December 2020

Research agenda ME/CFS

ZonMw

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Colophon

ZonMw is The Netherlands Organisation for Health Research and Development

Progress requires research and development. ZonMw funds health research and stimulates use of the knowledge developed to help improve health and healthcare.

ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research.

For further information on this publication or the programme, please contact the secretariat through e-mail (mecvs@zonmw.nl) or by telephone (+31 (0)70 3495 087).

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Background

On 29 October 2013, the Group ME-Den Haag presented the citizen's initiative "Recognise ME" to the Dutch House of Representatives. In the petition, the 56,000 signatories demanded more biomedical research into the causes of the disease myalgic encephalomyelitis (ME). In response to the petition, the Health Council of the Netherlands was requested to investigate the current state of scientific research into ME.

The Health Council of the Netherlands concluded that in the literature there is no agreement about whether ME and chronic fatigue syndrome (CFS) are two different diseases, and that often the overarching term ME/CFS is used. In their advisory report "ME/CFS", they recommended investing in research into ME/CFS through a long-term and substantial research programme. In line with this advice, the Minister for Medical Care and Sport requested ZonMw to develop a Research Agenda ME/CFS as a step towards designing the research programme. ZonMw appointed a steering committee for this made up of patients, care providers and researchers.

Working method

The steering committee drew up the research agenda based on information from various sources. First of all, literature about ME/CFS and, in particular, the advisory report of the Health Council of the Netherlands about ME/CFS that was published in 2018. Secondly, during conference visits, the steering committee collected information about the most recent state of research and current research projects. Thirdly, leading foreign researchers and clinicians were invited to complete an online survey about ME/CFS. Fourthly, in the autumn of 2020, working sessions were organised in which Dutch patients, researchers and care providers discussed promising lines for biomedical research into ME/CFS. Finally, on 19 November 2020, an online programme day was organised during which the proposed research agenda drawn up by the steering committee was submitted as a discussion document to Dutch patients, researchers, care providers and other interested persons. Information from all of these sources was discussed in the steering committee and was taken into account in drawing up the research agenda.

Research lines

It is the steering committee's express wish to establish a *biomedical* research programme for ME/CFS. As much foreign research into ME/CFS has not or has not been sufficiently validated, then room for replication studies must also be provided within the intended ME/CFS research programme. Research in the intended research programme can concern the following research lines:

- *Fundamental research*
  Research into (chronic) immune activation, the immune metabolism and neurological abnormalities; medical imaging research into abnormalities in brain function; research into cellular energy metabolism.
- *Epidemiological research*
  Research aimed at the development of ME/CFS within (epi)genetic factors, environmental factors and/or infectious causes; longitudinal research into the progression of ME/CFS; research aimed at a better description of ME/CFS.
- *Clinical research*
  The development of symptom management; testing of therapies known from other diseases or from abroad; research aimed at improving diagnosis.
- *Practice-oriented and action research*
  Projects aimed at disseminating (new) biomedical knowledge about ME/CFS; projects aimed at improving the treatment of ME/CFS patients in clinics and society.

Data collection and patient cohort

Providing a strict definition of the research population could be very important for the individual studies within the future programme. For that definition, researchers could use various sets of criteria for ME/CFS that have been drawn up in recent years. The research agenda's steering committee notes that in many studies into the causes and treatment of ME/CFS, the International Consensus Criteria

(ICC) for ME could be a good starting point. For research into an improved substantiation of the diagnosis ME/CFS (and possible sub-diagnoses) all characteristics that serve as diagnostic criteria in the various definitions of ME/CFS must be included.

A patient cohort set up within the research programme could provide data for the programme's individual research projects. This patient cohort must be properly characterised from an epidemiological perspective and followed over a period of several years. In building up the cohort, special attention should be paid to the inclusion of two groups of patients: young people and the severely ill.

Organisation research programme

The steering committee envisions a 10-year biomedical research programme into the causes, diagnosis and treatment of ME/CFS. In view of the intended research programme's proposed length, the steering committee expects it will need a total budget of 28.5 million euros. In that 10-year period, the steering committee wants to develop the research infrastructure for ME/CFS research in the Netherlands by, amongst other things, encouraging (international) collaboration and by focusing on transdisciplinary, multicentre research. Within this programme, research, education, professional practice and policy must collaborate as broadly as possible.

Collaboration with patients and patient organisations is also vital, as they form an important source of knowledge and contacts that researchers should use. Therefore, patients and their representatives have an important role in setting up and realising the research programme, just like they had in the drawing up of the research agenda. As ME/CFS is a relatively unknown disease, the steering committee wants to pay particular attention to implementing knowledge about ME/CFS and the results from the research programme. Only then will the research programme have a genuine impact on improving the health and societal position of ME/CFS patients.

1 Introduction

1.1 Background

On 29 October 2013, the Group ME-Den Haag presented the citizen's initiative "Recognise ME" to the Dutch House of Representatives. In the petition, the 56,000 signatories demanded more biomedical research[1] into the causes of the disease myalgic encephalomyelitis (ME). They noted that ME was not adequately diagnosed and treated and that it was incorrectly categorised as a psychosomatic condition. In response to the petition, the Health Council of the Netherlands was requested to investigate the current state of scientific research into ME. That report was published on 19 March 2018.[2]

The Health Council of the Netherlands concluded that in the literature there is no agreement about whether ME and chronic fatigue syndrome (CFS) are two different diseases and that often the overarching term ME/CFS is used. The Health Council of the Netherlands recommended investing 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 Research Agenda ME/CFS in which future biomedical research lines are formulated. The research agenda serves as the first step towards realising a research programme in this area.

For the drawing up of the research agenda, ZonMw appointed a steering committee Research Agenda ME/CFS made up of patients, care providers and researchers. The membership of the steering committee can be found in Annex A.

In May 2020, ZonMw sent a progress letter to the Minister for Medical Care and Sport about this trajectory together with a draft version of the research agenda. In the text below, you will find the final version of the research agenda as drawn up by the ZonMw steering committee ME/CFS and approved by the ZonMw board.

1.2 Commission

In its commissioning letter to ZonMw, the Ministry of Health, Welfare and Sport (VWS) stated that it wanted a future research programme to concentrate on biomedical research. This research should focus on three aspects:

- Research that can lead to an improved evidence-base for the diagnosis of ME/CFS (and any meaningful subcategories);
- Research into the aetiology of ME/CFS;
- Research into the treatment of ME/CFS.

With this wish, the Ministry followed the recommendations given in the Health Council of the Netherlands' advisory report. The Health Council of the Netherlands' recommendations formed the starting point for the research agenda (see the summary of the advisory report from the Health Council of the Netherlands and the recommendations concerning scientific research in Annex B). Two important focus areas stated in the commissioning letter are the alignment with research outside of the Netherlands and the involvement of patients in the drawing up of the research agenda.

