

**Report of the External Review Committee  
of the 2014 evaluation of CARIM (Cardiovascular Research Institute Maastricht),  
School for Cardiovascular Diseases  
FHML Maastricht University and Maastricht University Medical Centre+**

***Introduction***

Scope and context of this review

This assessment covers the research, the Research Master programme and the PhD training programme as carried out in, or in collaboration with and under responsibility of the Cardiovascular Research Institute Maastricht (CARIM), School for Cardiovascular Diseases. For several decades already, CARIM has a strong position in the international cardiovascular research and aspires to be one of the top institutes for translational cardiovascular research in Europe.

The assessment is executed by an External Review Committee (ERC) at the request of the management of CARIM and of the Dean of the Faculty of Health, Medicine and Life Sciences (FHML) following approval by the Executive Board of Maastricht University. The assessment of the institute is carried out in accordance with the rules of the Standard Evaluation Protocol (SEP) 2009-2015, the protocol for periodic research assessment in the Netherlands (updated June, 2010). This protocol has been drawn up by the Association of Universities in the Netherlands (VSNU), the Netherlands Organisation for Scientific Research (NWO) and the Royal Netherlands Academy for Arts and Sciences (KNAW). The main criteria in SEP evaluations are quality, productivity, societal relevance and vitality and feasibility.

The terms of reference

In accordance with the SEP, the terms of reference of the ERC are defined as a major tool to advise the Board and Management of CARIM to sustain and improve quality of their research and education programmes and to give foundation to strategic decision-making procedures. The focus of the assessment should be on the educational programmes and on the scientific research programme, which should include judgment of CARIM's scientific productivity, the relevance of the research and the institute's viability. The Dean of the FHML has asked the ERC to pay special attention to the relation between the strategic choices of CARIM and the further development of the Cardiovascular Center Maastricht (CVC), and to CARIM's ability to respond adequately to new developments in the field, based on its strategy. In addition, the Dean appreciates the ERC's opinion whether the CARIM's PhD training programme sufficiently reflects the broad area of research, CARIM is engaged in, and the quality of the programme. Finally, the ERC has been asked to pay attention to the duration of the average PhD trajectory within CARIM.

The mission of CARIM

As described in the self-evaluation report 2007-2012 the mission of CARIM is to:

- Improve current knowledge of the processes underlying cardiovascular diseases by carrying out pioneering and excellent scientific research extending from 'molecule to patient to population', i.e. the epidemiology of cardiovascular and metabolic diseases;
- Stimulate and facilitate the collaboration between basic and clinical scientists, as an essential factor in ultimately improving health care;
- Develop into an internationally recognised centre of excellence in cardiovascular medicine;
- Train Master's students, PhD students and MD students to become independent researchers and post-docs to become leading scientists who are capable of functioning in multidisciplinary research programmes at universities or companies;
- Evaluate new findings, products and techniques for applicability in health care, often in collaboration with private companies;
- Publish scientific results in highly ranked journals.

## The strategic goals

Based on a SWOT analysis and its follow-up strategic meeting, the strategy for the coming years has been divided into the following areas: research, collaboration, infrastructure, funding, CVC (translation to the clinic), education and publication strategy. A regular series of strategic meetings specifically addressing the question of how CARIM has to respond to the changes in the scientific landscape will be installed.

The future research strategy of CARIM is to:

- Keep the strength of the current Theme I (Thrombosis and Haemostasis) and II (Cardiac Function and Failure) intact and explore that these can be even further strengthened by a cardio metabolic programme, taking into account the links with the new Cardiovascular Center Maastricht (CVC) within Maastricht UMC+;
- Redefine the Vascular Biology theme (Theme III) following discussions about combining macro- and microvascular research;
- Develop, in collaboration with the Heart and Vascular Center (HVC) of the Academic Hospital Maastricht, into an internationally recognised centre of excellence in cardiovascular medicine;
- Intensify projects with other schools of Maastricht University such as NUTRIM, CAPHRI and MHeNS;
- Extend strategic alliances and collaborative programmes with other programmes within the Netherlands (such as Chemelot) and outside (such as the Helmholtz-Institute in Aachen and the RWTH Aachen University Clinic);
- Enhance integration into international collaborative projects, particularly in view of the opportunities of the EU Framework Program for Research and Innovation (Horizon 2020);
- Establish an excellent PhD programme and train Master's students in cardiovascular research.

CARIM has the ambition to be one of the leading research institutes in translational cardiovascular research in Europe, and to be a top ten player in the period leading up to 2020. It wants to be considered as a world leader in the fields of atherosclerosis research, atrial fibrillation and heart failure. It also wants to continue to provide important international contributions in the field of molecular imaging. As during the past years, cardiovascular scientists from around the world are encouraged to join CARIM, because CARIM values open communication, close cooperation, high ambitions, good facilities and a critical learning environment.

## The External Review Committee and the mode of operation

The External Review Committee (ERC) consists of six internationally recognised leading scientists, well acquainted with the current research practice of relevant disciplines and who cover the various other areas of CARIM's (managerial) activities (see annex 1). They have all signed a declaration of independence to avoid future discussions about potential conflicts of interest (see annex 4). The ERC was supported by the managerial staff of CARIM, including the secretary. Several weeks in advance of the site visit, the members of the ERC received the self-evaluation report regarding the self-assessment of the research activities and educational programme of CARIM, and the terms of reference for the evaluation and the visiting programme. On a secluded website of CARIM a complete set of these data and other relevant documentation was made available to the committee, like the evaluation protocol (SEP), recent annual reports of CARIM, the evaluation report for the 2007 evaluation of CARIM, the latest CARIM midterm and the 2012 document Cardiovascular Center Maastricht (CVC), the joint and integrated further development of the Heart and Vascular Center (HVC) and CARIM into one international center of excellence.

