Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) 185–192

www.elsevier.com/locate/nmd

Workshop report

227th ENMC International Workshop: Finalizing a plan to guarantee quality in translational research for neuromuscular diseases Heemskerk, Netherlands, 10–11 February 2017

Raffaella Willmann [a,*], Filippo Buccella [b], Annamaria De Luca [c], Miranda D. Grounds [d] on behalf of the 227th ENMC workshop study group [1]

[a] University of Basel and Swiss Foundation for Research on Muscle Diseases, Switzerland
[b] Duchenne Parent Project, Italy
[c] University of Bari, Bari, Italy
[d] University of Western Australia, Perth, Australia

Received 23 October 2017

1. Introduction

Twenty-seven representatives of scientific journals, funding agencies, industry and academia from seven different countries (USA, Italy, Switzerland, Netherlands, Belgium, United Kingdom, Australia), and patient representatives met in Heemskerk in the Netherlands, on the weekend of the 10th–11th of February 2017 to help finalize a plan to guarantee quality in translational research for neuromuscular diseases. This workshop was the first to bring together a wide range of stakeholders to discuss the important issue of translational efficiency. The workshop is the fruit of the constant efforts of the TREAT-NMD Alliance to improve animal model studies for neuromuscular disorders with the final goal of accelerating research and effective treatment development.

2. Background

In the last few decades, the low predictive power of pre-clinical studies to translate into successful clinical trials for neuromuscular diseases has caused deep frustration for the communities of patients and their families, clinicians, scientists and industry [1–4]. Clinical trials are extremely expensive to fund (compared with most basic science research projects) and trials can be a major imposition on a patient population. This applies especially in cases of complex progressive and wasting diseases, where few patients are available, and/or vulnerable children at a young age are involved. At the same time, there is an increasing pressure to undertake clinical trials. Therefore it is ethically important to very critically select which drug or treatment will proceed to a clinical trial. The lack of rigorous and consistent design of the pre-clinical tests conducted with animal models between different laboratories is one reason for the failure in translation. The problem of experimental laboratory research delivering efficacy data that turn out not to show any efficacy in patient studies is not new. This has been discussed thoroughly in the communities for both rare and common diseases [5–10], and numerous editorials and commentaries have addressed the issue of transparency and reproducibility in biomedical research with increasing support for use of the ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines [11] to improve the quality of pre-clinical research [12–15]. While clinical trials fail for a variety of reasons, we should work toward the goal that none failed because they were based on poorly designed, conducted, or reported pre-clinical efficacy studies.

The pre-clinical phase of research needs to distinguish between two distinct forms of studies. The first is **exploratory studies**, aimed at understanding a given physiological pathway or molecular mechanism, generating hypotheses, and investigating new possibilities or methods that can provide initial 'proof-of-concept' data to identify merit of a potential therapy. The next phase is **confirmatory studies** which aims to provide compelling evidence that the treatment efficacy is worth being tested in humans and that it justifies the enormous financial and emotional effort required for a clinical trial. Indeed, even a phase 1 trial should require strong evidence of a likely benefit and not be limited to a pure safety evaluation, especially for rare diseases. Ideally this second pre-clinical phase should include further testing of the

* Corresponding author. University of Basel and Swiss Foundation for Research on Muscle Diseases, Switzerland.
E-mail address: raffaella.willmann@unibas.ch (R. Willmann).
[1] Listed at the end of this report as workshop participants.

https://doi.org/10.1016/j.nmd.2017.11.002

benefits of the intervention by an independent research group to confirm that it has merit. The formal "pre-clinical" trials of a therapy in laboratory animals should be considered as a variant of a clinical trial for humans, and should be designed with the same scientific rigor and with proper controls (as for a true clinical trial), in order to be meaningful and to deliver information to help determine the optimal regime, dosage etc. Organizations like the National Institutes of Health (NIH) [6] and TREAT-NMD [16] have developed guidelines for best practices and standard operating procedures to optimize the efficacy of pre-clinical experiments using animal models, and subsequent formal pre-clinical trials.

Unfortunately, many of the published pre-clinical studies that are conducted as exploratory research [17] are then used alone, without further testing and formal validation, to promote and sustain the conduct of a clinical trial, driven by the urgency of finding treatments for suffering patients, and sometimes commercial interests. This is a major issue to address. In addition to the pressure of time, the lack of confirmatory studies before undertaking clinical trials can result in large part from problems related to (a) lack of funding for confirmatory studies and (b) difficulty with publication of confirmatory or negative results.

2.1. Funding to undertake confirmatory studies

It is highly competitive to obtain research funding: novel research that is considered 'cutting edge' or likely to provide a 'breakthrough' is far more likely to get supported than the essential but sometimes expensive and time-consuming confirmatory studies. These are required to validate the merit of an 'exciting new' proposal, yet, at best they will support the merit of this intervention (but this is not a novel) or at worst they may produce a disappointing negative result. Both are valuable in the context of whether to proceed to an expensive clinical trial or not. It is increasingly apparent that many clinical trials that fail are, retrospectively, deemed to have been based on inadequate pre-clinical data.

