

ENMC Impact Report 2017

# Our year in highlights

EUROPEAN  
NEURO  
MUSCULAR  
CENTRE



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# 1 Message from the Chair of the Executive Committee

Founded in 1992, the European Neuromuscular Centre (ENMC), born out of the vision of the patient organisation EAMDA and with the financial support of AFM, is now 25 years old. An age to be proud of, I do believe and an occasion to look back and evaluate what has been achieved and developed (for a historical overview see BOX 1).



*Dr Raffaella Willmann, Chair of the Executive Committee*

Delving in these memories, we felt that it was time for a more detailed impact analysis to investigate how effective ENMC workshops are in helping the researchers' community to develop new collaborations, diagnostic guidelines, care strategies; how successful workshops really are in developing actions that ultimately improve the quality of life of people with neuromuscular conditions. Read about our analysis on pages 7-9.

Follow the variety of interesting topics discussed in the nine workshops held in 2017 on pages 10-20. See how the ENMC network develops and what patients' participation at workshops means nowadays, on pages 20-22. And look forward for more ENMC 25th anniversary events and initiatives in 2018!

**Dr Raffaella Willmann,**  
*Chair of the Executive Committee*

## BOX 1: Historical overview of the ENMC

The beginnings were a simple idea: research needs communication; experts need to meet to discuss hot topics and find together solutions, agreements and to plan next research steps.

The first years of the ENMC showed the success of this approach, with workshops tackling urgent topics of that time: the consensus on diagnostic criteria, which would set the basis for the definition of clinical and molecular features of neuromuscular disorders. The main formats of ENMC workshops were set in those days and are still the key of their success: small groups of experts discuss over two and half days, set themselves deliverables, publish outcomes in a short lay report published on the ENMC website and in an extensive report published in *Neuromuscular Disorders*. Meanwhile, the organisation quickly grew into an independent Foundation supported by several European patient organisations and recorded a huge interest of the community in applying for workshops. Ten years later the founders sensed the need of the community to create a network for an effective planning and management of the first upcoming clinical trials. The Clinical Trial Network, launched in 2001, had the scope of implementing Cochrane

reviews and patient registries and encouraging trial organisers to hold ENMC workshops for a structured planning of their clinical projects. 5 Years later, this effort inspired the leaders of the TREAT-NMD Network to apply for European funding for what would have become the main driving force in Europe for the neuromuscular scientific community. Research has leaped forward with giant strides since then and the ENMC has been accompanying this progress seeing the evolution of discussions from basic research into areas addressing standards of care, clinical trial readiness and international patient registries.

At its 20th anniversary the ENMC refreshed the structure of its sponsored workshops, paying particular attention to the value of involving people affected by neuromuscular conditions in every meeting. Giving voice to patients often resulted in important contributions during the discussions and is now an essential component of each workshop's program. The special workshop organized in January 2018 for the 25th anniversary of ENMC reflects this commitment and confirms again the ENMC as central, independent and appreciated hub at which the scientific community can refer to and merge efforts for the patients' community.

## 2 The mission of the ENMC

More than 25 years ago, a group of scientists and clinicians, together with parents of children affected by a neuromuscular condition, started the European Neuromuscular Centre (ENMC). They had in mind the ultimate goal to improve diagnosis, accelerate the search for effective treatments and improve the quality of life of people with a rare neuromuscular condition. To achieve this goal, it was, and still is, of

utmost importance that experts in this field of orphan disorders share their knowledge and experience and collaborate in research worldwide. The ENMC encourages and facilitates this through the organisation of small-sized, interactive workshops for multidisciplinary groups of researchers and clinicians and persons affected by a neuromuscular condition – a unique concept in the scientific community.

### ENMC Mission Statement

The mission of ENMC is to encourage and facilitate communication and collaboration in the field of neuromuscular research with the aim of improving diagnosis and prognosis, finding effective treatments and optimizing standards of care to improve the quality of life of people affected by neuromuscular disorders.



*“Connecting people”*

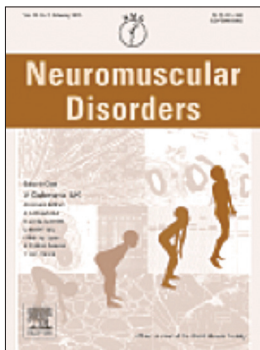
### 3 The impact of 25 years' ENMC workshops

On the 24th of November 2017, the ENMC celebrated its 25th Anniversary. Since its foundation, 234 ENMC workshops have taken place which outcomes were published on the ENMC website by means of lay reports. To get insight on the impact these workshops had on the neuromuscular community, an extensive field evaluation was performed.

*The ENMC office, Ms Annelies Zittersteijn (left) and Dr Alexandra Breukel, celebrating the 25th Anniversary of the ENMC on November 24th 2017, with their colleagues from the Dutch Muscle Disorders Patient Association.*



#### 3.1 Publication of workshop outcomes



The first important outcome of each workshop is a full scientific workshop report written by the organizers of the workshop and published in the journal "Neuromuscular Disorders". The goal of these publications is to share

the outcomes of the workshop with the neuromuscular field. These outcomes form the basis for follow-up research to improve diagnosis, treatment and care of persons affected by a neuromuscular condition.

Another target audience of ENMC's dissemination policy is the lay public. Through publication of the lay reports on the website and messages on social media like Twitter and LinkedIn, ENMC tries to reach affected people and their families worldwide.

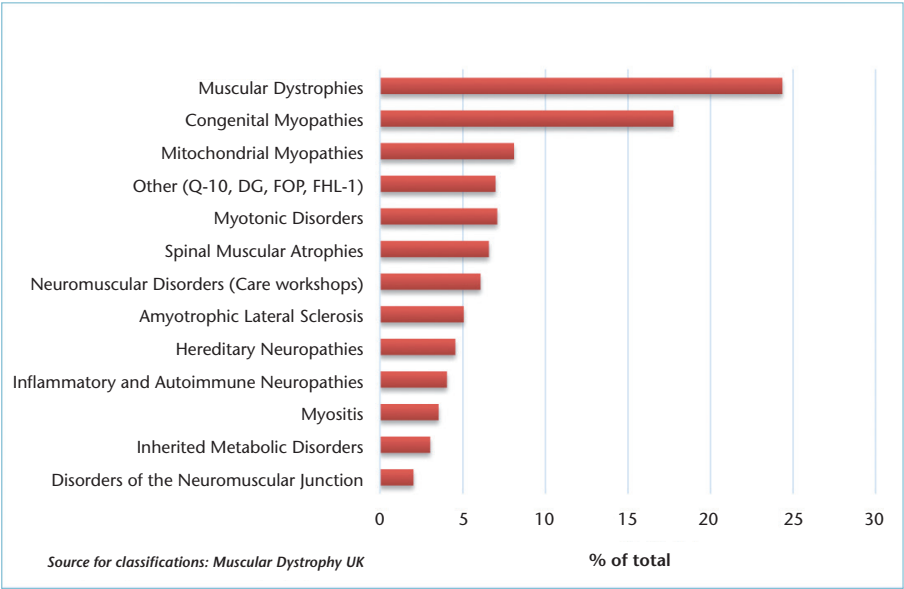


#### 3.2 The neuromuscular disease classes and care topics in 25 years' ENMC workshops

In 2017, the ENMC performed an analysis to assess the impact of workshops on the neuromuscular field. An evaluation on the disease classes revealed a strong representation of muscular dystrophies and congenital myopathies whereas disorders of the neuromuscular junction and inherited metabolic disorders and many ultra rare conditions were topic of one