The programme of the site visit, which took place from 4 to 6 June, 2014, in Maastricht (see annex 2), included presentations on CARIM and its various research themes, poster presentations and demonstrations by staff members and PhD students, and presentations of the Master and PhD programmes. The ERC had discussions with (PhD) students regarding the training programme, and with tenure trackers, Top Talents and post docs regarding their training programme and career prospects. The

ERC also met - before and at the end of the audit - with the Dean of the FHML, the Scientific Director and the Board of CARIM, and the Director of the HVC.

## **Evaluation**

### Overall impression

The ERC acknowledges the detailed description of CARIM's activities and ambitions in the "CARIM Self Evaluation 2007-2012" report, which provides a good overview of the efforts that have been made since the last ERC evaluation in 2007 to sustain and improve quality of CARIM's research and education programmes and strategic decision-making procedures. Since 2007, CARIM has been involved in several transitions that are critical for further and successful development of CARIM into an international top institute: an ongoing process of extensive renewal at both the institutional level (change of scientific director, two new theme leaders, refocusing of the research programme) and the university level (merging of two faculties and the academic hospital into Maastricht UMC+, novel alliances at the national and (EU-) regional level), and a rejuvenation of leadership in research projects. Some of these transitions are still going on.

With respect to the scientific director and theme leaders, the ERC is convinced that they are excellent scientists and managers, particularly to create cohesion between the staff members of CARIM. As the scientific director will retire in 2017, it is advised to look for a successor in time, to guarantee a gradual transition of leadership. With respect to the merging of the two faculties and the university hospital, there is a risk that due to differences in culture, management control and legal entity between the university (including CARIM) and the hospital, further development of translational medicine may slow down. However, the ERC is confident that CARIM is of high quality and can become an international top institute in translational cardiovascular research. The growing cooperation between CARIM and the hospital in the CVC, and the further development of strategic alliances and networks at the national and (EU-)regional level are important for this ambition and may open up new roads to innovation, staff recruitment and funding (especially Horizon 2020). The latter may also compensate for the expected reduced funding (notably when in 2014/2015 the large public-private subsidies for technological top institutes, TTI's, like the Center for Translational Molecular Medicine, CTMM, will cease) and annual budget cuts (8-10% by the FHML from 2011 onwards).

### Evaluation of the research themes

According to the SEP, each research group or programme (i.e. theme) should be assessed according to the four criteria. The committee may use qualitative and quantitative indicators (on a five-point scale) and indications.

#### *Theme I: Thrombosis and Haemostasis*

The focus of Theme I (with four programmes) is directed at deciphering impairments of (coagulation) proteins, platelets, and the vessel wall in relation to the development of venous as well as athero-thrombosis. Theme I explores the multifactorial cause of thrombosis. The ERC considers this relatively small theme very well focused, innovative, and productive with an excellent output and valorisation. The programmes within Theme I are strong and coherent and score similar on each criterion. For all 4 programmes, junior staff members are in place and are coached by Theme I, CARIM and the FHML to become future PIs within Theme I.

The **quality** is ranked as 5 (excellent) based on:

- The high output and relevance of the scientific results
- The leadership of the group as demonstrated by the recruitment of talented investigators, the research management, successful funding from outside and the creation of international collaboration with groups in Germany, the UK, France and the USA
- The high international academic reputation in the field of thrombosis and haemostasis

- The coherence of the programme including athero-thrombosis, venous and arterial thrombosis

The **productivity** is ranked as 4-5 (very good to excellent) based on:

- The large number of publications in high-ranking journals (Impact Factor above 10)
- The number and quality of completed PhD theses
- The contributions to translational medicine, e.g. the 'Thrombosis Expertise Centre'
- Use of research facilities (protein engineering and molecular imaging agent development) by third parties
- The development of intellectual property (more than in the other themes)

The **societal relevance** is ranked as 5 (excellent) based on:

- The interaction (and recognition by) with stakeholders, such as the Dutch Heart Foundation and the Dutch Thrombosis Foundation and industry, shows the societal quality of the work
- The role of one of the PIs from Theme I as chairman of the Scientific Advisory Board of the Dutch Thrombosis Foundation
- The role of one of the PIs from Theme I as president of the Netherlands Society on Thrombosis and Hemostasis
- This theme stands out in the relatively large number of spin-offs most of which realised within the scope of CTMM programmes
- The Vitamin K cookbook for patients with thrombosis to provide more knowledge on the level of vitamin K in the diet

The **vitality and feasibility** is ranked as 4 (very good) based on:

- The process of changing the research themes to include athero-thrombosis (in conjunction with Theme III)
- State of the art research facilities on protein structure analysis, thrombin generation and platelet aggregation microscopy under flow conditions

In line with the 2007 ERC recommendations, there is now more interaction with clinical departments, especially in the CVC and with the Maastricht study on diabetes mellitus and cardiovascular disease. This translational research should be further stimulated, for instance with diagnostic trials and better use of large and complex data. As the patient population of the Maastricht hospital is rather small to study relevant clinical applications (bleeding and thrombotic disorders, thromboembolism, personalized medicine), the theme will profit from a larger (local, national and (EU-)regional) network to perform this, preferably with combined use of common research and expertise of other themes. An example is the collaboration with Theme II to study the thrombosis risk in patients with atrial fibrillation. The Thrombosis Expertise Centre (TEC), as part of Theme I in collaboration with the CVC, is another very good local initiative with potency for regional extension.