2.2. Publication of results

Most scientific studies face the need for publication, to expose the results for wide public scrutiny and to demonstrate the activities of the researchers. There is an intense pressure for researchers to publish in high profile journals for career advancement; balanced against this is the need for commercial journals to attract readers and citations in order to stay viable and relevant. Consequently, many journals compete to publish top papers of 'breakthrough science' often with suggestive titles and novel impressive results. Negative results can be difficult to publish even when based on a strong rationale, an important hypothesis and top methodology, as well as on a rigorous approach and a robust evidence, despite the fact that such a negative result can be highly informative and valuable [18]. Similarly, confirmatory studies that may (or may not) provide impressive validation of results, are considered not novel and are therefore also hard to publish: this represents a big disincentive to undertake such time-consuming, yet essential additional studies. The benefits of such publications are greatly strengthened if standardized validated protocols and guidelines are used to compare the efficacy of different interventions using a standard animal model, since this allows ready comparison between results from different groups: only then can the relative merit of different interventions be rigorously evaluated, and compared.

In conclusion, while freedom, creativity and flexibility should be encouraged in exploratory basic research, the implementation of rigor and quality in the conduct and reporting of confirmatory pre-clinical animal studies (even if results are negative) would be of great benefit for improved planning of successful clinical trials especially for neuromuscular diseases. In parallel, the issue of investing time and funding to thoroughly characterize animal models, their natural histories and variability of analysis, and to define best practices and standard experimental protocols, definitely deserves more attention [19].

It is increasingly evident that the responsibility to improve the predictive power of pre-clinical experiments should not solely depend on the decision of a single laboratory. A previous TREAT-NMD workshop ("Update on standard operating procedures in pre-clinical research for DMD and SMA" held in Schiphol, the Netherlands, on April 26, 2015 and supported by Duchenne Parent Project Netherlands; workshop report by van Putten et al., submitted) made it clear that the direct involvement of all stakeholders (including journals, grant funding organizations and regulatory agencies) in this discussion, is of key importance to raise awareness on the issue of study quality and to obtain changes in the way that this quality is understood and achieved.

THE WORKSHOP aimed to:

1. Increase the mutual feedback between pre-clinical scientists, clinicians, industry, funding and regulatory agencies when designing a clinical trial on the basis of pre-clinical data, or when evaluating the negative outcome of a clinical trial.
2. Raise awareness with funding agencies for the need of funds for variability studies, natural history studies and confirmatory studies with a low level of novelty; and to emphasize the requirement for high quality standards to be applied in studies funded by patient organizations.
3. Reach a consensus on reporting guidelines for pre-clinical studies; including a plan for the implementation of recommended guidelines by journals and funding agencies, as well as on the importance to publish independent confirmatory studies or negative results.

2.3. Day one: Preparatory talks

Miranda Grounds (University of Western Australia) on behalf of the organizers, presented a brief overview of the major problems involved, the program and the desired outcomes, and outlined issues associated with the generally high failure rate of clinical trials for neuromuscular diseases. This emphasized the steps required to improve the transition from early proof-of-concept pre-clinical studies in animal models to more rigorous

pre-clinical testing to select the best drug/intervention and increase the success rate for clinical trials. As stated previously, *"In rare diseases, the answer to effective therapies is not so much "more shots on goal" but "better shots on goal"—we simply can't afford the standard high failure rate of clinical development programs"* [16].

Session 1: Variability in human studies and clinical translation of pre-clinical animal outcomes. The first session opened with **Volker Straub** (Newcastle University, UK) analyzing parallels in human and animal outcomes. He illustrated how animal models can fail in predicting efficacy in humans and that the variability in mice and humans, as well as the inappropriateness of single animal models, can add to discrepancies between pre-clinical and clinical trials. He underlined why clinical trials in humans are key to evaluate real efficacy of drug interventions, and how important natural history studies are to identify the right cohorts and the outcome measures for a specific study (see also [20]). After a comparison of challenges linked to outcome measures, using the example of those commonly used in Duchenne Muscular Dystrophy (DMD) and the *mdx* mouse model of this disease, he concluded that animal model studies remain important in the process of selecting potential drugs, and that several measures should be implemented by the different stakeholders to improve the predictive value of the animal studies and limit research waste. Examples are the creation of standardized experimental procedures for animal models by disease expert groups, the investment of funds by governments to optimize, validate and run translation tools, the refinement of animal model assessment based on clinical bedside findings that were not predicted by animal testing ("back-translation"), the adoption and implementation of the ARRIVE guidelines by publishers, and more attention by funding agencies toward high quality of the funded research [21].