Furthermore, the Ministry requested a prioritisation of the knowledge questions identified. As the research agenda provides the basis for a future research programme, it should also be possible to use the agenda to determine the (financial) resources needed to realise the research programme.

[1] This research agenda understands biomedical research to be: research that investigates (the improvement of) the physical function of the body, from the molecular level to the level of the entire organism. Research purely aimed at patients' psychological functioning therefore falls outside of the scope of the research agenda.
[2] Health Council of the Netherlands; ME/CFS. The Hague: Health Council of the Netherlands, 2018; publication no. 2018/07.

1.3 Aim

The aim of the research agenda is to identify urgent knowledge questions that require further research. Answering these knowledge questions must ensure that patients with ME/CFS can be helped better in the future.

Another priority of the research agenda is to create sufficient support among stakeholders. The intended ME/CFS research programme will become part of a complex field of interested parties, who will use the research programme outcomes in their professional practice. All these interested parties must support the research agenda to ensure that the research programme outcomes make a genuine difference for patients' situations. Only then can the situation of patients improve.

1.4 Working method

In its working method, the steering committee has, in accordance with the commission from the Ministry of Health, Welfare and Sport, allowed itself to be led by the recommendations from the Health Council of the Netherlands for establishing an ME/CFS research programme. The Health Council of the Netherlands stated that the Netherlands needs to make up ground in biomedical research into ME/CFS. Dutch research must align with foreign biomedical research, and Dutch researchers must contribute to the international development of knowledge about ME/CFS. Therefore, in the process of identifying knowledge questions, particular attention will be paid to research carried out abroad and the perspectives of foreign researchers.

The research agenda's working method has also taken into account the aim of acquiring support for the research agenda through, for example, the composition of the steering committee and by organising regional work sessions and a national programme day about ME/CFS. Patients and their representatives, researchers and care providers are part of the steering committee of the Research Agenda ME/CFS. Careful consideration has also been given to disseminating and implementing knowledge from the research agenda to strengthen the support for it.

The Research Agenda ME/CFS has drawn upon information from various sources:

Literature

In compiling the research agenda, the steering committee first of all made use of the advisory report ME/CFS published by the Health Council of the Netherlands in 2018. In this report, the then state of science about ME/CFS in the Netherlands and abroad was discussed. Further, the secretariat of ZonMw provided additional literature based on desk research. Finally, the steering committee members and other interested persons put forward literature about ME/CFS and policy concerning ME/CFS. The literature underlying the draft version of the research agenda is summarised in Annex C.

Conferences

Besides consulting the literature, the steering committee also obtained information about the most recent state of science and current research by attending conferences. One steering committee member participated in the conference "Accelerating Research on Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)" of the National Institutes of Health, in Bethesda (United States) in April 2019. His report was shared within the steering committee. Another steering committee member, together with a researcher selected by collaborating patient organisations, two patient representatives and a ZonMw programme manager took part in the "Invest in ME Research International ME Conference" (IIMEC14) in London (United Kingdom) in May 2019. Their conference reports were shared within the steering committee.

Survey research

To ensure that the research agenda was well aligned with foreign research, the steering committee selected a group of foreign researchers and clinicians in the area of ME/CFS and requested them to fill out an online survey. The survey concerned the content and organisation of ME/CFS research, biomedical ME/CFS research, and how Dutch research can best be aligned with foreign research. The entire questionnaire can be found in Annex D. The research results were analysed by the ZonMw secretariat and are summarised in Annex E. The outcomes were also discussed within the steering committee.

Work sessions

In the autumn of 2020, work sessions were organised for Dutch patients, researchers and care providers to inspire enthusiasm for the intended research programme. The work sessions were an opportunity for care providers, researchers and patients to explore possibilities for biomedical research into ME/CFS in the Netherlands. The commitment and enthusiasm of researchers from different disciplines and areas of expertise stimulates research into ME/CFS in the Netherlands and increases the likelihood of the future ME/CFS research programme being successful. Participants in the work sessions who gave written consent for their inclusion in the list, can be found in a list of persons consulted in Annex F.

These work sessions took place in collaboration with four interested academic research institutions, namely: Erasmus MC in Rotterdam, LUMC in Leiden, Amsterdam UMC and Utrecht University. During the work sessions, highly promising research lines into ME/CFS were discussed and aligned with the proposed research agenda. New insights from these work sessions have also been incorporated in the research agenda.

Programme day

Finally, on 19 November 2020, an ME/CFS programme day was organised. The steering committee's research agenda was submitted as a discussion document to Dutch patients, researchers, care providers, and other interested persons on the programme day. Furthermore, during this meeting, foreign speakers gave presentations about the latest biomedical ME/CFS research developments. Participants in the programme day that gave written consent for their inclusion in the list, can be found in a list of persons consulted in Annex F.

The programme day aimed to inform those present about foreign ME/CFS research and focus attention on the intended ME/CFS research programme, and the possible funding opportunities that could arise from this. At the same time, the proposed research agenda was assessed during the programme day against the vision of the stakeholders in ME/CFS research in the Netherlands. Just like during the work sessions, the programme day results were incorporated in the final version of the research agenda.

2 Research programme ME/CFS

The steering committee Research Agenda ME/CFS drew up the research agenda with the following focus areas and content based on the information available to the group. It is the express wish of the steering committee to establish a *biomedical* research programme. Contributions from a large number of experts and stakeholders in the Netherlands and abroad have been incorporated in this research agenda.

2.1 Target group

Until more knowledge exists about the causes of ME/CFS, it is difficult to accurately define the intended research programme's target group. There is no gold standard in clinical practice to describe the ME/CFS population. Every attempt to define the target group can unintentionally include or exclude patients from the population who you might want to investigate or treat. Also, during the research programme, new insights in (the pathophysiology of) ME/CFS can arise with associated new definitions of ME/CFS. A final definition of the target group for the entire programme based on the definition so far is therefore not possible at this moment. Rough limits can, however, be given.

All of the research within the ME/CFS research programme must aim to improve the health and/or societal position of patients with ME/CFS. ME/CFS is a complex pattern of symptoms and fatigue symptoms are only a part of this. ME/CFS must be investigated in all of its complexity within an ME/CFS programme. Therefore, an ME/CFS programme must not fund research into chronic fatigue as such, or research that is aimed at chronic fatigue as a consequence of diseases or disorders other than ME/CFS. Forms of fatigue that occur independent of ME/CFS can only be investigated in the research programme in so far as these occur in relation to ME/CFS.