The group is internationally renowned for its expertise in protein engineering of (variant) coagulation proteins which are used for structure function analysis. Mass spectrometry and 700 MHz protein NMR have been acquired for protein structure determination and both protein/protein and protein/drug interaction. The role of coagulation proteases in the onset and progression of atherosclerosis and thrombosis is studied in a large cohort of individuals at risk of coronary vascular disease. Translational lines with many clinical departments are in place on the design and synthesis of molecular imaging agents for PET, SPECT and MRI. Flow assays for thrombus formation and novel procedures for platelet function are used to determine the contribution of platelets to disease.

Theme I stimulates the general use of technical (core) facilities, for instance in programme 2 (Vascular aspects of thrombosis and haemostasis); this also should be further encouraged.

The expected reduced funding (by the University, but also externally) poses a real threat for this theme. The ERC recommends further strategic discussions how to cope with this threat.

### *Theme II: Cardiac Function and Failure*

Research within Theme II (with 12 programmes) focuses on heart failure, ventricular arrhythmias and atrial fibrillation. The main aims are to gain insights into the basic biology of heart failure and arrhythmias

and to develop early diagnostic and therapeutic strategies based on concepts developed in the laboratory and in clinical practice. Within this theme there is a wide variance between the programmes in the assessment based on the criteria. Three of the twelve programmes are not performing as well as the others: 'Mitochondrial disease', 'Clinical heart failure' and 'Intermediate cardiac metabolism'.

The **quality** is ranked from 3 (good) to 5 (excellent) based on:

- The high output and the relevance of the scientific outcomes of most of the programmes
- The high international academic reputation in the field of clinical and experimental cardiology of most of the programmes
- The leadership of (primary) individuals such as in cardiomyopathy, gene regulation, atrial fibrillation and electro mechanics
- The decision to create a common experimental cardiology laboratory which comprises PIs from both clinical and preclinical programmes
- The strategy to strengthen complex genetics

The **productivity** is ranked as varying from 3 (good) to 5 (excellent) based on:

- The number of publications about clinical and experimental cardiology in high ranking journals by most of the PIs
- The contributions to translational medicine, e.g. the 'Complex Arrhythmia Unit' and the 'Heart Failure Unit'
- The number of completed PhD theses of which several *cum laude* defenses

The **societal relevance** is ranked from 3 (good) to 5 (excellent) based on:

- Societal impact: the continuing increase of life expectancy of the (Dutch) population is associated with a higher incidence of cardiac arrhythmias and cardiac failure which are the research topics of this theme
- The role of one of the PIs from this theme as chairman of the Scientific Advisory Board of the Dutch Heart Foundation
- The start-up of several spin-off initiatives

The **vitality and feasibility** is ranked from 2 (satisfactory) to 5 (excellent) based on:

- The strengthening complex genetics by instituting a chair in genetic epidemiology and statistical genetics
- The creation of a theme transcending (I and II) experimental cardiology laboratory for PIs in clinical and experimental programmes

Heart failure and arrhythmia research has been strengthened through the creation of a common experimental cardiology laboratory ('Greater Cardiology Lab'), which comprises several PIs (clinical and pre-clinical) within Cardiology. The clinical heart failure programme is particularly focused on the management of non-ischemic, non-valvular cardiomyopathies.

The ERC is pleased to note that Theme II has become an internationally recognised group renowned for its outstanding research in arrhythmias. Regarding atrial fibrillation, the research group is a member of a number of national and transatlantic high-profile scientific networks. The coherence in this programme has been improved by the start of invasive and non-invasive characterisation of atrial electrophysiological complexity in patients. As part of the integration of clinical/preclinical research programmes, patient cohort (including a biobank) and epidemiologic studies have been instituted.

To the opinion of the ERC, the interaction between arrhythmias - both atrial fibrillation and ventricular arrhythmias - and heart failure research should be enhanced. Electrical management of heart failure appears a successful topic. Theme II has the unique opportunity to expand on sharing complimentary expertise in experimental and clinical mechanisms e.g. electrical heart failure due to atrial fibrillation and ventricular ectopy, sudden arrhythmogenic death in diastolic heart failure, genetics of arrhythmias and heart failure. Complex genetics can set the stage for such integration. Additionally, molecular biophysics, including computational modelling to integrate clinical and preclinical data, should be considered in this respect. In this way the 'Greater Cardiology Lab' is just one of many facilities capable to implement this integration.

The implementation of complex genetics with a recently founded chair has been quite an important development for Theme II, from which in particular the programmes of sudden arrhythmogenic death, atrial fibrillation, electrical management of heart failure and cardiomyopathies will profit and integration within these programmes should be promoted. This discipline which makes use of large data sets, will need to be further developed to a solid group (or even core facility in the framework of the CVC), for structuring the programme and acquiring funds in competition (Horizon 2020). The ERC welcomed the developments of complex genetics in this theme, which has been greatly stimulated and structured by the recently founded part-time chair. Because of its relevance to the research lines of a number of PIs in Theme II but also in Theme I and Theme III (many of them dealing with complex multifactorial diseases with some heritable factors), complex genetics expertise should be further reinforced in CARIM. Fruitful cooperation with the existing large department of genetics needs to be given high priority.

