committee will rank the proposal based on the assessment about the quality and relevance. The programme committee will use a ranking matrix for this;
12. **Awarding or rejection**
    Based on the final assessment and ranking, the programme committee will submit the research proposals for awarding or rejection to the ZonMw board. On behalf of the board, applicants will receive an award letter or motivated rejection from the director of ZonMw.

6.3.2 Quality criteria

The general criteria for the quality of a project proposal are:

1. **Objective and question or remit**
   This criterion concerns the subcriteria clarity, scope and originality. The objective is clear and tangibly formulated and results in a concrete and verifiable research question. Further, the scope of the question or remit is important: what is the importance of the subject, is there adequate theoretical substantiation, which knowledge and experience is already available and what will the project add to this? Finally, a research proposal may not be a duplication of previous or current projects.
2. **Action plan**
   The action plan is clear and satisfactory for the purpose of the question or task concerned. It describes the methods and analyses chosen, including the theoretical and/or empirical justification. It indicates to what extent similar work is ongoing or has been carried out previously or elsewhere.
3. **Project group or person**
   This can concern the experience and production of the group in recent years (publications, reports, guidelines, protocols, interventions, but also grants acquired and participation in (inter) national networks) and the impact of the products.
4. **Feasibility**
   For each type of project, it must be plausible that the applicant answers or realises the intended question or task with the available expertise, people and facilities in the planned time. The project description includes attention for facilitating and limiting factors. The applicant ensures – if applicable – concrete commitment from parties, target groups and intermediate target groups.

6.3.3 Relevance criteria

The general criteria for the relevance of the project are:

1. **Objectives**
   The contribution of the project to programme objectives: does the project satisfy the description of the programme and the priorities and points of attention within this (see Chapter 3)?
2. **Innovation**
   Is the project innovative and does it yield new insights?
3. **Societal/scientific importance**
   Does the project meet societal needs and does it fill scientific gaps?
4. **Ratio costs/benefits**
   What is the balance between effort, input, deployment of resources and (expected) outcomes and yield?
5. **Diversity**
   From the perspective of its general policy priorities, ZonMw explicitly includes diversity in the assessment of project proposals. This concerns diversity in gender (differences according to sex), culture (cultural differences and prevention and care for citizens of different ethnicities) and age (extra attention for young people and the elderly). In the research proposal, the applicant sufficiently describes how and why the aspects stated receive no attention, if that is the case. In the quality assessment, it will be examined whether these factors have been adequately elaborated upon in the project plan.
6. **Animal models**
   In the context of the transition to animal-free research, ZonMw encourages researchers to develop and/or apply alternatives for animal experiments. Therefore, the programme committee will pay extra attention to the justification for this if experimental animals are part of a project proposal. What is the relationship between the animal model chosen and the research question? What is the methodological and statistical rationale for the experiments?
7. **Knowledge utilisation**
   Attention to knowledge transfer and the utilisation of project results.

6.3.4 Programme-specific criteria

The programme-specific criteria for assessing the project are:

1. **Subject**
   The main objective of all research in the ME/CFS research programme is to improve the quality of life and/or societal position of patients with ME/CFS. As a result, the programme will not fund research into chronic fatigue in and of itself or research that is aimed at chronic fatigue as a consequence of illnesses or disorders other than ME/CFS. Forms of fatigue that are independent of ME/CFS can only be investigated within the research programme insofar as these occur in relation to ME/CFS.
2. **Target group**
   In the case of research with human subjects, projects must provide a substantiated description of the study population based on literature appropriate to the specific research question. This description will be assessed for how well it matches the research question but also for how this relates to the advantages and disadvantages of the various sets of criteria to define ME/CFS (see Section 2.2.)
3. **Internationalisation**
   All proposals must tie in with (international) scientific literature. International collaboration is considered to be most important within both programme lines and will be supported financially. Forms of international collaboration must be tangibly described within research proposals.
4. **Collaboration**
   Collaboration between the disciplines immunology, microbiology, neurobiology, cell biology (epi)genetics and cardiology counts as an advantage in the assessment of the proposal, but it is also possible to enter into collaborations with other biomedical disciplines or other subjects.
5. **Consolidation research field**
   At a later stage of the programme, new research should preferably supplement research already funded in the programme. This will consolidate research lines and the development of a research infrastructure.
6. **Specific target groups**
   Within the programme, there is a certain amount of emphasis on research aimed at young people or severely ill patients. During the assessment of research proposals related to severely ill (for example bedridden) patients, extra attention must be devoted to the burden on patients as a consequence of participating in research. Proposals will be assessed for whether the expected benefits of the research sufficiently weigh up against possible permanent, negative health effects due to participating in the project.
7. **Patient participation**
   Applicants must convincingly give patient participation a place in the project and justify this in the project proposal. This explanation will count towards the assessment.