A strict definition of the research population could be very important for the individual studies within the programme. Research groups can only be compared if there is a good description of those groups concerned. In recent years, various sets of criteria have been developed for ME/CFS that researchers could use for this purpose. These sets of criteria cover (partially) overlapping groups of patients and the one set results in a more limited ME/CFS population than another (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;[3]
- The Canadian Consensus Criteria (CCC) for ME/CFS from 2003;[4]
- The International Consensus Criteria (ICC) for ME from 2011;[5]
- The criteria for SEID of the American Institute of Medicine (IOM) from 2015.[6]

In particular, specificity plays an important role in choosing which of the different sets of criteria to use. For example, the Health Council of the Netherlands advised no longer using the Oxford criteria[7] because these define a group that is too broad and heterogeneous in nature. In the literature, post-exertional malaise (PEM) [8] is described as the most characteristic symptom of ME/CFS. Therefore, PEM has been set as a condition in more recent sets of criteria for ME/CFS, such as the CCC, the ICC, and the IOM. Now the CDC also uses the IOM criteria from 2015 and no longer the CDC criteria

[3] Fukuda K, Straus SE, Hickie I et al.; The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994; 121: 953 – 9.
[4] 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.
[5] Carruthers BM, van de Sande MI, De Meirleir KL et al.; Myalgic encephalomyelitis: international consensus criteria. J Intern Med 2011; 270: 327 – 38.
[6] 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.
[7] Sharpe MC, Archard LC, Banatvala JE et al; A report–chronic fatigue syndrome: guidelines for research. J R Soc Med 1991; 84: 118 – 21.
[8] The definition of PEM is also the subject of debate and varies between sets of criteria. In the advisory report of the Health Council of the Netherlands, PEM was described as an exacerbation of complaints after a physical or mental exertion that previously did not give rise to any problems. The type, severity and duration of post-exertion malaise symptoms can vary, and that also applies to the time interval that passes between the exertion and the exacerbation of the symptoms. The exacerbation of the symptoms is not in proportion to the size of the effort.

from 1994 in which PEM was not a condition. However, the IOM criteria have been developed as a practical instrument in the clinic and cover a somewhat broader group of patients. The ICC build further upon the CCC and come to the most narrow definition of the ME/CFS population. Although the ICC are highly specific, they use their own, somewhat divergent definition of PEM, which seems to capture a slightly different group of patients than other definitions.

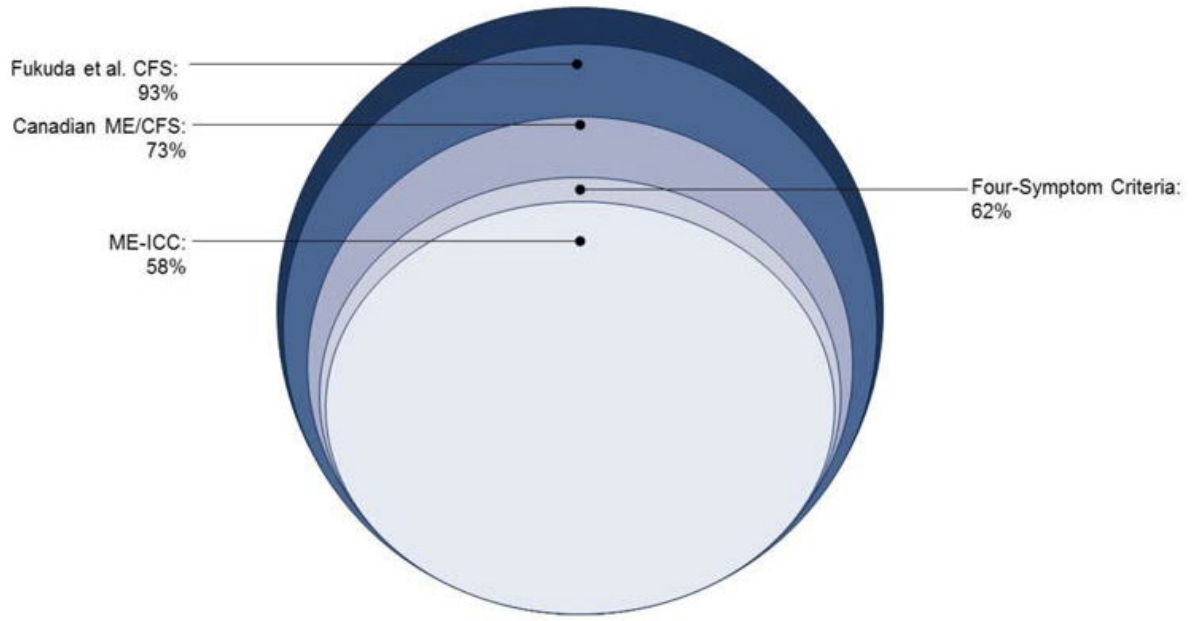

Figure 1: Comparison of different sets of criteria for ME/CFS according to patient numbers.
The International Consensus Criteria for ME (ME-ICC) from 2011 form the most recent and strict description of ME/CFS; patients who satisfy this set of criteria can currently be viewed as a core of the ME/CFS population. 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 figure does not include the IOM criteria for SEID, but these also cover a larger part of the ME/CFS population than the ICC. The population's outer limit is formed by patients who only satisfy the Centers for Disease Control and Prevention criteria from 1994 ("Fukuda"). This figure provides a comparison of the numbers of ME/CFS patients and so does not make a substantive comparison between the types of patients that fall under the different sets of criteria.

Source: Jason LA, 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 Medicine 2015; 3: 82-93.

Alignment with the current state of science is also an important consideration in the choice for a definition of ME/CFS. As a result, research proposals must seek a good alignment with the (recent) scientific literature and the definitions of ME/CFS this contains.

Activities that have taken place within the trajectory for realising the research agenda provide insight into the use of a set of criteria for ME/CFS in current research. Biomedical researchers who took part in the survey research seem to have a preference for the use of the Canadian Consensus Criteria (CCC). On the programme day, speakers who talked about their research into the development of ME/CFS stated that they use the International Consensus Criteria (ICC) in their current research. The

work sessions revealed, for example, that the UK ME/CFS Biobank (UKMEB) for ME/CFS makes use of both the CDC-1994 criteria and the CCC and IOM criteria.

Discussions about the sensitivity and specificity of various sets of criteria for ME/CFS make it difficult to choose a specific set. As researchers use different definitions of ME/CFS throughout the literature, it is difficult to compare research results and build up knowledge about ME/CFS. So how should researchers now define their research populations within an ME/CFS programme?

The Health Council of the Netherlands makes no concrete recommendation about which set of criteria should be used in research into the aetiology and treatment of ME/CFS. The research agenda's steering committee states that the ICC could be a good starting point in many such studies. The Health Council of the Netherlands recommends that for research into an improved substantiation of the diagnosis ME/CFS – and possible sub-diagnoses – all characteristics that serve as diagnostic criteria in the various definitions of ME/CFS must be included. The steering committee agrees with this advice.

In any case, researchers must be aware of the advantages and disadvantages of using different sets of criteria. In the research proposals, researchers must provide a motivated description of the research population based on the literature that fits their specific research question. It will be assessed whether this description is appropriate to the research question, but also how this relates to the advantages and disadvantages of the different sets of criteria to define ME/CFS.