The experiments within Theme II require access to experimental animal facilities (notably with large animals like dogs). As the existing (central) facility is no longer up-to-date and cannot further be improved to fulfill all current requirements of researchers and (Dutch and EU) legislation, the ERC strongly recommends replacement by a new facility in the very near future.

Theme II has a few spin-offs. It should be more active in this respect as is Theme I, and needs more support of a central valorisation office (i.e., the technological transfer office "Biomedical Booster"). Several initiatives for external funding (Horizon 2020) are promising.

The reduction in first money funds – mainly assimilated by appointing less support staff and PhD students - especially puts pressure on PIs to attract researchers (this is not only applicable for Theme II but basically for all themes; see also under Funding).

### *Theme III: Vascular Biology*

Following the leave of Prof. Daemen and several of his co-workers in 2012, a number of changes in programmes and leadership of this theme have taken place. The programme "Plaque Instability" had to be modified and is now being rebuilt under new PI leadership in the Department of Pathology with a strong emphasis on molecular and imaging techniques. The research in Theme III (with 11 programmes) is now centred around microvascular dysfunction; athero-thrombosis; arterial stiffening; vascular smooth muscle cell plasticity; endothelial dysfunction; vascular calcification; advanced glycation, and inflammation. These processes are studied in the context of specific cardiovascular diseases that are major burdens to an ageing society (with chronic diseases), namely diabetes and the metabolic syndrome, hypertension and chronic kidney disease, stroke and cognitive impairment, acute coronary syndrome and heart failure, aortic aneurysm and venous disease. This is an ambitious interdisciplinary endeavor which requires collaboration with other themes and clinical departments and research schools such as MH&NS. It is expected that it will create opportunities for successful grants from Horizon 2020 and KIC's in the field of health.

The programmes within Theme III are coherent and score similar on each criterion.

The **quality** is ranked as 4 (very good) – 5 (excellent) based on:

- Large number of publications about clinical and preclinical aspects of vascular biology and medicine in high impact scientific international journals
- Leadership had undergone a change following the leave of Professor Daemen. The group has managed to keep its high level of performance with new members entering
- The Maastricht study is nationally and internationally a unique large cohort study on the metabolic syndrome
- The high international academic reputation

The **productivity** is ranked as 4 (very good) – 5 (excellent) based on:

- The large number of publications in high ranking scientific journals
- The number and quality of PhD theses

- State of the art imaging facilities (the Hybrid PET MRI scanner is the only one in the Netherlands and one of the few in the world)

The **societal relevance** is ranked as 5 (excellent):

- High societal impact; the key processes which constitute the research programme are studied in the context of cardiovascular diseases that are major burdens to an ageing society

The **vitality and feasibility** is ranked as 4 (very good) based on:

- Intensive cooperation with the other CARIM themes and research schools within the FHML
- A Vascular Network Group has been created to optimise the interaction between basic and clinical scientists

An imaging platform will be added for use by all themes.

The Maastricht Study is an epidemiological study in 10,000 individuals that focuses on the causes and consequences of the metabolic syndrome, type 2 diabetes and cardiovascular disease, and uses extensive phenotyping of the microcirculation, the macrocirculation and the heart. It is a unique, very large and important cohort study on diabetes and glucose metabolism. The study can significantly contribute to the scientific knowledge of type 2 diabetes. The first round of this study concerns mainly phenotyping, mostly performed by a substantial number of studies of PhD students. The involvement of an internationally recognised scientist to oversee the study and assist the theme leader (who carries several other responsibilities) should be discussed.

The ERC considers the long-term funding of this study a serious challenge.

The ERC believes that further re-organisation of Theme III - by sharing focus, concepts, facilities and platforms - can improve quality and productivity.

Most programmes of Theme III make use of animal facilities. Thus, also for this theme a new up-to-date centralized animal facility is urgently needed. This also holds for the other themes, especially Theme II. In this respect, another centralized (general or core) facility which also is important for CARIM's research, has been recently funded, the Maastricht Centre for Systems Biology (MaCSBio).

The vascular biology theme is currently being re-structured, and the outcome of this determines to a large extent the vitality of this theme. The ERC is interested to know the consequences for the management of Theme III, on which aspects the programme will be focused and how the funding will be organised.

### Funding

In the past years, CARIM has been very successful in collecting funds from both the university (direct funding) as well as from external sources (grants and contract funds) like NWO/ZonMw, CTMC, Dutch Heart Foundation, Netherlands Thrombosis Foundation and EU- funds. More than 50% of the funding of CARIM was derived from such third parties. Lately, the economic crisis has led to budget restrictions by the government which also affects universities. In addition, more competition among research groups and changes regarding the funding policies of the external organisations create a challenge for research institutes to be successful in the future.

The annual budget of CARIM in 2012 (approximately M€ 25) was 15 % higher than in 2007, mainly due to an increase of contract research grants (in 2011). Overall direct funding was more or less stable. The volume of research grants obtained in national and international competition varied over time. Funding by grants and contract funds increased for all themes. With 262.8 FTE (full-time equivalent) staff, 98.4 FTE PhD students, and a budget of approximately M€ 25 in 2012, CARIM is one of the largest cardiovascular research institutes in Europe, producing more than 500 refereed scientific (WI-1) articles in high impact journals and an average of about 30 PhD dissertations per year.