workshop in the 25-year period (see table on the next page). Of the 24 dedicated Care workshops, medical care topics like respiratory insufficiency and cardiac myopathy were most popular, whereas patient-driven topics like pregnancy, pain and fatigue were the focus in one workshop.

Distribution of disease classes (in %) discussed at ENMC workshops in the last 25 years



3.3 The impact of ENMC workshops on people affected by a neuromuscular disorder

To analyse the implementation of deliverables of the workshops, a survey was done in a 5 year cohort of ENMC workshops (2010-2014). The main outcome of this survey was that **89%** of all workshop deliverables were reported as ‘completed’ or ‘started’. Of the completed deliverables **78%** was actually implemented in the neuromuscular field; bringing

knowledge and new collaborations to researchers, improving designs of clinical (pharma-driven) trials and innovating diagnostic tools for the patients.

Some quotes from the survey illustrating the implementation in the field:

“Outcome measures discussed at the Inclusion Body Myositis ENMC workshop were used in clinical trial sponsored by Novartis.”

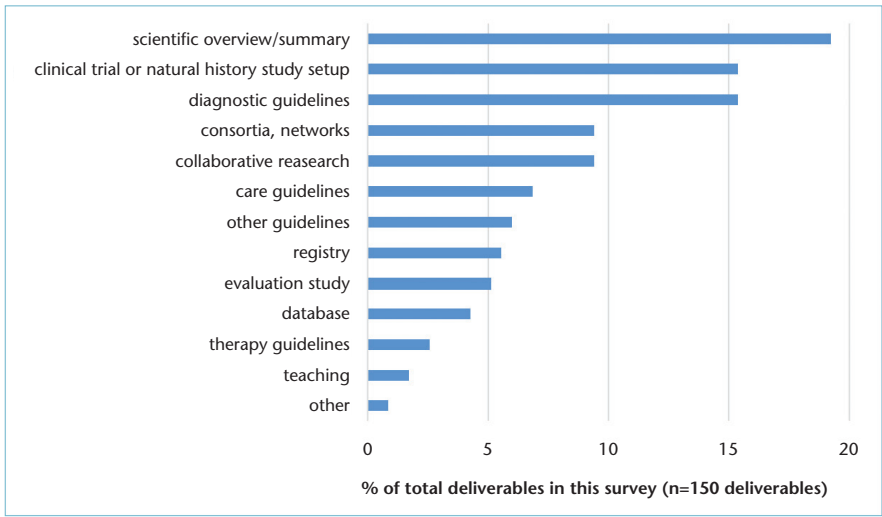
“Our recommended Diagnosis tests agreed upon at the workshop are in place in all Diagnosis genetic labs for Myotonic Dystrophy type 2.”

**The impact of the SMA workshop 209:**  
“An overview of natural history studies helped with protocol development for the Roche FIREFISH, AveXis-101 and NURTURE studies, and this workshop was followed up by SMA workshop 218.”

The data showed that scientific overview (knowledge sharing), clinical trial or natural history study set-up, diagnostic guidelines, consortia and collaborative research were the most frequent deliverables of an ENMC workshop (see table below).

Whereas diagnostic guidelines were the result of many ENMC workshops in the past, nowadays the focus shifts towards consensus on therapy and care guidelines. Set-up of registries and databases added up to 10% as deliverables of ENMC workshops.

Deliverables in ENMC workshops (survey period 2010-2014)



Workshop organizers say they learned that a multi-disciplinary group of participants from various countries is required to reach consensus. Sometimes it was recognized that a deliverable was too ambitious or outside the reach of the consortium. And on the contrary, sometimes a workshop led to unexpected extra developments and (patient-driven) turn of priorities.

Lack of resources (financial, time, personnel) was the main reason (67%) why deliverables were delayed or never implemented. Follow up problems (lack of commitment and/or collaboration) caused that 10% of the deliverables never started.

**The overall conclusion of the analysis is** that ENMC is in line with its mission: “To encourage and facilitate communication and collaboration in the field of neuromuscular research”. And it supports that ENMC should keep doing what it does best: organising workshops which scientists have applied for, that

bring the consortia (back) together to exchange the state-of-the-art knowledge on neuromuscular conditions and initiate new collaborations and research projects.

The ENMC succeeds to achieve its vision “Improving diagnosis and prognosis, finding effective treatments and optimizing standards of care to improve the quality of life of people affected by neuromuscular disorders”; the ENMC is proud of the high level of deliverables achieved and implemented in the neuromuscular research field and the patient community. The ambition for the future is to increase further implementation of workshop deliverables in the neuromuscular community by supporting applicants in identifying pitfalls on the feasibility of their deliverables ahead. Outcomes will be presented at the International Congress on Neuromuscular Diseases (ICNMD) on the 8th of July, 2018 (in Vienna, Austria). A publication on the impact data will be submitted to a scientific neuromuscular journal.

## 4 The ENMC workshops in 2017

With the progress in neuromuscular research and the development of new drugs and therapies for neuromuscular conditions, the need to get together and collaborate increases. In 2017, a total of nine workshop applications were submitted to the ENMC.

Of these nine applications, five were granted an award for an ENMC workshop to take place either in 2017 or 2018. The large number of workshops approved in 2017 (almost 60%), is indicative for the high quality of the submitted applications.

### 4.1 Summary of ENMC workshops held in 2017

In 2017, a total of nine workshops were organised in the Netherlands, both in NH hotel, Naarden and at Castle Marquette, Heemskerk. The workshops are listed in the table below.