2.2 (International) collaboration and research infrastructure

All proposals within an ME/CFS research programme must align with the (international) scientific literature. In addition, insofar as it is relevant, the proposals will also be assessed for international collaboration. To encourage international exchange, funds must also be reserved within the intended ME/CFS programme budget to allow researchers to participate in an NWO fellowship programme. In this way, researchers can transfer the expertise they acquired abroad to Dutch research institutions.

In the intended research programme, ME/CFS will be investigated as a multisystem disease from the perspective of various biomedical disciplines. In doing so, the emphasis is on immunology, microbiology, neurology, cell biology, (epi)genetics and cardiology. Collaboration between these disciplines can be an advantage for awarding funding, but it is also possible to enter into partnerships with other biomedical disciplines or subjects. Thus cross-fertilisation can take place, and new perspectives can be put forward. Transdisciplinary collaboration facilitates the formation of theories and the integration of research results. It is therefore highly desirable in the case of ME/CFS.

Via the research programme, the steering committee wants to establish a research infrastructure for ME/CFS in the Netherlands. Biomedical studies in the programme must strengthen each other and also bear fruit at an international level. The projects and the programme must exhibit a mutual coherency in which fundamental research, epidemiological research and clinical research are interwoven as described in Section 2.5. The aim is to build up a network in which researchers, care providers and patients structurally collaborate.

2.3 Data collection and patient cohort

Data collection is an important point of attention in the realisation of the intended ME/CFS research programme. One way of facilitating data collection and coherency in the research programme is to build up a Dutch patient cohort. This patient cohort must be properly characterised from an epidemiological viewpoint and followed over several years. Use can be made of Dutch ME/CFS patient organisations' networks to recruit patients for this cohort. The cohort must be large enough to be able to draw statistically significant conclusions, also about possible subgroups. In addition, the cohort must be a good reflection of the intended target group (young, old, degree of disease burden, etc.).

A separate mandate must be given to establish a patient cohort, and financial resources must be reserved for this within the research programme's budget. This mandate should also include which data at the very least should be elaborated and what the minimum size of the cohort – and possible subgroups – should be to achieve statistically significant results.

In the patient cohort's composition, considerable attention should be paid to the quality of patient selection for the research. This quality must be safeguarded by following an established diagnostic protocol and an assessment that is performed by expert and experienced clinicians. For this purpose, connections should possibly be made with experts abroad.

The recruitment of patients for the patient cohort will lead to a heterogeneous population from which the data collected must be classified based on known sets of criteria for ME/CFS (see also Section 2.1). Biomaterials and data (blood, brain scans, cardiovascular data, questionnaires, etc.) must be taken and stored in as standardised a manner as possible. For this, it might be helpful to use standards for clinical research, such as the Common Data Elements for ME/CFS of the American National Institute of Neurological Disorders and Stroke. Standardising data facilitates the alignment of research results with other research in the Netherlands and abroad and is therefore encouraged by ZonMw.

In the structure of the cohort, special attention will have to be paid to the inclusion of two groups of patients: young people and the severely ill. The work sessions and the programme day revealed that investigating young people and adolescents with ME/CFS merits special attention because ME/CFS seems to develop differently in these groups. In line with the advisory report of the Health Council of the Netherlands, the research programme should also focus on investigating severely ill patients since they have not generally been part of investigations until now. This concerns patients who are housebound or completely bedridden and dependent on care. The limitations of these patients require a specific approach and logistics. Inclusion of this group will require house visits by research nurses who have been specifically trained for this. The survey among foreign researchers and the work sessions revealed that much experience can be obtained from abroad for this purpose. During the assessment of research proposals that concern this group, extra attention must be paid to the burden experienced by patients due to participating in the research. The research's expected benefits will always have to be carefully weighed up against the possible permanent, negative health impacts that could occur due to participation.

Research into the incidence and prevalence of ME/CFS within the Dutch population and research into the role of environmental factors in the development of ME/CFS can be realised in different ways, for example, by using an existing population cohort. However, within the population cohort to be used, it is important to define and investigate ME/CFS in the right manner. Due to the shifting definitions of ME/CFS, such research is probably more appropriate in a later phase of the programme. For research within the existing population cohort, it is expected that additional questionnaires and tests selected by the ME/CFS researchers will need to be submitted. The research projects will have to reserve funding to use existing population cohorts and deploy ME/CFS-specific questionnaires and tests within these population cohorts.

ZonMw encourages the sharing of data generated in the research by means of its Open Science policy. ZonMw strives to realise the production of data that is findable, accessible, interoperable, sustainably stored and reusable (FAIR). From 2021 onwards, new rules about Open Access publishing will come into force and ZonMw will make Open Access publishing compulsory. Projects within the intended programme ME/CFS must satisfy the requirements set by ZonMw for the publication and sharing of data.[9]

2.4 Replication studies

A lot of foreign research into ME/CFS has not or has not been sufficiently validated, as a result of which the value of the research results remains unclear. Furthermore, in science, there is a general trend towards a positive publication bias in research results. In response to this, the Royal Netherlands Academy of Arts and Sciences recently issued a report about the importance of publishing negative research results and the importance of replication studies.[10]

This also applies to ME/CFS. So far – as the advisory report from the Health Council of the Netherlands also shows – few sufficiently substantiated studies have been carried out into the causes of ME/CFS. The Health Council of the Netherlands advises tackling this problem through replication

[9] See: https://www.zonmw.nl/nl/over-zonmw/open-science-fair-data
[10] Royal Netherlands Academy for Arts and Sciences; Replication Studies – Improving reproducibility in the empirical sciences. Amsterdam: KNAW, 2018.

studies in the area of ME/CFS. Therefore, besides original research, the intended ME/CFS research programme will also provide room for replication studies, for example into pharmacological treatments. The replication studies carried out have to use the same definition of ME/CFS as the research replicated and will therefore probably make use of older definitions of ME/CFS. However, in these replication studies, older definitions of ME/CFS can also be combined with more recent and specific definitions, as a result of which new insights into ME/CFS could arise.

2.5 Research lines

For *fundamental research*, the steering committee recommends the following research lines:
- Research into (chronic) immune activation (e.g. after viral infections and host-microbe interaction and the intestinal microbiome), immune metabolism and neurological abnormalities;
- Brain imaging research to examine disruptions in the functioning of the brain;
- Research into cellular energy metabolism linked to cell function.

For *epidemiological research*, the following subjects merit attention:
- Research targeted 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 prognostic studies;
- Research aimed at a better description of ME/CFS, so that a better diagnosis can be established, and subgroups and comorbidities can be determined.