In the highly competitive field of cardiovascular medicine in which CARIM operates, together with the increasing restrictive financial conditions like the termination of the TTI-grants and the expected reduction

in annual faculty budget, it will be - even more than indicated in the 2007 evaluation - a challenge to maintain and improve these high levels of in- and output.

Continuous networking and combining forces, i.e. promoting and intensifying functional collaboration with other local and (EU-)regional institutes are needed to recruit excellent researchers and to compete successfully for (EU- and NWO-)grants in the field of translational cardiovascular research. Good initiatives are the regional Thrombosis Expertise Centre (TEC) and the Complex Arrhythmia Unit, both are also crystallisation points of the CVC. SENECA, the Theme I initiative for an Initial Training Network (a Marie Curie action within Horizon 2020) between CARIM, RWTH Aachen, the Karolinska Institute Stockholm and King's College London, aimed at joint/double doctorates between these institutions, is another promising example. Individual financial incentives as well as an increase of the strategic budget are needed, and their policy should be reconsidered.

### Challenges and strategic alliances

Since the last review, significant progress has been made in the development of the Cardiovascular Centre Maastricht (CVC), the unique vehicle for the translation of new fundamental insights of CARIM's research into clinical innovation in the HVC of the hospital. The foundation of CVC to provide excellence in cardiovascular patient care, research and education looks promising with the start of two crystallization points (TEC and Complex Arrhythmias Unit), combined with the allocation of an annual budget of approximately 1 M€ from the hospital. The ERC already mentioned differences in culture, management control (HRM strategies) and legal entity (governance structure and IP regulations) between CARIM as part of the university (basic research and innovations which may lead to patient care in the future) and the HVC as part of the hospital (operational excellence in patient care) and which may slow down further development. Referring to the increasing restrictive financial conditions, this threat deserves special attention.

The implementation of complex genetics by instituting a chair for a well-known scientist is a very appropriate decision and requires further discussion about the interaction with the department of genetics and how other themes (I and III) may profit from this expertise.

The local cooperation with several research schools (like CAPHRI, GROW, NUTRIM and MH&NS), especially in the Maastricht Study and the CVC, is still limited and should be further encouraged.

The international cooperation like strategic alliances with (EU-)regional institutes - also thanks to CARIM's location nearby the border - is going well and should be further stimulated. It offers CARIM access to people, innovation and shared (EU-)grants.

Regarding perceived poorly performing programmes, CARIM needs to find a way to cut these programmes, and in this progress may also deliberate a modification of the currently rather inflexible organisational PI-structure.

### Tenure track

The elegant Tenure Track Programme of CARIM and the Top Talent Programme of the FHML/university allow talented young scientists to obtain a permanent employment contract. In 2012 the first 'tenure tracker' obtained a permanent position at CARIM; she may also serve as a role model for female scientists. In this respect, the ERC appreciates that, instead of focussing exclusively on expertise, a balanced (50/50) pool of male/female 'tenure trackers' has been created.

The PI-system is becoming rather inflexible because PIs belong to the tenured or permanent staff and are relatively young. It is a great challenge for CARIM to make this system of (programme) leaders more flexible and also open for talented females; at present only one of the recently appointed PIs is female.

Although the formal procedures for programmes like Tenure Track and Top Talent seem clear, young researchers still experience some lack of transparency in the communication, especially with respect to

these procedures, future perspectives and the way (PI-)vacancies are filled. The ERC is concerned about this, and believes that – besides more transparency - a mentor is particularly crucial in coaching advanced PhD students and postdocs.

### Valorisation and infrastructure

Valorisation is overall good to excellent, particularly in Theme I with a number of spin-offs. Many recent valorisations have been within the scope of CTMM programmes. As the funding of CTMM will soon end, there should be renewed attention for valorisation with Theme I as an example.

The animal facilities of the faculty are no longer up-to-date, they cannot longer be improved to fulfill all current requirements of researchers and (Dutch and EU) legislation and thus require replacement in the very near future. As there is a strong emphasis on translational research in CARIM, the ERC considers a new animal facility essential for CARIM's competitiveness in scientific quality and grant acquisition. It will offer opportunities for combining experiments, e.g. by using multiple organs and tissues from single animals by different schools and research groups, thereby responding to the societal ambitions for Replacement, Reduction and Refinement (three R's, or 3V-alternatives) of animal experiments. A state-of-the-art animal research facility is absolutely necessary, at least for a medical school, to compete with leading institutes in a particular field, to do excellent research in a proper way, to speed translational research, to acquire grants and projects, and to attract industrial partners.

The ERC noticed that a large budget (> M€ 20) is available for a new animal facility (called VivariUM) and that progress has been made towards final decision-making. Hopefully, the new animal facility, complying with Dutch and EU legislation regarding animal housing and research, but closely linked to the research schools of Maastricht UMC+, can be opened within the next two or three years. To address the current unsatisfactory situation which lasts already for some years, the ERC has written a separate letter to the Dean and the Executive Board of the university (see annex 3).