#### ENMC workshops in 2017

Date	Workshop No.	Workshop Title
20-22 January	226	Towards validated and qualified biomarkers for therapy development for Duchenne Muscular Dystrophy
10-11 February	227	Finalizing a plan to guarantee quality in translational research for neuromuscular diseases
3-5 March	228	Airway clearance techniques in Neuromuscular Disorders
17-19 March	229	Limb Girdle Muscular Dystrophies - Nomenclature and reformed Classification
24-26 February	230	Improving future assessment and research in IgM anti-MAG peripheral neuropathy: a consensus collaborative effort
12-14 May	231	International Standard for CIDP Registry and biobank
16-18 June	232	Recommendations for treatment of mitochondrial DNA maintenance disorders
15-17 September	233	Clinical trial readiness for Calpainopathies
8-10 December	234	Chaperone dysfunction in muscle disease: Therapeutic Approaches





*The organisers of the 226th ENMC workshop on biomarkers in Castle Marquette, Heemskerk, The Netherlands.*

*From left to right: Prof. Annemieke Aartsma-Rus, Dr Lee Sweeney, Prof. Elizabeth McNally, Young Scientist grant winner Dr Pietro Spitali and Prof. Alessandra Ferlini.*

## **Workshop 226 on “Towards validated and qualified biomarkers for therapy development for Duchenne Muscular Dystrophy (DMD)”**

The 226th ENMC workshop was a follow-up meeting of the 204th ENMC workshop on biomarkers in DMD, where two markers (dystrophin and magnetic resonance imaging (MRI)) were identified as candidate surrogate endpoints. The latter are biomarkers that are used as a primary outcome measure in clinical trials instead of functional outcome measures such as the 6 minute walk test. In Europe biomarkers can only be used as surrogate endpoints after going through a rigorous regulatory process to officially qualify them for this purpose. In parallel, work has been ongoing to identify additional biomarkers in serum and urine, which are attractive because of the low invasivity of sample collection.

The aims of the 226th ENMC biomarkers workshop were:

- To discuss dystrophin and skeletal muscle MRI as biomarkers, in order to be able to prioritize and align the work that still needs to be done
- To compare the biomarkers detected in blood and urine to select the most suitable candidates and discuss future tests to confirm their usefulness

- To set up a way for collecting, storing and sharing blood and urine for biomarker identification and validation.

During this workshop it became clear that for MRI, many gaps identified in the previous ENMC workshop were solved. Alignment was reached on a proposed path for qualifying MRI and dystrophin quantification with the regulatory agencies. Furthermore, there was consensus on which criteria new candidate biomarkers need to fulfill. Biomarkers need to be specific, reproducible, reliable and robust. Finally, the group agreed that a virtual biobank is needed and that this can be achieved using existing platforms such as Eurobiobank ([www.eurobiobank.org](http://www.eurobiobank.org)) and BB-MRI (Biobanking and Biomolecular Resources Research Infrastructure, [www.bbmri.eu](http://www.bbmri.eu)).

A committee overseeing these biobank activities is required with equal representation of patients, academics, industry and other experts. The management part of this biobank should be funded by patient organisations and industry. Efforts will be undertaken to initiate this committee in a timely fashion.



## Workshop 227 on “Finalizing a plan to guarantee quality in translational research for neuromuscular diseases”

Translatability, defined as the passage from the preclinical study phase on animals to the clinical phase on persons, was the leading topic at the 227th ENMC workshop. High quality translational research data are critical to successfully move new drugs from laboratory bench to patient bedside especially for rare neuromuscular diseases. Therefore, it is crucial that researchers designing pre-clinical studies collaborate at an early stage with the clinical researchers who are in charge of designing human trials, in order to closely match the conditions using the same drug under investigation.

In this workshop, representative stakeholders acting at different stages of preclinical research (experimental study design and outcome measures, publication and funding) were invited to agree on measures to improve more efficient and effective translation of preclinical work and collaboration among professionals. After a first series of introducing talks and testimonials, the participants divided into discussion groups.

The following deliverables were agreed upon:

- 1 A teaching course to be held at the ICNMD 2018 to train researchers, clinicians and scientists on the pitfalls and challenges of research translation.
- 2 Journal editors agreed to make an effort in requiring some standards in reporting preclinical trials by explicitly stating them in the instructions for authors.
- 3 Funding agencies proposed to improve awareness on high quality preclinical research among smaller patient organisations that do not have an expert scientific commission in place to evaluate project quality and to take a leading role in educating such organisations. Furthermore, they proposed to use the leverage they have on industry to require strong preclinical data before engaging in a clinical trial.



*The group of the 227th ENMC workshop on translational research held in February 2017 in Castle Marquette, Heemskerk, The Netherlands.*

## Workshop 228 on “Airway clearance techniques in Neuromuscular Disorders”



*The organizers of the 228th ENMC workshop held in March 2017 in NH Hotel Naarden, The Netherlands. From left to right: Prof. Jesus Gonzales, Prof. Uwe Mellies, Dr Michel Toussaint and Dr Michelle Chatwin.*

In the past 20 years, seven workshops have been organised on respiratory insufficiency in neuromuscular disorders (NMDs), varying from SMA, ALS, DMD, myotonic dystrophy to congenital myopathies/dystrophies. The need for separate workshops illustrates that these different NMDs may affect the respiratory muscles to varying degrees and at different life stages (from infancy, through childhood to adulthood). In the 228th ENMC workshop on airway clearance techniques in neuromuscular disorders, an attempt was made to look for common features and discuss Airway Clearance Techniques (ACTs) as universal tools to facilitate clearance of pulmonary secretions in patients not being able to effectively cough and clear pulmonary secretions on their own.

Amongst others, the following major topics were discussed during the workshop proceedings:

- 1 The pathophysiology of secretion encumbrance in people with NMDs.
- 2 The effect of respiratory tract infection on respiratory muscles, lung volumes and blood gas exchange in people with NMDs.
- 3 Detailed description of all peripheral and proximal ACTs available for use in patients with weak respiratory muscles.
- 4 The limits of effectiveness of each ACT, the need for a learning period/training, financial cost, availability and possible complications.
- 5 Specific treatment algorithms (protocols) were defined for ACT management in NMDs.

## Workshop 229 on “Limb Girdle Muscular Dystrophies (LGMD) - nomenclature and reformed classification”



*Ms Madelon Kroneman at the 229th ENMC workshop, representing the patient's voice on changing the LGMD nomenclature*

This workshop had the difficult task of revisiting the definition of LGMD and to discuss and propose a new classification system for LGMD sub-types that will be most useful to patients, researchers and clinicians and comply with classification systems established by OMIM (Online Mendelian Inheritance in Man), Orphanet and ICD (International Classification of Diseases)-11.