Greater insight into the cause or biological mechanisms of ME/CFS will allow more targeted and innovative therapies to be developed. For benefits in the somewhat shorter term with regard to *clinical research*, it is already possible to start with:
- Testing of (existing) treatments that alleviate important symptoms;
- Testing of treatments known for other diseases, such as frequently occurring comorbid conditions with ME/CFS;
- Identifying and testing ME/CFS therapies used abroad;
- Research targeted at an improved diagnosis, for example physiological tests/exertion tests, biomarkers, serology.

Finally, the steering committee recommends allocating room within the programme for *practice-oriented and action research* targeted at:
- Implementing (new) biomedical knowledge about ME/CFS in the Dutch healthcare system and among Dutch healthcare providers, medical assessors, guideline developers, etc. (see also Section 3.2: Use of knowledge);
- Improving how ME/CFS patients are treated in clinics and by society, in line with existing experiential studies under Dutch ME/CFS patients (see also Annex C).

3 Organisation of the programme

3.1 Duration and phasing

The Health Council of the Netherlands advised instituting a long-term research programme. The steering committee therefore started from the idea of a biomedical research programme with a duration of 10 years. Such a comprehensive programme is necessary given the ground that the Netherlands need to make up with regard to research into ME/CFS. An active research infrastructure in which productive collaboration takes place needs to be put in place. Furthermore, there are currently major knowledge gaps regarding the causes, diagnosis and treatment of ME/CFS. The proposed fundamental, epidemiological and clinical research must provide answers to these questions. All project proposals must be co-assessed by internationally renowned experts in biomedical ME/CFS research.

As the research into ME/CFS is still very much under development, the steering committee thinks it is not advisable to stipulate precise lines of research for a period of 10 years. That would mean losing the possibility to adjust the programme based on research outcomes and/or new insights. It is, however, clear that in the initial years of the programme, priority must be given to building up a patient cohort and establishing a research infrastructure. Then individual research proposals within a programme can subsequently build further upon these facilities.

It is also proposed that the next four years are filled as well as possible with internationally assessed project proposals for one of the research lines stated in Section 2.5. After the first three years, the research lines for the next four years can be set out based on a self-evaluation that is conducted in collaboration with the research committee and the field. The subsequent four years can also partly focus on the implementation of the results from the initial years. The last two years of the programme must be fully devoted to completing current projects and implementing results.

3.2 Knowledge utilisation

Knowledge transfer and implementation of research results are vital for improving everyday life for patients and daily practice for care providers. As a result, ZonMw attaches considerable importance to this. Knowledge transfer, the implementation of societal and scientific outcomes of the research, and communication about these, are structurally embedded in all ZonMw programmes. Disseminating the knowledge acquired from the research projects and the use of this knowledge by researchers, care professionals and patients will therefore receive a lot of attention throughout an ME/CFS research programme. This will be further detailed in the programme text of the research programme.

It is expected that the intended ME/CFS programme will have a large fundamental biomedical component. For these research results, the implementation must mainly be seen as a transition to new (and possibly more applied) research. Where the programme concerns more applied research, the results of the research projects will have to be implemented within the relevant professional groups and organisations. Researchers who receive funding from ZonMw will be required to actively collaborate on knowledge transfer and the implementation of the outcomes. It could be important to involve parties from outside the research group in the implementation. Research proposals must describe the preparations and approach for the implementation, and this will be assessed during the evaluation of proposals.

A more comprehensive way the research programme can facilitate the transfer and utilisation of knowledge is to stimulate the knowledge infrastructure through mutual collaboration between research, education, practice and policy. Little is known yet about the causes, diagnosis and treatment of ME/CFS. University hospitals and universities must collaborate as broadly as possible in the research programme to remedy this and to improve the position of ME/CFS patients within the programme’s duration. Within the research programme, this collaboration will be supported in the calls for proposals by encouraging the formation of consortia and the realisation of multicentre research. Participants from different centres will be obliged to maintain intensive contact with each other about the progress and outcomes of the studies. Multicentre research also encourages the transfer of knowledge from research to clinical practice. A good regional spread of the consortia is therefore important so that patients can participate in and benefit from the (knowledge accumulated within) the

research programme. With this approach, a knowledge infrastructure for ME/CFS will be developed within the Netherlands.

Communication plays an important role in achieving societal and scientific impact. ZonMw therefore considers communication about the research carried out in the programme to be important. It will facilitate the mutual sharing of (interim) research results through meetings for project leaders. Here, project leaders from different research projects can keep each other informed about advances within their research and discuss possible (shared) problems. Besides making the research more efficient, the meetings also facilitate collaboration and the realisation of the desired Dutch infrastructure for research into ME/CFS.

ZonMw also encourages the communication of research results to a wider public. With this type of communication, research can be tested against the observations and experiential knowledge of stakeholders. Continuous communication about the research increases the involvement of the field and strengthens the opportunities for implementation. In addition, communication about (interim) research results can have a short-term positive effect on the public perception of ME/CFS and, consequently, how patients are treated within clinics and by society. A possibility for sharing interim and final results is establishing an (online) ME/CFS knowledge platform. This can be used to share results from the programme and other relevant developments from the Netherlands and abroad for both a scientific public as well as for care providers and patients. ZonMw can also share this information via its internal communication channels, such as its newsletters and in social media.

3.3 Patient participation

Patient participation can help to further the progress of research within healthcare. Collaboration with patients and their family ensures that the research is better connected with everyday practice. ZonMw therefore encourages patient participation in all of its projects and studies. Patients and their representatives were closely involved in drawing up the research agenda. For example, patients and their representatives were part of the steering committee responsible for drawing up the research agenda. ZonMw supported them in this role through a patient liaison officer. Patients and their representatives have played a prominent role in all activities that were part of the trajectory, such as the work sessions and the programme day. They formed an important source of knowledge about ME/CFS and contributed access to their valuable network of contacts with (foreign) researchers to the trajectory. The patient organisations represented within the steering committee have indicated to ZonMw that they would like to participate in a programme committee ME/CFS. ZonMw has indicated that if it receives a commission to establish a programme ME/CFS, then the patient organisations will play an important role in writing the programme text and realising the research programme.

4 Budget

Given the future biomedical ME/CFS research programme's proposed length, the steering committee expects to need a total budget of 28.5 million euros. The steering committee provides the following argumentation for this based on its deliberations about the importance of the various types of research within the proposed research programme. The number of studies that will be awarded funding for the different types of research is a reflection of how important the steering committee considers those studies to be. The financial prognosis of the different types of research is based on ZonMw's experience with similar research in other ZonMw programmes. This experience provides reference amounts for the different types of research, which are based on averages. The amounts stated are indicative.

Patient cohort

For the research involving patients stated in the research agenda, a patient cohort needs to be built up. Investments are associated with this. A protocol will need to be developed and, following approval from the programme committee, implemented. One aspect of this protocol is the description of the inclusion of patients and the storage of data and biomaterials. Which data storage and biobank facility can best be used for this purpose? The basic premise is the reuse of the data and biomaterials obtained. The steering committee estimates the associated costs to be 3.0 million euros.