Three recent initiatives should be mentioned in particular. In view of the importance of cardiovascular genetics for CARIM's research programme, in particular for the programme on heart failure and cardiac hypertrophy, it was important to establish a new chair of complex genetics/genetic epidemiology. The international network of this new chair, together with the expertise of the department of genetics which is centred around monogenetics, may lead to a genomics-based cardiovascular research platform working at the highest level in the newly launched CVC. Systems biology (MaCSBio) is a good initiative; it is an opportunity to relate this as a general tool or core facility more closely to genetics. At present, systems biology is not yet explicitly visible within CARIM and separated over the programmes. The Vascular Network Group of Theme III is a promising facility with many interactions between basic researchers of several schools and clinicians, for example in the field of inflammation. Although several scientists of the network have basic knowledge of immunology, novel innovative expertise is needed, from outside and at chair level.

### The educational programme

The ERC judges the PhD programme very positively. It is broad, flexible and clearly structured; it is up to date and meets the current criteria for a high quality PhD training programme. The programme offers excellent training of a new generation of creative researchers. The number of PhD students is relatively large, but almost all of them get a job after finishing the thesis. The advice to put more effort into monitoring the quality of supervision of PhD students has been successfully implemented in the CARIM Research, Education and Supervision (CARES) plan. This plan provides more transparency for all stakeholders, a better monitoring of the progress during the PhD trajectory, improvement of the quality of the PhD thesis, preparing the PhD student (for example with so-called transferable skills) for the job market, also outside the university, and a strict schedule to finish the PhD (training) trajectory in time. The web-based PhD monitoring programme which has recently been developed by all research schools in collaboration with an IT company, TRACK.2, offers a useful supplement.

Currently the PhD duration is 62.9 months (more than 5 years). Although this seems long, the ERC acknowledges some rather inevitable causes for this delay, not mentioned above. Firstly, the competitive Dutch system requires to comply with increasing standards of PhD theses, in the health sciences sometimes even leading to about four refereed publications in the thesis (only submission is not enough). Secondly, as a consequence - the time it takes to publish the paper. Thirdly the subsequent thesis administration, and finally - if applicable - the integration of the PhD period into the clinical education track.

Nevertheless, the PhD-duration needs to be reduced, particularly from a financial point of view and career perspectives (e.g., to prevent loss of career potential). One way is to replace the number of mostly low impact publications (the majority has an impact factor below 3-4 IF) by a few ones with higher impact factor.

The ERC is hopeful that the implementation of the CARES plan and the new TRACK.2 plan also reduces the average time it takes to obtain a PhD.

### **Conclusions**

Taking all the previous mentioned arguments into account, the outcome for the evaluation for the School overall is the following:

*Quality:* very good to excellent (4-5)

*Productivity:* very good to excellent (4-5)

*Societal relevance:* excellent (5)

The relevance is very high, since cardiovascular diseases remain one of the leading causes of death in the Netherlands (currently 27%, and about 33% 10 years ago) and the Western world. So, there is a continuous need for dedicated translational research on prevention, diagnosis and treatment of cardiovascular diseases.

*Vitality and feasibility:* very good (4)

Once the animal facilities have been improved (see annex 3) this may be very good to excellent (4-5)

*Overall:* very good to excellent (4-5).

### Summary of the recommendations

Fund raising will be even more important for CARIM than in the past period. EU- funding programmes like Horizon and EU-regional programmes offer a long-term support, and CARIM should explore the possibilities to improve its grant acquisition. The ERC recommends to stimulate networking and collaboration (locally, nationally and internationally) in order to compete successfully for grants in the field of translational cardiovascular research. Further strategic discussions are needed on how to cope with the expected reduced funding (from the university as well as externally).

Translational research is strong but should be further stimulated and CARIM should keep working on enforcing and intensifying the collaboration of HVC-CARIM in CVC.

The animal facility urgently needs to become up-to-date as has already been recommended in a letter of the ERC to the dean. ERC recommends a new animal facility which is essential not only for CARIM, but the whole faculty's competitiveness in scientific quality and grant acquisition

Systems biology should be enforced. It is recommended to further discuss the need of this area for CARIM, the FHML and other faculties in Maastricht, and an interfaculty centre should be created.

Regarding perceived poorly performing programmes, CARIM needs to find a way to cut these programmes, in spite of the rather inflexible organizational PI structure. At the level of the three CARIM themes, the further reorganisation of Theme III, and partially Theme II, is necessary in order to maintain and improve quality and productivity.

Valorisation of research outcomes in Themes II and III should be further explored and requires more discussion. The funding and initiation of the Maastricht Study is a major recent accomplishment of Theme III.

Complex genetics needs to be further developed into a solid group for structuring the programme and acquiring funds in competition (Horizon 2020). Fruitful cooperation with the existing large department of genetics needs to be given high priority.

While the high quality of the PhD theses/programme must be maintained, options to reduce the duration of the PhD track should be explored

The imaging facility should become a self-sustained interfaculty unit, independent from CARIM, and collaboration with the newly established University Professors should be enforced.

The transparency in the communication of Tenure Track procedures should be improved.