It was felt that the overall term, LGMD, should be retained but the definition should be clarified. The consensus was that the definition would include the following factors:

- Genetic cause of the disease
- Progressive, predominantly proximal muscle weakness
- Condition which primarily affects skeletal muscle
- Achievement of walking at some point
- Weakness is caused by the loss of muscle fibres
- Elevated serum creatine kinase activity detected in the blood
- Degenerative changes on muscle imaging over the course of the disease and changes in muscle tissue (biopsy) that are in accordance with a muscular dystrophy

- For a new disease to be considered a LGMD, the disease must have been identified in at least two different families.

Several potential sub-type classification systems were proposed and discussed. It was agreed that a system that incorporates the name of the protein affected in the muscle cell and includes the mode of inheritance would be the most informative for patients and useful for genetic counselling.

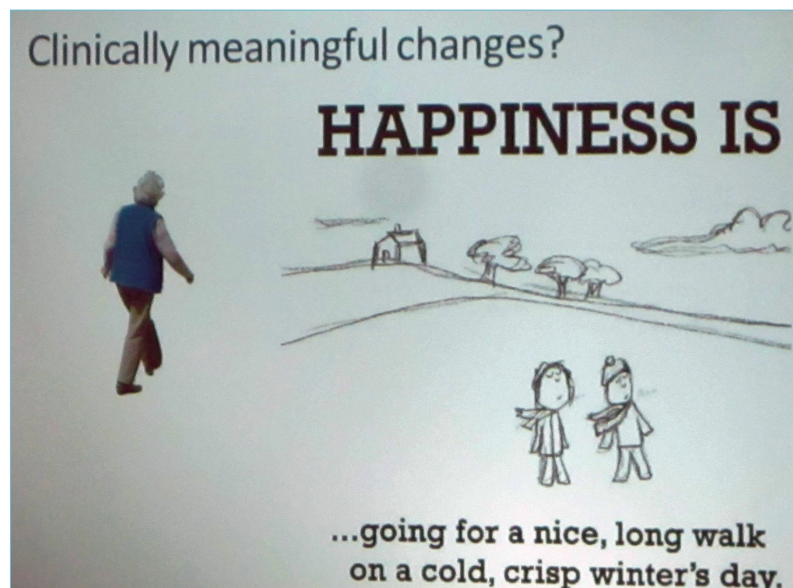
Patients and patient organisations were asked to give their opinions on the new definition and classification. The overall consensus was that the new classification added clarity to the field of LGMD. The workshop acknowledged that appropriate support from clinicians and patient organisations would be important in establishing the new nomenclature. Several action plans of how to disseminate this proposal were identified.

## Workshop 230 on “Improving future assessment and research in IgM anti-MAG peripheral neuropathy: a consensus collaborative effort”

A collaborative group of clinical experts in the field of peripheral neuropathy and patients and their representatives met for the 230st ENMC meeting with the purpose of improving the future assessment and treatment of patients diagnosed with IgM anti-myelin associated glycoprotein (anti-**MAG**) in peripheral **Neuropathy (IMAGiNe)**.

The group embraced the principle that specific valid functional outcome measures should be developed for studying and following the clinical picture of patients with this specific condition. The IMAGiNe project will collect data retro- and prospectively to classify patients and understand their natural history of the disease, the neurological and haematological characteristics of the disease and their responses to treatment. The project will include all worldwide centres with disease expertise with at least 10 participants.

At the workshop, new avenues in diagnosis, disease classification, pathogenesis and treatment, were explored in collaboration with the attending haematologists, who are essential to this effort. Current outcome measures were evaluated and a new disability scale with focus on patients was designed. The outcome parameters to be measured in the IMAGiNe project will collect data on the impairments, disabilities, quality of life and treatment expectations of the patients. Following the development of scales, consensus was reached regarding the definition “being a responder to treatment”. The IMAGiNe project will lead to proposals for new therapeutic strategies, with a plan to commence the first clinical trial utilizing novel outcomes by the end of 2018.



*The patient-reported outcome values of a treatment were addressed by two persons affected by CIPD; Ms P. Blomkwist-Markens (from GBS/CIDP Foundation International) and Mr L. Mazaway.*



## Workshop 231 on “International standard for CIDP registry and biobank”

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy causing severe disability. CIDP is a remarkably heterogeneous disorder with several atypical clinical phenotypes. Furthermore, despite various sets of diagnostic criteria, not all patients with treatable CIDP are identified. Despite proven effective treatment, at present no clinical or biological variables are available to predict treatment response. Further research is urgently needed to define the diagnostic, clinical and electrophysiological boundaries of CIDP and its subtypes, and to define the role of biomarkers (e.g. nerve ultrasound, blood characteristics) in supporting the diagnosis, in monitoring disease progression and in predicting response to treatment and long-term safety and efficacy outcome. To address these research questions, an international registry with a large number of patients is needed to allow validated prognostic models to predict efficacy in individual patients with CIDP.

Eight currently ongoing international CIDP registries were compared to assess the most optimal infrastructure of collecting data and biomaterials.

An international consensus was reached regarding criteria needed to include CIDP patients in the registry, the collection of a minimal dataset of clinical and diagnostic assessments and of biomaterials and the need of using standardized protocols to collect biomaterials (serum, cerebral spinal fluid, nerve biopsy). Biomaterials are now stored in participating centers or coordinating centers. This requires the development of a central database (INCbase) on which data from existing databases can be uploaded. All participating centers remain owner of data and can withdraw data from INCbase.

A Task force was set-up to combine current data of existing CIDP registries, to harmonize the current registry protocols and to set up a central database. The Task force has proposed a plan to include the first new CIDP patient into the registry by March 2018. For dissemination to the field, the proposed consensus/registry protocol will be presented and discussed in the coming Peripheral Nerve Society meeting taking place in July 2018, in Baltimore, USA.



*The organisers and Young Scientists grant winners of the 231st ENMC workshop on CIDP, taking place in spring 2017 in Naarden, The Netherlands. From left to right: Dr Hiew Fu Liong, Dr Filip Eftimov, Dr Carina Bunschoten, Dr Max Adrichem, Prof. Yusuf Rajabally, Dr Eduardo Nobile-Orazio.*

## Workshop 232 on “Recommendations for diagnosis and nucleoside treatments of mitochondrial DNA maintenance disorders”



*The participants of the 232nd ENMC workshop having lunch in the front garden of Castle Marquette, Heemskerk, The Netherlands.*

Tiny structures called mitochondria, present in almost all human cells, produce energy that drives chemical reactions in the cells and hence regular cell functioning. Mitochondria contain their own DNA, which is called “mitochondrial DNA” abbreviated as mtDNA. This mtDNA is essential for the normal functioning of mitochondria. An important group of mitochondrial diseases, called “mtDNA maintenance disorders”, is caused by mutations in genes that encode proteins needed to replicate and maintain mtDNA. This results in mtDNA damage and is associated with many clinical problems that severely affect patients. Depending on the particular affected gene and other factors, different symptoms appear. In some cases, the disease mainly affects the muscle function, which may lead to respiratory failure and death in infancy or childhood. Other clinical presentations include severe dysfunction of the liver, gastrointestinal tract or the central nervous system, which are often fatal at early ages.