Research infrastructure and multicentre research

Realising the research programme requires a durable infrastructure for Dutch research into ME/CFS. The Netherlands needs to catch up in this respect. One instrument for realising a research infrastructure is to require project proposals to be submitted by consortia and to involve multicentre research. These are often expensive proposals with a duration of 4 years that each require a budget of 1 to 1.2 million euros.

In collaboration with the research field and before the call for proposals is published, ZonMw must devote considerable attention to providing information about the call: what are the specific substantive requirements with respect to the proposal? Which conditions will apply to the collaboration? How must the patient participation be arranged in the proposal? In the various calls of the programme, the aim is to award funding to several consortia and multicentre proposals. In doing so, the national spread of the proposals is an important point for attention. The funding of eight proposals will involve an investment of almost 10 million euros.

Monodisciplinary research

The intended ME/CFS research programme must also provide opportunities for monodisciplinary projects that provide a demonstrable added value to the projects awarded funding within the consortia and multicentre research. These monodisciplinary projects can concern the fundamental, epidemiological and clinical research lines proposed in the research agenda, including research that is not patient-oriented. Based on five projects and assuming an amount of 400,000 euros per proposal, and the fact that projects embedded in a consortium proposal or in multicentre research will be encouraged, this will require a total budget of 2 million euros.

Clinical research

For ME/CFS patients, the investigation of fundamental research questions means that they will have to wait a long time before the research results can have an effect on their daily lives. Therefore it is also important to encourage clinical research in the programme. The application of research results from this clinical research might have positive effects in the shorter term on the daily life of (groups) of ME/CFS patients. For example, this concerns studies into testing (existing) treatments that alleviate important symptoms, testing known therapies for other disorders, such as comorbid disorders that frequently occur with ME/CFS, and identifying and testing ME/CFS therapies used abroad. A budget of 4 million euros will be required to fund eight projects in this area, assuming a budget of on average 500,000 euros per project.

Population research

To answer questions with respect to incidence, prevalence and environmental factors responsible for the development of ME/CFS, the steering committee assumes four to six studies with an average budget of 500,000 euros each. That amounts to a total budget of 3 million euros. Among other things, this budget can be spent on using data from a Dutch population cohort and possible adjustments to their data collection.

Practice-oriented and action research

This research is mainly aimed at improving how ME/CFS patients are treated in clinics and society, and it is aligned with existing experiential studies among Dutch ME/CFS patients (see also Annex C). This means initiatives aimed at care professionals who work in primary care and at umbrella organisations for company doctors and doctors affiliated with insurance companies. It is estimated that with the awarding of three to four projects, an amount of 1.5 million euros will be needed.

International exchange

Within the ME/CFS programme budget, funds must be reserved for researchers to participate in an (NWO) fellowship programme. With this funding instrument, efforts will be made to seek connection with international research groups and research programmes, and to encourage the development of a Dutch infrastructure. This will be done, for example, by imposing specific requirements on a fellowship awarded with respect to the setting up of Dutch research that aligns with international research. The awarding of three fellowships will involve about 1.5 million euros.

Communication and implementation

ME/CFS is a relatively unknown disease. It is vital for the position of patients that knowledge about ME/CFS and the research programme results are implemented in both the research field and everyday practice. For this purpose, ZonMw can actively deploy various communication and implementation instruments that are available to it. The publication of results on websites is a convenient instrument that will certainly be deployed. However, the steering committee thinks that more is required. Meetings must be organised where knowledge transfer can take place, such as project leaders meetings, seminars for care professionals, et cetera. Working with consortia and multicentre research also provides a basis for centralising scientific knowledge about the causes and treatment of ME/CFS. Networks need to be formed and a platform developed on which the results are accessible to everybody. This requires more communication, implementation, and knowledge transfer costs than is the case for more standard research programmes. It is estimated that 3 to 4 million euros will be needed for these activities.

Table 1: Indicative estimated budget ME/CFS research programme *

Aspect	**Amount in M€**
Patient cohort	3.0
Research infrastructure/multicentre research	10
Monodisciplinary research	2.0
Clinical research	4.0
Population research	3.0
Practice-oriented and action research	1.5
International exchange	1.5
Communication/implementation	3.5
Total	**28.5**

* This substantiation of the budget excludes the costs for realising the programme.

Research agenda ME/CFS

Annexes

ZonMw

Annex A: Composition of ME/CFS Research Agenda Steering Committee

Chairman
J.K. (Jan) van Wijngaarden

Steering committee members
Prof. dr. J.W. (Jan Willem) Cohen Tervaert
Drs. L. (Lou) Corsius (ME/cvs Vereniging)
Prof. dr. H. (Hemmo) Drexhage
Drs. Y. (Ynske) Jansen (Steungroep ME en Arbeidsongeschiktheid)
Prof. dr. A.D. (Aletta) Kraneveld
T. (Theo) Kuiphof (ME/CVS Stichting)
Prof. dr. P.J. (Peter) v.d. Spek
F.C. (Frans) Visser *(tot 13 april 2020)*
R. (Rob) Wijbenga (Groep ME-Den Haag)

Observer Dutch Ministry of Health, Welfare and Sport
R. (Renske) van Tol

Annex B: Summary of the advisory report on ME/CVS by the Dutch Health Council

ME/CFS

No. 2018/07

Executive summary

Health Council of the Netherlands

ME/CFS is a serious chronic disease that substantially limits the activities and quality of life of people suffering from it. Patients with ME/CFS have been campaigning for recognition and better treatment of their condition for years. In response to a citizens' initiative, the Lower House asked the Health Council to provide insight into what is scientifically known about the disease and what developments are to be expected. The ME/CFS Committee investigated this subject. This committee consisted of experts from various fields and patient representatives. Different views on ME/CFS were represented.

The disease: symptoms, pathogenesis and diagnosis

People with ME/CFS suffer from a substantial reduction in the ability to engage in pre-illness levels of social and personal activities, which lasts longer than six months. They suffer from severe fatigue that is not caused by exertion and is not substantially alleviated by rest. Minor physical or mental effort can already exacerbate the complaints. Almost all patients have a disturbed sleep. Neurocognitive problems (concentration, memory, comprehension) and orthostatic intolerance (such as dizziness, nausea, headache, weakness) are also common. In addition, pain, fever and enhanced sensitivity are symptoms that may occur.

The committee notes that little is known with certainty about the pathogenesis of the disease. Various body systems can be involved, such as the immune system, metabolic system, cardiovascular system, central nervous system, neuroendocrine system, microbiome and genome. Therefore, it is called a 'multisystem disease'. It is unclear how these systems interact in the development of ME/CFS. There may also be several diseases that fall under ME/CFS.