Annex 1

**Members of the External Review Committee CARIM, June 2014**

Dr. Pim van Aken (chairman)  
Professor emeritus of Medicine  
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Annex 2

## **Program ERC CARIM 2014**

Date: Wednesday June 4 – Friday June 6, 2014

### *Wednesday June 4*

Morning: Arrival ERC members in Maastricht, NH Hotel Maastricht, Forum 110, 6229 ER Maastricht  
Bestuurszaal, Bestuurstoren University Hospital, MUMC+

13.00-14.00: Lunch ERC members and Board Members School

14.00-15.30: Installation of the External Review Committee (ERC) by Prof. A. Scherpbier, Dean FHML

- Introduction Research School by Prof. Th. Unger

- Overview Dutch research funding system by Prof. T. Hackeng

- Overview program ERC

- Discussion

15.30-16.00: Closed meeting ERC members

Bonte zaal, UNS 50 H.1331

16.00-16.15: Introduction CARIM program by Prof. Th. Unger, Scientific Director CARIM

16.15-16.45: Presentation Theme I 'Thrombosis and Haemostasis' by Prof. T. Hackeng

16.45-17.45: Discussion

17.45-18.00: Closed meeting ERC members

Chateau Neercanne, Cannerweg 800, 6213 ND Maastricht

18.30: Drinks and dinner ERC with Dean FHML, Director and Board Members School

### *Thursday June 5*

Bonte zaal, UNS 50 H.1331

9.00-9.30: Presentation Theme II 'Cardiac Function and Failure' by Prof. H. Crijns

9.30-10.30: Discussion

10.30-10.45: Closed meeting ERC members

10.45-11.00: Coffee break

11.00-11.30: Presentation Theme III 'Vascular Biology' by Prof. C. Stehouwer

11.30-12.30: Discussion

Oxfordlaan 70

12.30-12.50: Meeting with Dean FHML concerning animal facilities

12.50-13.30: Lunch and closed meeting ERC

4<sup>th</sup> floor 'Terras', University Hospital, MUMC+

13.30-16.00: Viewing CARIM posters including guided tour CARIM facilities

UNS50 4.324A (Theme I), MUMC 5 H2.046 (Theme II), UNS 50 1.351A (Theme III)

16.00-18.00: Meeting with Tenure Trackers, Top Talents and post docs; per Theme  
De Groote Societeit, Vrijthof 36, 6211 LE Maastricht

18.30: Informal (buffet) dinner with CARIM scientific staff, technical staff and PhD students

### *Friday June 6*

#### *UNS50 1.351A*

Presentations on The Cardiovascular Center (CvC)

8.30-8.50: CvC, by Prof. M. Jacobs, director Heart Vessel Centre

8.50-9.05: The Maastricht Study, by Ronald Henry

9.05-9.20: Thrombosis Expertise Center, by Hugo ten Cate

9.20-9.35: Arrhythmia Unit, by Harry Crijns

Rode Zaal (Coen Hemkerzaal), UNS 50 k 0.480

9.40-10.10: Presentation PhD training program by M. van Bilzen

Several locations

10.10-11.10: Time slot for CARIM Course Week

Rode Zaal (Coen Hemkerzaal), UNS 50 k 0.480

Presentations on new developments (Moderator: Prof. Th. Unger)

11.10-11.20: The vascular contribution to cognitive impairment, by Robert van Oostenbrugge

11.20-11.30: Vascular Network Group, by Koen Reesink

11.30-11.40: Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation, by Uli Schotten

11.40-11.50: Novel RNA targets in heart failure, by Stephane Heymans

11.50-12.00: Regulation alternative splicing, by Elisabetta Castoldi

12.00-12.10: Marie Curie ITN, by Tilman Hackeng

Bestuurszaal, Bestuurstoren University Hospital, MUMC+

12.30-13.00: Lunch

13.00-14.30: Closed meeting ERC

14.30-15.30: Feedback to Board, Director Research School and Dean FHML

15.30-17.00: Closed meeting ERC, including site visits upon individual requests members ERC (several locations)

17.00: End

Annex 3

### **Letter to the Dean FHML concerning animal facilities**

To Prof.Dr. A.J.J.A. Scherpbier  
Dean of the Faculty of Health, Medicine and Life Sciences  
Maastricht University  
P.O. Box 616  
NL - 6200 MD Maastricht

Amstelveen, June 24, 2014

Dear Professor Scherpbier,

On behalf of the External Review Committee (ERC) of CARIM, once again I would like to draw your attention to the animal facilities of your institution, which seem to be no longer up-to-date and therefore require replacement in the very near future.

On various occasions in the CARIM self evaluation 2007-2012 references are made to the construction of the VivariUM, a new animal facility, where laboratories and equipment are shared by multiple users. This should replace the present Central Animal Facilities (CPV), which cannot longer be improved to fulfil all current requirements of researchers and (Dutch and EU) legislation. At the moment, much of the animal research of CARIM and other schools takes place in peripheral laboratories which are allocated within the departments. Besides, the SWOT analysis states that animal experiments are increasingly performed extra muros; clearly, this is not efficient and costly.

This situation has been noticed already several years ago, also by some members of the ERC. About one third of the animal research projects approved by the animal experiments committee (DEC) are performed within CARIM. So, it is obvious that in the SWOT analysis of CARIM the non-competitive state of the present animal facilities and the apparently capricious pace of development of the new VivariUM are seen as real threats. The discussions during our visit on June 4-6, 2014, with principle investigators of CARIM and others confirm this.