This workshop focused its discussion on the clinical recognition, diagnosis and treatment of two specific mtDNA maintenance disorders: thymidine kinase 2 (TK2) deficiency and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). At the moment, deoxynucleoside therapy for TK2 deficiency is being tested and if this research further confirms the benefit of this promising therapy, regulatory approval will lead to larger availability of the first specific and effective treatment for this disease. Other topics intended to benefit patients included: 1) a more rapid diagnosis of TK2 deficiency; 2) clearer guidelines to help physicians choose the most appropriate option among the multiple innovative therapies for MNGIE; and 3) potential new future clinical trials of deoxynucleoside therapy for other mtDNA maintenance disorders.

## Workshop 233 on “Clinical trial readiness for Calpainopathies”



*The participants of the 233rd ENMC workshop held in September in NH Hotel Naarden, The Netherlands. With Mr Bruno Kullmann, President of the Associazione Italiana Calpaina 3 Onlus, and his carers Mr Massimo Pica and Mr Stefano Angiolini on the right.*

Calpainopathy or Limb-Girdle Muscular Dystrophy type 2A is due to mutations in CAPN3, a gene encoding an enzyme named calpain 3. This disease is characterized by slowly progressive muscle weakness affecting selectively the musculature of both girdles. There is no treatment for this disease to date.

The emergence of novel therapeutic approaches in the field, like gene therapy, has prompted a much awaited discussion between physicians and researchers about the readiness for clinical trials in calpainopathy.

In most countries, it appears that LGMD2A is usually the most frequent form of LGMD. Most of the patients present a classical clinical phenotype with a significant, selective involvement of the posterior compartment of the thigh. Although it seems to be rarely severe in LGMD2A, assessment and monitoring of respiratory function should be part of the standards of care. Cardiac issues on the other hand are rarely observed and are probably coincidental. Muscle imaging could be used as well as a monitoring tool to follow the progression of affected muscles. Experts highlighted the value of muscle biopsies for

diagnosis and research purposes. Despite the introduction of Next Generation Sequencing in the diagnostic algorithm of primary calpainopathy, biopsy analysis can be of tremendous help for a better understanding of the correlation between protein expression and clinical course.

The discussion pointed out that for now, no specific clinical outcomes have been clearly defined, highlighting the need of additional data on the clinical evolution of LGMD2A in preparation of future clinical trials. The importance of patient registries was also discussed. LGMD2A specific registries exist in few countries and there is an international database handled by Coalition to Cure Calpain3. A global European database would be of great interest while a global worldwide register seems out of reach at this point due to divergent policies regarding data protection across the Atlantic. Among other therapeutic options, an AAV-mediated gene transfer approach was presented with promising results. Nevertheless, it is clear that more fundamental studies are still needed at a time when the function itself of calpain 3 is not fully understood yet.



## Workshop 234 on “Chaperone Dysfunction in Muscle disease”

Chaperones are essential for the development and maintenance of skeletal muscle. This large group of proteins ensures that other proteins keep their correct structure and function, or facilitates their degradation if this is not possible. Thus, chaperone dysfunction is responsible for many rare hereditary myopathies. Correcting chaperone function may be a therapeutic option.

The participants reported on various aspects of the involvement of chaperones in a large variety of muscle diseases and disease processes, ranging from primary defects in chaperone genes such as DNAJB6, BAG3 and HSPB8, to the involvement of chaperones in the larger group of degenerative myopathies

including sporadic inclusion body myositis (sIBM) and beyond. Because the activity of the chaperones can be increased by different drugs, the main scope of the workshop was to identify opportunities to use the available current knowledge for direct therapies. One therapy, known to increase the activity of protein chaperones, arimoclolol, is already entering the second phase of clinical trials in patients with sIBM. Chaperonopathy patients had their own representatives at the workshop who made highly appreciated contributions focusing on the difficulties in diagnosis and therapies for ultra-rare disorders (See § 4.5 for the story of Ms Laura Zah, parent of a boy affected by a chaperone dysfunction).

“It was a great meeting!”

“It was one of the most exciting and stimulating meetings I ever attended.”

“I want to thank you for inviting us to attend the ENMC workshop. It is because of you that we had the opportunity to represent our children and make connections that may be helpful in the future.”

Another discussion topic was related to the use of large datasets and patient cohorts to study these diseases. The group agreed to establish a database with natural history and biomarkers in chaperonopa-

thies. Consensus was reached on clinical features of chaperone dysfunction and on sharing of putative chaperone gene variants with other clinical and basic researchers.



*Participants of the 234th ENMC workshop on Chaperone Dysfunction in Muscle Disease. For the last time in NH Hotel Naarden!*

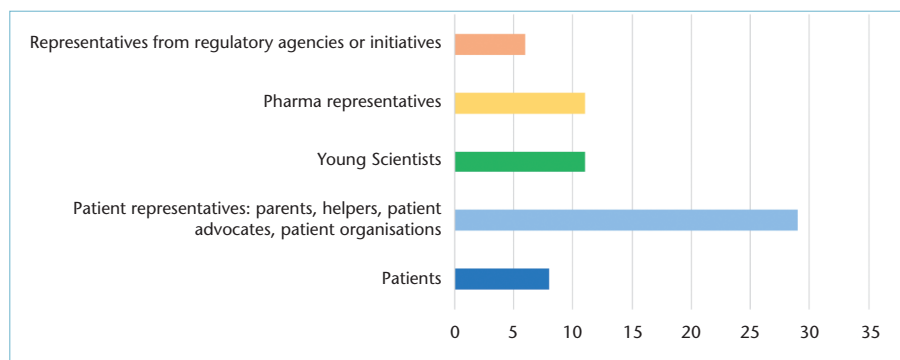
## 4.2 Participants at ENMC workshops in 2017

The ENMC strives for diversity in the group of workshop participants to ensure that consensus can be reached at the meetings by having all relevant decision makers around the table. This strategy also favours a broader dissemination of workshop outcomes within the international neuromuscular community, using the local networks of all workshop participants.