The diagnosis of ME/CFS is made based on symptoms. There is no agreement in the scientific literature on the criteria that should apply. The committee believes that the diagnostic criteria proposed in 2015 by the Institute of Medicine (currently: National Academy of Medicine) provide for the time being a good tool for practitioners.

As with the pathogenesis, there is little to say with certainty about the prevalence and the course of the disease. Presumably, there are 30,000 to 40,000 patients in the Netherlands with ME/CFS, most of whom are female. Their chance of spontaneous recovery is low.

Treatment of ME/CFS

Treatment of ME/CFS cannot be aimed at addressing the causes of the disease, due to lack of knowledge. However, sometimes it is possible to relieve the symptoms of the disease. It is important for the physician and patient to explore the options together. For example, patients may benefit from medicines such as sleeping pills, analgesics and agents that positively influence intestinal motility. The

majority of the committee believes that cognitive behavioural therapy (CBT) can also be considered as an option for treatment. Four members take a different view. They indicate that many patients with ME/CFS have negative experiences with the therapy and object to the form of CBT for ME/CFS applied in the Netherlands.

ME/CFS in practice

Many physicians have preconceptions about ME/CFS and about the patients who suffer from it. They are inclined to suggest that the disease is psychological. As a result, patients do not experience empathy from their physicians and feel that they are not taken seriously, which does not improve their health and reinforces their social isolation. A survey from the Dutch ME/cfs Association reveals that 75% of the patients rate the quality of care as highly inadequate. Patients also frequently experience problems in the assessment of claims on income, care and other provisions because the limitations of their functional capabilities are not recognised. This is partly due to misinterpretation of the rules. Sometimes patients are found to be fit for work because an insurance physician believes that no physical abnormality can be proven or an unequivocal diagnosis cannot be made. However, according to the applicable rules, these are not good reasons to disregard someone's limitations. The point is that there is a consistent set of impairments, limitations and disabilities. The committee reiterates that ME/CFS is a serious disease that, by definition, generally leads to substantial restrictions on functional possibilities. Furthermore, the committee believes that patients must be free to decide whether to have CBT – or, in the Netherlands not or hardly used as a self-standing treatment for ME/CFS, graded exercise therapy (GET) – as part of their treatment. Not choosing for CBT or GET may not lead to the judgement that the patient misses his chance of recovery or is to blame for not cooperating in his/her recovery.

Conclusions and recommendations

Scientific research on ME/CFS is needed to serve patients better. Meanwhile, it is essential that ME/CFS is a diagnosis that is made in practice, that patients' disease symptoms are taken seriously and treated as well as possible. Their functional limitations must also be fully recognised in the assessment of claims on income and other provisions.

The committee recommends the following.

- The Minister of Health, Welfare and Sport should commission ZonMw for a long-term, substantial research programme on ME/CFS. The research would primarily focus on substantiation of the diagnosis, pathogenesis and treatment of ME/CFS.
- Those responsible for training and further education of healthcare providers should ensure that education and training highlight the serious, chronic, multisystem disease ME/CFS and what healthcare providers can do for patients with this disease.

- The Federation of University Medical Centres and the healthcare insurers should designate a few university medical centres that – in collaboration with patient representatives, other hospitals, GPs, rehabilitation centres, sleep centres and other healthcare providers in the region – will open an outpatient clinic for ME/CFS, with associated healthcare networks and research groups.
- Medical disability assessors within the context of private and social disability insurance, the Social Support and Provision Act and the Long-term Care Act should recognise that ME/CFS is a serious disease that is accompanied by substantial functional limitations, and they should not regard a patient's decision to forego CBT or GET as inadequate recovery behaviour.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This publication can be downloaded from www.healthcouncil.nl.

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Annex D: online survey ME/CFS researchers from abroad

Personal details
Name:
Organisation:
Area of expertise:
Affiliation:
I participate in the following research collaborations on ME/CFS:

Questions internet survey:
Q1 Name:

Q2 Organisation:

Q3 Area of expertise:

Q4 I participate in the following research collaborations on ME/CFS:

Q5 What type of research would you recommend? (e.g. epidemiological research, fundamental/mechanistic research, replication studies, clinical studies, etc.)

Q6 From what scientific discipline would you recommend conducting research? (e.g. neurology, immunology, genetics, microbiology, metabolomica, mitochondrial function biology…)

Q7 Which body systems are relevant to the study of ME/CFS?

Q8 What research into the pathophysiology of ME/CFS do you find most promising?

Q9 What research on the diagnosis for ME/CFS do you find most promising?

Q10 What research on treatment of ME/CFS do you find most promising?

Q11 What kind of research do you think could best benefit the lives of patients in the short term?

Q12 How do you ensure a good definition of the research population?

Q13 Which criteria for ME/CFS would you use?

Q14 Which tests would you use?

Q15 What is the role of PEM/PENE?

Q16 Would you recommend targeting research on specific ME/CFS subgroups? (e.g. children, severely affected, etc.)

Q17 How would you adjust a study design to ensure enrollment of severely affected patients?

Q18 Which co-morbidities of ME/CFS do you consider relevant to ME/CFS research?

Q19 Do you consider the use of big data relevant for the research on ME/CFS?

Q20 Do you in your research use data from existing and/or recently conducted studies?

Q21 How would you stimulate the development of multi-disciplinary research and what is the most promising combination?

Q22 What Dutch researchers or research groups would you be interested to collaborate with on ME/CFS?

Q23 What (historical) developments in ME/CFS research are important to keep in mind when setting up new research on ME/CFS? In what way should these affect new research?

Q24 How do patients or patient groups participate in your research?

Q25 How would you engage other (particularly young) researchers in doing research on ME/CFS?

Q26 The foreseen Dutch research grants program on ME/CFS is scheduled be open for calls as of the beginning of 2021. Would you be willing to act as external reviewer to the grants committee, to assess the scientific rigour and relevance of the submitted research proposals?

Annex E: Analysis online survey researchers from abroad

Sabine de Jong
6 April 2020

Here we present a brief analysis of the research results from a short qualitative study among international researchers about research into ME/CFS. The research results were collected in the period 1 to 18 March 2020 among 23 international researchers and contribute to the content of a Dutch research agenda for ME/CFS.

Research disciplines involved

ME/CFS is a disease for which the pathophysiological background is largely unknown. The following body systems are correlated with ME/CFS: the immune system, the autoimmune and central nervous system, the cardiovascular system and the gastrointestinal system. One hypothesis is that the cellular metabolism in these body systems is deregulated, which causes the abnormalities found in these body systems.