6.4 Ad hoc procedure

Throughout the entire programme period, it is possible that ZonMw will publish a call or deploy a specific trajectory for the submission of scientific research that provides an answer to an urgent question. Projects aimed at urgent questions can be assessed via an accelerated procedure. This allows the programme committee to respond to recently emerging scientific research questions.

7 Monitoring en evaluation

7.1 Progress programme

As coordinators of the project teams, the programme leaders are responsible for the progress and success of the projects. The ZonMw programme team will follow the progress of projects awarded funding on the basis of progress reports, work visits and final reports. ZonMw is responsible for informing the programme committee in good time, and at least annually, about the progress of the projects. Based on this information, the programme committee assesses whether the research project – based on the original project proposal – is on course and whether the research needs to be adjusted. In doing this, the committee devotes attention to the manner and extent to which the researchers facilitate the transmission and/or utilisation of research results in practice. The programme committee is required to approve the final report of the project.

The programme committee informs the commissioning body, the Ministry of Health, Welfare and Sport, about the progress of the programme by means of an annual progress report. In this, it states on behalf of ZonMw how the programme activities have contributed to the programme objectives.

7.2 Interim evaluation

After 5 years, the programme will carry out an interim evaluation. In the interim evaluation the results achieved, (international) developments, experiences and funding rounds and other signals that reach ZonMw will be considered. Taken together, these signals can give reason to adjust the objectives of the programme.

Within the programme, it is also important to transition from initiating research and building up a research infrastructure to obtaining results, transmitting results and/or applying the results in practice. That might require a different area of expertise within the programme committee. Accordingly, the composition of the programme committee will be reconsidered after a period of 5 years.

Due to the changing approaches and objectives of the second phase of the programme, ZonMw will evaluate the personnel budget of the programme after 5 years as well. The interim evaluation will have an effect on the objectives of the new funding rounds published, but also on the projects with a duration of more than 5 years, which were awarded funding during the first funding round. ZonMw will therefore very strictly assess the progress of these projects after 5 years. ZonMw will also examine whether the outcomes expected in the remaining years of the project still reflect the (modified) objectives of the programme. The funding of the remaining years of the long-term projects depends on a positive assessment from the programme committee. In concrete terms, this means that the programme's long-term projects will be funded in two steps.

If so desired, the programme committee can consult external (foreign) experts about adjustments to the programme. Other interested parties, such as patients and healthcare practitioners, will be involved in the adjustment of the programme too. ZonMw will consult with the observer from the Ministry of Health, Welfare and Sport about proposals for a possible adjustment of the programme. These proposals are part of the annual plans of ZonMw, which are submitted to the Ministry of Health, Welfare and Sport for approval.

7.3 Final evaluation programme

In 2030, the final evaluation of the programme will take place in accordance with the ZonMw procedures. The final evaluation concerns both a process evaluation and an effect evaluation, based on the mission, basic premises, objectives and intended outcomes of the programme as described in Chapter 2. In the final evaluation, the programme priorities, approach and procedures, outcomes, timetable and finances will be considered. The outcomes of the final evaluation will be described in a programme report for the Ministry of Health, Welfare and Sport.

8 Budget

The biomedical research programme ME/CFS has a duration of 10 years in which the programme lines Biomedical research and Improving practice will be realised. The programme has a budget of 28.5 million euros. The programme's execution costs will be higher than is usually the case for ZonMw programmes because a guidance committee has been added to the standard assessment process. Consequently, twice as many meetings must be prepared and carried out by the ZonMw office: namely of the guidance committee as well as the programme committee. This also has an effect on the personnel budget for the programme.

Most of the programme budget will be spent during the first 5 years of the programme during which the large research consortia will be funded. The allocation of the funds can be found in the programme budget (Figure 3). The programme will be funded by the Ministry of Health, Welfare and Sport.