In 2017, clinicians and basic researchers formed the majority (68%) of in total 204 workshop participants.

Almost 40 patients and patient representatives attended the ENMC workshops (see graph below) resulting in a high level of patient participation (20%) this year. Also the number of young scientists was higher compared with previous years. The ENMC aims to maintain this high level of participation by young scientists and patient representatives in the coming years. Representatives from regulatory agencies, such as the European Medicine Agency, and pharmaceutical companies were also well covered in the ENMC workshops last year.

### Type of participants at ENMC workshops 2017

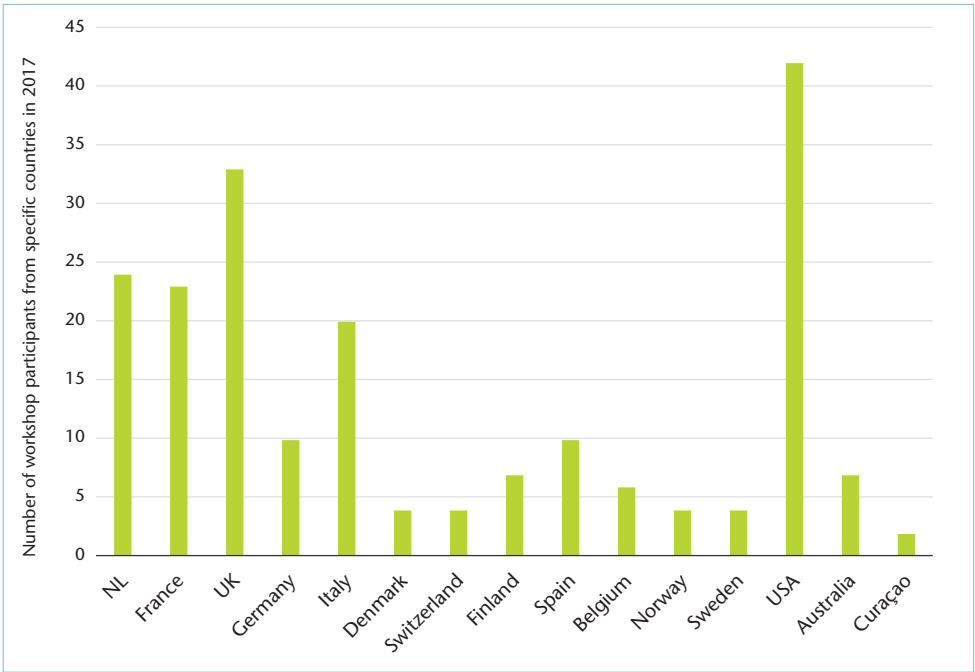


4.3 Countries represented in ENMC workshops in 2017

One of the key criteria for workshop approval by the ENMC is the geographical balance of the participants. The ENMC considers a wide coverage of countries in the workshops important, to make sure that consensus reached at ENMC workshops on diagnostic and/or therapeutic guidelines can be

implemented across Europe and beyond. This will help standardization of the health care for people affected by a neuromuscular condition which in the end may guarantee the best quality of diagnosis and treatment of patients worldwide.

Country representation in ENMC workshops 2017

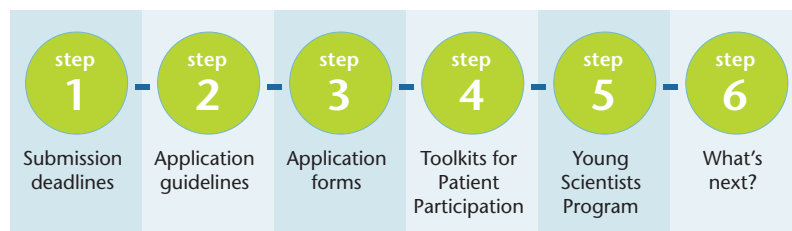


Also in 2017, many countries from all over the globe were represented at ENMC workshops, with a large contribution by ENMC member countries (Netherlands, France, UK, Germany, Italy, Denmark, Switzerland and Finland) and the USA.

Several countries, not included in the graph below, were represented only once in 2017 like Serbia, Czech Republic, Georgia, Israel, Malaysia, Brasil, South Africa and Japan.

New workshop application guidelines available, please check our website on:  
<https://enmc.org/workshops/how-apply/>

## IT ONLY TAKES 6 STEPS TO APPLY:



*If you have any questions regarding the application procedure, please do not hesitate to contact the ENMC office at [enmc@enmc.org](mailto:enmc@enmc.org).*

### 4.4 The ENMC from the perspective of a patient, Ms Sarah Hofstätter-Brumhard

**Ms Sarah Hofstätter née Brumhard, proud of her Facebook group “IBMPFD - patients, family, and friends”, which was initiated at an ENMC workshop.**

In 2015, the 215th ENMC workshop was held on the topic of IBMPFD, Inclusion Body Myopathy with early-onset Paget disease and Frontotemporal Dementia. Sarah Brumhard (25) was invited to this meeting. She belongs to a family in Germany with several members affected by this severe condition. Sarah's father is one of them and the disease is progressing to such an extent that he is now fully wheelchair - bound and without the ability to lift his arms.

#### **Carrier of VCP mutation**

Sarah herself carries the mutation in the gene for producing the valosine-containing protein (VCP), a protein which is important in breaking down other proteins. Sarah knows what her future may look like, based on what kind of symptoms her affected family members experience. On the other hand, the onset of the disease and phenotype may vary between patients and Sarah remains with a lot of questions and uncertainties.

At the workshop she expressed that due to the rarity of IBMPFD, she does not know any other young adults with a VCP mutation in her near surroundings with whom she can talk to and share her fears and other emotions.



**“Since carriers are still pre-symptomatic at my age, it is hard to recognize them when you are walking down the street!”**

Sarah studies informatics at the University in München.

During dinner, Sarah's problem was discussed and the idea was born of setting up a Facebook account particularly for this group of pre-symptomatic carriers of the VCP gene mutation. Neuromuscular conditions do not discriminate between country borders, hence going to the world-wide internet was the best way to reach peers. In November 2017, Sarah informed the ENMC that she, with the help of Dr Virginia Kimonis, started a Facebook group, which is meant for patients but also for family members.

Today, this is a very active group consisting of more than 62 members most of them either patient or carrier of the VCP gene mutation.



The Facebook group, named "IBMPFD-patients, family and friends" is a private community. If you would like to join, you can use the search term "IBMPFD-patients, family and friends" on the internet to make your request on the front Facebook page.