In our view, an up-to-date animal facility is a multi-user facility for all faculty schools, within the university and the academic hospital. Its service should also be offered to other partners in the region. This core facility combines the expertise of several researchers on animal research and makes more efficient use of the existing staff and equipment. It also allows the staff to better facilitate temporary research support required for projects in collaboration with industry. As there is a strong emphasis on translational research in CARIM, the ERC considers the new VivariUM absolutely essential for CARIM's competitiveness in grant acquisition. It offers opportunities for combining experiments, e.g. by using multiple organs and tissues from single animals by different research groups, thereby responding to the societal ambitions for Replacement, Reduction and Refinement (three R's, or 3V-alternatives) of animal experiments. The facility is absolutely necessary, at least for a medical school, to compete with leading institutes in a particular field, to do excellent research in a proper way, to speed research, to acquire grants and projects, and to attract industrial partners.

In our closed meeting with you, on June 5, 2014, we were pleased to hear that a large budget (> M€ 20) is available for the VivariUM and that progress has been made to final decision-making. We hope that the new animal facility, complying with Dutch and EU legislation regarding animal housing and research, but closely linked to the schools, can be opened within the next two or three years.

Replacement, reduction and refinement of animal experiments are of paramount importance, for society and for researchers, also within CARIM. In this respect, we note that the two-yearly Willy van Heumen award for alternatives on experimental animal use has been given to Prof.Dr. J. van Heemskerck on the occasion of the 8th Work Congress on alternatives and animal use in life sciences (Montreal, Canada, August 25, 2011). Everyone agrees that the use of animals for scientific purposes should be minimalised as far as possible. However, within the strategic choices of the research profile of CARIM, it is inevitable that animals are used, including large animals like goats, pigs and dogs (e.g., within theme II). For several reasons, we would like to stress the necessity of facilities for dog experiments. First of all, important aspects of arrhythmias or conduction diseases can only be studied in dogs because of the specific properties of the conduction system and the anatomy of the atria as compared to other experimental animals. Secondly, these aspects of electrical cardiac disorders are traditionally a very strong part of the UM's and

CARIM's research portfolio. Third, there are only two academic institutions with capabilities to perform dog experiments in the Netherlands so that excluding dogs from the plans for a Vivarium would weaken the competitiveness of Dutch academic cardiovascular research significantly.

Some of the societal topics mentioned above are listed in the (draft) leaflets\* enclosed. These folders with general information regarding animal research have been established with the cooperation of one the members of the ERC and of the Dutch society for the prevention of cruelty to animals ("Dierbescherming").

Sincerely yours,

On behalf of the external review committee of CARIM,

Prof.Dr. W.G. van Aken, Chairman

Copy to Prof.Dr. M. Paul, Chairman of the Executive Board of Maastricht University

\*see [http://www.informatiedierproeven.nl/files/Brochure%20SID/ZoDoende%20Brochure\\_2012-Digi.pdf](http://www.informatiedierproeven.nl/files/Brochure%20SID/ZoDoende%20Brochure_2012-Digi.pdf)

**Competence and independence of peer review committee members**

1. A member of the peer review committee bases his/her assessment primarily on:
  - the Standard Evaluation Protocol 2009-2015; Protocol for Research Assessment in the Netherlands
  - if applicable: additional instructions of the Board of Maastricht University and/or of the Dean of the Faculty of Health, Medicine and Life Sciences
  
2. In giving a judgement on the quality of research, a member of the peer review committee grounds his/her assessment on the following information:
  - the self evaluation report and accompanying documentation
  - if applicable: additional information provided on request of the peer review committee
  - interviews, lectures and talks carried out within the framework of the assessment
  
3. A member of the peer review committee meets the generally known quality demands within scientific research, including:
  - competence and professionalism
  - independence and objectivity
  - care and consistency
  - transparency and impartiality
  
4. A member of the peer review committee experiences no personal, scientific, financial or any other potential conflicts of interest in participating in the research assessment of the School for Cardiovascular Diseases (CARIM) of the Maastricht University Medical Centre<sup>+</sup> and is therefore both qualified and competent to carry out his/her task as an independent assessor.
  
5. A member of the peer review committee reports any potential conflicts of interest in advance to the chairman of the review committee.

I declare that I have read the above-mentioned and that I will follow these to the best of my ability.

Place and date: Maastricht, 4<sup>th</sup> June 2014

Signature:.....

Name: .....

## Annex 5

### Abbreviations

CAPHRI	School for Public Health and Primary Care
CARES plan	CARIM Research Education and Supervision plan
CARIM	School for Cardiovascular Diseases
CTMM	Center for Translational Molecular Medicine
CVC Maastricht	Cardiovascular Center Maastricht
ECOS	Research School Accreditation Committee
ERC	External Review Committee
EU	European Union
FHML	Faculty of Health, Medicine and Life Sciences
GROW	School for Oncology & Developmental Biology
Horizon 2020	the EU Framework Programme for Research and Innovation
HVC	Heart and Vascular Center
IF	Impact Factor
KIC	Knowledge and Innovation Community (within Horizon 2020)
KNAW	Royal Netherlands Academy of Arts and Sciences
Maastricht UMC+	Maastricht University Medical Centre+ (MUMC+)
MacsBio	Maastricht Centre for Systems Biology
MHeNS	School for Mental Health and Neuroscience
NUTRIM	School for Nutrition, Toxicology and Metabolism
NWO	Dutch Foundation for Scientific Research
PI	Principle Investigator
SEP	Standard Evaluation Protocol
SWOT analysis	Strengths, Weaknesses, Opportunities and Threats analysis
TEC	Trombosis Expertise Centre
TRACK.2	web-based PhD monitoring program developed in collaboration with an IT company
TTI	Technological Top Institute
VSNU	Association of universities in the Netherlands