ME/CFS is therefore considered to be a multisystem disease and a Dutch research programme should therefore provide opportunities to examine ME/CFS from the perspective of different disciplines. The researchers who completed the survey emphasised the importance of immunology, neurology (including medical imaging brain research), cardiology and cell biology. Multidisciplinary, international collaboration between these disciplines seems to be desirable within the research programme. Equally, it must be possible for individual research projects to enter into collaborations with other disciplines or other subjects. Then cross-fertilisation can take place, and new perspectives can be put forward.

Type of research

The researchers think that the Dutch research programme should mainly focus on fundamental research, epidemiological research and clinical studies.

Fundamental

Consulted researchers accord the highest priority to carrying out fundamental research into ME/CFS. There are many research questions that could contribute to a better understanding of the pathophysiology of ME/CFS; there must be room for this diversity within a ME/CFS research programme. Based on the online survey, the following research lines deserve to be given prominence:

- Research into (chronic) immune activation or neurological abnormalities;
- Brain imaging research to investigate disruptions in brain metabolism;
- Cell research in which the cellular metabolism is investigated;
- Research that can contribute to developing physiological tests and/or finding a clinically usable biomarker for ME/CFS.

Epidemiological

Epidemiological research can focus on both prospective and retrospective studies using existing data. For this, the patient groups need to be well defined, the data need to be standardised (where possible) and body material may be collected too. Possible lines of questioning are:

- Research targeted at the aetiology of ME/CFS: an (epi)genetic basis for ME/CFS, the influence of environmental factors or research into infectious causes;
- Longitudinal research into the progression of ME/CFS and prognostics studies;
- Research targeted at a better description of ME/CFS, which can contribute to a better diagnosis; in doing so, subgroups and/or comorbidities could also be established;
- A comparison of how ME/CFS is diagnosed in different countries to increase the possibilities for comparative analyses of the research results.

Clinical

When it comes to improving the situation of patients via biomedical research, the researchers see most opportunities in clinical research. However, the chance that clinical research yields relevant results is greater once the pathophysiology of ME/CFS is understood. Interesting areas for clinical studies are:

- Research aimed at improving diagnosis, e.g. through physiological testing such as exertion tests and biomarkers;
- Testing treatments based on hypotheses about the pathophysiology of ME/CFS;
- Testing therapies that are known from related diseases;
- Testing treatments that alleviate the most important symptoms;
- Research in subpopulations to examine whether these gain more benefit from specific treatments than other groups. For the time being, this should mainly focus on children or the group of patients that is most seriously ill, for example. Eventually, this research could be based on biomarkers.

Carrying out research

The survey provides several recommendations for realising ME/CFS research that are important for establishing a research programme:

- First of all, *who* is the subject of the research? Until we have a better understanding of the pathophysiology of ME/CFS, there is no clinical standard that can be used to define the ME/CFS population. How ME/CFS studies have been described over the years differs, which has consequences for a comparative analysis of the results from different studies. At present, many researchers trust the “Canadian Consensus Criteria” for defining the population of their studies. Even so, a *motivated* choice should be made for each study.
- Secondly, *how* will this research be carried out? On the one hand, researchers must think carefully about this so that they do not unnecessarily burden patients. Therefore, researchers who completed the survey made house visits or allowed biomaterial or questionnaires to be sent by post. On the other hand, it is challenging to find similar control groups in terms of lifestyle for the research proposed under – certainly the most ill – ME/CFS patients. In the context of feasibility, the proposed research should describe a solution to this problem in advance.
- Finally, the researchers stated that in ME/CFS research, it is important to take ME/CFS-specific factors into account. The start/case history of the disease, disease duration and/or time of day during which the body material is taken are several such factors that could give rise to relevant distinctions in, for example, epidemiological research.

Annex F: List of consulted persons

Researchers, healthcare providers, patients, policy makers and other stakeholders participated in varying compositions in the working sessions and the programme day. Table 1 shows the number of participants per meeting. Table 2 lists the participants in the working sessions and the programme day who gave written consent for their names to be included in the research agenda.

Table 1: amount of participants working sessions and programme day

Meeting	Date	Amount of participants
Working session Rotterdam	25 Augustus 2020	13
Working session Leiden	28 October 2020	18
Working session Amsterdam	2 November 2020	33
Working session Utrecht	4 November 20202	29
Programme day	19 November 2020	165

Table 2: participants working sessions and programme day (each of these participants gave permission to publish their name in the research agenda)

1 Ona Albizu	41 Carolien van Leijen
2 Peter van Baarlen	42 Esther Leijte
3 Ronald Bartels	43 Henk Lindeman
4 Heleen Beckerman	44 Paul Lucassen
5 Celia Berkers	45 Evy Maas
6 Anneke Blom	46 Olivia Manusama
7 Marco Borhem	47 Jos van der Meer
8 Jos Bosch	48 Paula Metselaar
9 Martine Brandt	49 Frank Meuter
10 Evelien van der Brink	50 Fenny Michel
11 Brian Buddenberg	51 Renate van der Molen
12 Dan Cohen	52 Max Nieuwdorp
13 Ellie Corazolla	53 Cor Oosterwijk
14 Annemiek van der Doe	54 Antoine van Orsouw
15 Mieke van Dokkum	55 Martina den Otter
16 Aafje Dotinga	56 Jolien Plantinga
17 Miek de Dreu	57 Celine Ripzaad
18 Petra van Driel	58 Simone Ros
19 Marleen Eijckholt	59 Pierre de Roy
20 Fernando Estevez-Lopez	60 Magda van Schijndel
21 Marijke Geutskens	61 Simone Schweizer
22 Dink van Ginkel	62 Peter Sloot
23 Daphne Gorter	63 Martijn Spruit
24 Jorg Hamann	64 Michiel Tack
25 Michelle van der Heijden	65 Tanja Valeri
26 Sigrid Heinsbroek	66 Mary-Anne Verhoofstad
27 Bob van Heukelom	67 Ruud Vermeulen
28 Anouk Holthausen	68 Celine Verweij
29 Rini Holthausen	69 Arnaud Vincent
30 Witte Hoogendijk	70 Egbert Vis
31 Riekelt Houtkoper	71 Berber Vlieg-Boerstra
32 Hanneke Hulst	72 Clemens Vloedgraven
33 Ettie de Jong	73 Remco Westerink
34 Brigit de Jong	74 Eelco Wicherts
35 Frans Kingma	75 Guido van Wingen
36 Maarten Klatte	76 Saskia de Wit
37 Natasja Koldijk	77 Marjon Wormgoor
38 Erwin Kompanje	78 Nico Wulffraat

39 Sophie Kooman	79 Marcel de Zoete
40 Cor Langedijk	80 Anke Zoontjens

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ZonMw is The Netherlands Organisation for Health Research and Development

Progress requires research and development. ZonMw funds health research and stimulates use of the knowledge developed to help improve health and healthcare.

ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research.

For further information on this publication or the programme, please contact Sabine de Jong through e-mail (mecvs@zonmw.nl) or by telephone (+31 (0)70 3495 087).

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