#### 4.5 The ENMC from the perspective of a patient's parent, Ms Laura Zah

A 12-year-old boy, Alexander, was recently diagnosed with a rare genetic mutation in the BAG3 gene. This mutation is associated with myofibrillar myopathy and axonal neuropathy, that results in cardiac and respiratory failure. It is expected to progress rapidly and be fatal in childhood or adolescence. The parents of Alexander, Stephan Greenspan and Laura Zah, have started a nonprofit, charitable organization called Alexander's Way Research Fund Inc., that promotes collaboration among scientists, researchers and patient advocacy groups. Their primary aim is to speed up research, development and delivery of treatments for children and young adults who are affected by Bag3 Myofibrillar Myopathy and other related neuromuscular conditions.

Both parents participated in the 234th ENMC workshop on chaperone dysfunction (see page 19). Stephan brought his perspective as a father and patient advocate and mother Laura as a nurse. Laura has a Doctorate of Nursing Practice with focus on patient advocacy and policy change.



*From left to right: the three organizers of the 234th ENMC workshop: Prof. Mike Hanna, Prof. Chris Weihl and Prof. Bjarne Udd. On the right, Ms Laura Zah and Mr Stephan Green, founders of Alexander's Way.*

Laura sent this letter to thank the participants for this workshop, which took place in December 2017.

*"We want to thank you for the opportunity to relate our experience with the rare BAG3 mutation and to voice our challenges and hopes. We appreciate your arduous work and devotion to science, which will ultimately benefit those affected by chaperone dysfunction. We also appreciate every offer of guidance from you that we have received for treatment and cure.*

*We undertook the challenging task of representing our children to the world's best minds in the field of chaperone diseases. It seemed like a once in a lifetime chance to get the answers to help our children. The remarkable thing is that we received support and appreciation beyond our expectations: the warm reception we received was accompanied by the promise of continued advice, collaboration, and an ongoing interest in our problem. We were also made to feel that our willingness to contribute fibroblast and myoblast samples was valuable to research. We are looking forward to continuing this collaboration for developing a cure for Bag3 disease. We hope that the exposure from this conference will lead us to finding more families affected by this condition. We invite them to join our mission of developing treatments and cure for the sake of our children. Our children are competent individuals that contribute to our society and we hope they will be able to continue to do so. We thank you again for your devotion, expertise and continued work and of course for giving us a chance to be heard not only as an organization, but as people".*

**Laura Zah,**  
President of Alexander's Way Research  
Fund, Inc., [www.alexandersway.org](http://www.alexandersway.org)



## 5 ENMC at international neuromuscular conferences

To meet scientists and clinicians and create awareness about the ENMC, several local and international conferences were attended in 2017.

- ENMC staff joined the **Eurordis multistakeholder symposium** in Brussel in February 2017. Topic of this meeting was to discuss how patients with rare diseases more quickly and easily gain access to orphan drugs.
- ENMC had a booth at the **Dutch Muscle Patient Association Day** in September 2017, creating awareness about the possibility for patients and caregivers to play an active role at the international ENMC workshops.
- Representatives of the Executive and Research Committee were present at the **World Muscle Society Congress** held in St-Malo from 3-7 October 2018. The ENMC had a good visibility near the Auditorium and many young scientists and potential future workshop organisers visited the booth to discuss application procedures and share their ideas for an ENMC workshop.
- The Executive Committee members Dr Raffaella Willmann and Dr Anna Ambrosini manned the ENMC booth at the **TREAT-NMD conference** in Freiburg in November 2017. Many researchers and patient representatives were visiting the booth and learned about the ENMC workshops.

## 6 Resources and financial management in 2017

### Financial summary 2017

Annual accounts for the year 2017 were compiled in accordance with Guideline C1 for the reporting of Small sized non-profit organizations as published by the Dutch Accounting Standards Board. The financial accounts are drawn up in Euros.

In the summary table below, the overall income and expenses over the year 2017 are shown in comparison with the figures for the financial year 2016. Details are given in the annual report 2017, which can be downloaded from the website [www.enmc.org](http://www.enmc.org).

Statement of income and expenses for the year 2017 in Euros (€)		
	2017	2016
<b>INCOME</b>		
Member contributions	210.000	210.000
Associated member contributions	5.000	5.000
Company Forum contributions	63.957	44.274
Other contributions	32.792	12.290
<b>Total income</b>	<b>311.749</b>	<b>271.564</b>
<b>EXPENSES</b>		
Personnel expenses	149.034	121.031
Rental expenses	11.997	11.126
Activity (workshop) expenses	87.114	120.361
Organisational expenses	40.274	48.617
<b>Total operating expenses</b>	<b>288.419</b>	<b>301.135</b>
Operating result	23.330	- 29.571
Interest income	502	1.686
<b>Net result</b>	<b>23.832</b>	<b>- 27.885</b>
<b>APPROPRIATION OF RESULTS</b>		
Continuity reserve	-	-
Reserve for 25th Anniversary	- 8.009	30.000
Reserve for additional workshop costs	- 15.155	93.000
Other free reserves	46.996	- 150.885
	<b>23.832</b>	<b>- 27.885</b>
<b>CASH AT BANKS ON 31 DECEMBER</b>	<b>491.595</b>	<b>485.613</b>

### Opinion of the auditors

The independent accountants have verified and approved the annual accounts. For a full PDF version

of the annual accounts report of 2017, please visit the ENMC website.



## 7 Governance 2017

The European Neuromuscular Centre (ENMC) was founded as a non-profit organisation on 24 November 1992 under Dutch law. The foundation is supported by financial contributions of nine European patient organisations for neuromuscular disorders and other related organizations. The statutory location is in Baarn in the building of the Dutch Neuromuscular Diseases Association.

### 7.1 The ENMC Executive Committee

The ENMC is governed by an Executive Committee consisting of representatives of ENMC member organisations.

*Composition of the ENMC Executive Committee on 31 December 2017:*

Dr A. Ambrosini (Italy)  
Dr A. Méjat (France)  
Dr A. von Moers (Germany)  
Dr I. Meijer (The Netherlands)  
Dr J. Rahbek (Denmark)  
Dr E. Sterrenburg (Vice-Chair, The Netherlands)  
Dr R. Willmann (Chair, Switzerland)  
Vacancy (United Kingdom)

### 7.2 The ENMC Research Committee

The ENMC Research Committee is responsible for reviewing the scientific content and quality of the workshop applications and advises the Executive Committee on awarding the grants for ENMC workshops.