Figure 3: Budget biomedical research programme ME/CFS

1. Obligations	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	Total
Programme												
Projects: Consortium 1	-	5,000,000	-	-	-	-	-	-	-	-	-	5,000,000
Projects: Consortium 2	-	5,000,000	-	-	-	-	-	-	-	-	-	5,000,000
Projects: Consortium 3	-	-	-	5,000,000	-	-	-	-	-	-	-	5,000,000
Projects: Monodisciplinary	-	-	-	4,400,000	-	-	-	-	-	-	-	4,400,000
Projects: Fellowships	-	650,000	500,000	-	-	-	-	-	-	-	-	1,150,000
Projects: Improving practice	-	-	750,000	-	-	-	750,000	-	-	-	-	1,500,000
CIP	-	25,000	35,000	40,000	40,000	90,000	40,000	30,000	40,000	30,000	130,000	500,000
General costs												
Committee costs (travel costs and attendance fees)	-	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	200,000
General costs	-	100,000	100,000	10,000	10,000	50,000	10,000	10,000	10,000	10,000	6,676	316,676
Programme costs ZonMw	-	494,592	502,458	508,668	516,534	524,745	530,541	538,821	497,835	506,667	512,463	5,133,324
Preparation costs research programme	300,000	-	-	-	-	-	-	-	-	-	-	300,000
Total obligations	**300,000**	**11,289,592**	**1,907,458**	**9,978,668**	**586,534**	**684,745**	**1,350,541**	**598,821**	**567,835**	**566,667**	**669,139**	**28,500,000**

2. Liquidity overview	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	Total
Programme												
Projects: Consortium 1	-	500,000	1,000,000	1,000,000	1,000,000	1,000,000	500,000	-	-	-	-	5,000,000
Projects: Consortium 2	-	500,000	1,000,000	1,000,000	1,000,000	1,000,000	500,000	-	-	-	-	5,000,000
Projects: Consortium 3	-	-	-	500,000	1,000,000	1,000,000	1,000,000	1,000,000	500,000	-	-	5,000,000
Projects: Monodisciplinary	-	-	-	1,500,000	1,500,000	-	1,400,000	-	-	-	-	4,400,000
Projects: Fellowships	-	400,000	350,000	200,000	200,000	-	-	-	-	-	-	1,150,000
Projects: Improving practice	-	-	-	250,000	250,000	250,000	-	-	-	-	-	1,500,000
CIP	-	25,000	35,000	40,000	40,000	90,000	40,000	30,000	40,000	30,000	130,000	500,000
General costs												
Committee costs (travel costs and attendance fees)	-	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	200,000
General costs	-	100,000	100,000	10,000	10,000	50,000	10,000	10,000	10,000	10,000	6,676	316,676
Programme costs ZonMw	-	494,592	502,458	508,668	516,534	524,745	530,541	538,821	497,835	506,667	512,463	5,133,324
Preparation costs research programme	300,000	-	-	-	-	-	-	-	-	-	-	300,000
Total expenditure	**300,000**	**2,039,592**	**3,007,458**	**5,028,668**	**5,536,534**	**3,934,745**	**4,000,541**	**1,848,821**	**1,317,835**	**816,667**	**669,139**	**28,500,000**

3. Advance payments commissioning body	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	Total
Available according to commissioning letter	-	*28,500,000*	-	-	-	-	-	-	-	-	-	
Desired advance payment by commissioning body	300,000	2,039,592	3,007,458	5,028,668	5,536,534	3,934,745	4,000,541	1,848,821	1,317,835	816,667	669,139	28,500,000
Liquidity prognosis ZonMw (total Table 2)	300,000	2,039,592	3,007,458	5,028,668	5,536,534	3,934,745	4,000,541	1,848,821	1,317,835	816,667	669,139	28,500,000
Difference	-	-	-	-	-	-	-	-	-	-	-	-

Progress requires research and development. ZonMw funds health research and also facilitates the use of the knowledge developed so that care and health can be improved.

The principal commissioners of ZonMw are the Ministry of Health, Welfare and Sport and the Dutch Research Council. For further information about the ME/CFS research programme please contact the Secretariat via email mecvs@zonmw.nl or phone +31 70 349 5087.

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