*Composition of the ENMC Research Committee on 31 December 2017:*

Prof. G.P. Comi (Italy)  
Dr D. Hilton-Jones (United Kingdom)  
Prof. H. Jungbluth (United Kingdom)  
Prof. P. Laforêt (France)  
Dr M. Olivé (Spain)  
Prof. G. Padberg (Chair, the Netherlands)  
Prof. M.A. Rüegg (Switzerland)  
Prof. U. Schara (Germany)  
Prof. W. Stenzel (Germany)  
Dr N. Voermans (the Netherlands)

### 7.3 The ENMC Office

The office takes care of the daily business of the ENMC.

*ENMC Office staff on 31 December 2017:*

Dr A. Breukel (Managing Director)  
Ms A. Zittersteijn (Operational Manager)  
Prof. G. Padberg (Research Director)  
Ms Mirte Edens and Ms Lisa Verwer (Workshop Assistants)

## 8 A special thanks to all our members and supporters

Thanks to the continuous support of the nine European patient organizations, the ENMC is able to facilitate and organise an average of eight workshops per year. With support from additional partner organizations, such as condition-specific associations

and members of the ENMC Company Forum, we are also able to invite participants from non-ENMC countries and facilitate the attendance of young scientists and patient representatives.

### ENMC full and associated members



### Members of the Company Forum



### Workshop-specific sponsors



## 9 Looking forward to 2018 and beyond

In 2018, the ENMC organizes five workshops, including the Special (235th) ENMC workshop on ‘The position of neuromuscular patients in Shared Decision Making’. This special workshop will take place in Milan, Italy.

Two review rounds are planned in 2018 (spring and autumn) to select new workshops. For 2019 already five workshops are planned.

### Preliminary ENMC programme 2018 and beyond ([www.enmc.org](http://www.enmc.org))

Workshop No./date	Topic	Workshop leaders
Workshop No. 235 19-20 January 2018	Special Anniversary Workshop: “The position of the neuromuscular patient in Shared-Decision-Making”	Prof. H. Lochmüller and Prof. A. Tibben in collaboration with the ENMC board
Workshop No. 236 1-3 June 2018	Bone protective therapy in Duchenne Muscular Dystrophy: Determining the feasibility and standards of clinical trials	Prof. V. Straub, Dr J. Wong, Prof. L. Ward and Dr R. Quinlivan
ENMC symposium at ICNMD, 8 July 2018	“ENMC: Your neuromuscular network for the next 25 years”	Prof. Padberg and Prof. van Engelen together with ENMC board members
Workshop No. 237 14-16 September 2018	GNE myopathy (also known as HIBM, Nonaka disease, and quadriceps sparing myopathy) (GNEM)	Prof. H. Lochmüller, Dr J. A. Urtizberea, Prof. Z. Argov and Prof. I. Nishino
Workshop No. 238 30 November-2 December 2018	Updating management recommendations of cardiac dystrophinopathy	Dr J. Bourke, Prof. D. Duboc, Dr M. Guglieri and Dr T. Evangelista
Workshop No. 239 14-16 December 2018	Clinicopathological Classification of Dermatomyositis	Dr A. Mammen, Dr Y. Allenbach, Prof. O. Benveniste, Prof. W. Stenzel
Workshop No. 240 25-27 January 2019	The involvement of skeletal muscle stem cells in the pathology of muscular dystrophies	Dr J. Morgan, Prof. K. Patel, Prof. F. Muntoni, Dr G. Butler-Browne
Workshop No. 241 15-17 February 2019	Towards a European Unifying lab for Kennedy’s disease	Dr M. Pennuto, Dr G. Sorarù, Dr L. Greensmith, Dr P.F. Pradat
Workshop No. 242 1-3 March 2019	Diagnosis and Management of Juvenile Myasthenia Gravis	Dr J. Palace, Dr E. Niks, Dr S. Robb, Dr P. Munot
Workshop No. 243 22-24 March 2019	Developing guidelines for management of reproductive options for families with maternally inherited mtDNA disease	Prof. J. Poulton, Prof. J. Stefann, Dr J. Burgstaller, Prof. B. McFarland
Workshop No. 244 24-26 May 2019	Protein Aggregate Myopathies	Dr M. Olivé, Dr R. Schröder

In addition, ENMC organizes a special symposium at the International Conference for Neuromuscular Disorders (ICNMD) in Vienna on Sunday July 8, 2018. Invited key speakers will present the contents and results of recently held workshops. They will discuss and reflect on the impact of the outcomes of their

workshops and on the future outlooks for the neuromuscular community. The results of the overall impact of ENMC workshops in the neuromuscular community, analysed by a retrospective impact analysis (see 3.1-3.3), will also be presented here and at upcoming international neuromuscular meetings.

A bibliometric analysis will be performed in the first quarter of 2018 by the Centre for Science and Technology Studies (CWTS), in Leiden, The Netherlands, to measure the value of ENMC publications in the neuromuscular literature.

### Changing meeting venues in 2018

The ENMC made the decision in 2017 to change its traditional meeting venue NH Hotel in Naarden after

so many years of good services, to a new meeting location: the Courtyard Marriott Airport hotel in Hoofddorp, The Netherlands. The reason for this relocation is to offer workshop participants a new and fresh workshop venue at a closer distance to Schiphol, Amsterdam.

### Budget for 2018

In this table the budget forecast for 2018 is presented.

Budget 2018	Actuals 2017	Budget 2018
<b>INCOME</b>		
Member contributions	210.000	210.000
Associated member contributions	5.000	5.000
Company Forum contributions	63.957	64.000
Other contributions	32.792	15.000
<b>Total income</b>	<b>311.749</b>	<b>294.000</b>
<b>EXPENSES</b>		
Personnel expenses	149.034	137.000
Rental expenses	11.997	11.500
Activity expenses	87.114	157.000
Organizational expenses	40.274	48.000
<b>Total operating expenses</b>	<b>288.419</b>	<b>353.500</b>
Interest income	502	500
<b>NET RESULT</b>	<b>23.832</b>	<b>- 59.000</b>
<b>APPROPRIATION OF RESULTS</b>		
Continuity reserve	-	-
Reserve for 25th Anniversary	- 8.009	- 21.991
Reserve for additional workshop costs	- 15.155	- 31.000
Other free reserves	46.996	- 6.009

# Colophon

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## IN MEMORIAM

**Prof. Giovanni Nigro – Napoli, Italy**

*13 October 2017*

This ENMC impact report is dedicated to Prof. Nigro who was among those who started the first ENMC initiative back in 1988 in Paris and was a signatory of the Consortium Constitution on November 24, 1992. He always supported the ENMC mission and vision, contributing for many years to the Research Committee, being one of the Honorary members.





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