Nathalie Goemans (University of Leuven, Belgium) addressed the issue of disease variability in patients, using the example of DMD, considered to be characterized by a predictable course but with high individual variability. Studies have shown that several factors, especially genetic and environmental factors, can influence disease progression and cause this variability. Genetically, the type of mutation correlates with the degree of performance over time [22,23], the reading frame rule explains some of the differences in disease progression in boys with the same type of mutation [24,25] and, in recent times, single nucleotide polymorphisms (SNPs) were identified as genetic modifiers [26–28]. The environmental factors include physiotherapy, the management of scoliosis and respiratory issues that shifted the origin of death from respiratory to cardiac causes and the use of corticosteroids that affects performance of lower and upper limbs as well as survival. For all these reasons, the development and validation of composite prognostic models could have significant value for clinical trial design and interpretation.

Andrea Klein (Children's University Hospital of Basel, Switzerland) and **Kanneboyina Nagaraju** (Binghamton University, USA) shared their views about what is needed for a more efficient cross-talk between clinicians and researchers in planning and evaluation of a clinical study. Andrea Klein illustrated that physicians may have very different opportunities to dedicate time to research depending on the type of institutions they are affiliated with, the protected time (and funding) for research that they may receive and the availability of discussion platforms like national or international conferences, to establish a competent network of collaborations. Furthermore, she underlined the need for expertise and training in many different fields, from pharmacology and statistics to regulatory requirements, and the need for a closer exchange of basic data between clinicians and researchers to improve the interpretation of pre-clinical work and the planning of clinical trials. She encouraged joint small meetings at the local, national or disease specific level where clinical and pre-clinical study results can be discussed, with a sharing of knowledge on different areas of expertise using dedicated platforms. Kanneboyina Nagaraju reported from his own recent experience the challenges with unfamiliar regulatory requirements and administrative procedures in translating research to an investigator-initiated clinical trial, and the change of culture when shifting from the hypothesis-driven basic research to the goal-directed clinical research. He also addressed the issue that translational projects are multi-investigator initiated but with no strategy in place to value single investigator contributions. A symposium held in 2011 by the Federation of American Societies for Experimental Biology identified a series of challenges and possible solutions to engage basic scientists in translational research [29] and concluded that the research community should expand translational research training opportunities, and encourage and support collaboration between basic and clinical investigators across research disciplines and sectors.

Session 2: Variability and reporting issues in pre-clinical research. The second session started with **Maaike van Putten** (Leiden University Medical Center, Netherlands) underlining the need for robust pre-clinical literature, since compounds for clinical trials are chosen because of efficacy shown in animals. Next to good natural history data for animal models, more rigor for pre-clinical study design and reporting is of key importance; particularly standardized outcome measures, sufficiently sized experimental groups, randomization and blinding. She pointed out that variability in outcomes of animal models can be high, and that this is mainly due to either individual variability of mice (gender, genetic background, and differently affected muscles), animal husbandry or differences in assessment methods from lab to lab. She showed some examples of variability in the histology and grip strength assays in *mdx* mice and preliminary data from a literature study showing that sample size calculations, randomization and blinding are not reported in the majority of the publications, while gender and age of mice are missing in 40% and 60% of the papers, respectively (unpublished observations). Maaike appealed to the awareness of researchers, journal editors and funding agencies for rigorous study design and publishing guidelines.

The following talk was a joint presentation by **Annemieke Aartsma-Rus** (Leiden University Medical Center, Netherlands) and **Annamaria De Luca** (University of Bari, Italy, who was unable to attend the workshop but provided slides and input

before the meeting). Annemieke clarified the difference between explorative, proof-of-concept studies on animals, and confirmatory, therapeutic efficacy studies, the latter requiring the rigor in design and publication addressed in the preceding talk [6,17,30]. She also addressed the issue of publishing where the current policy tends to favor publication of positive and novel results, and discard negative results, studies that confirm results obtained by others and studies that show inefficacy of a therapeutic approach. She proposed that outcome measures chosen to assess animal models should be multiple and possibly close to corresponding human outcomes, they should be not too dependent on animal volition and follow standardized assessment procedures (see for instance [31]). To this end, she described efforts done by the TREAT-NMD network in establishing standardized, consensus based experimental protocols (SOPs) [32,33]. Pharmaceutical companies are becoming aware of the importance of SOPs and of independent validation and request them from Contract Research Organizations and academic groups; the TREAT-NMD TACT Committee also requires adherence to SOPs when evaluating the translational potential of a new treatment.

Maria Sheean (European Medicines Agency (EMA)) illustrated the value of pre-clinical data for the EMA. She explained that pre-clinical drug development generates mainly three types of evidence required by the EMA: drug discovery, pharmacodynamics and safety. The available EMA guidelines on the pre-clinical aspects of research focus on safety (toxicology) and pharmacodynamics (Doc. Ref. EMEA/CHMP/SWP/28367/07). The latter includes, next to the mode of action and dose estimation, target specificity and medical plausibility, that both require adequate animal models of the disease. In the area of rare diseases, one of the criteria required for the orphan drug designation is the demonstration of "intent to treat", also expressed as medical plausibility, to support the rationale for the development of the product in the proposed condition and for the assumption of a clinical benefit. Therefore, inclusion of disease relevant endpoints in studies to complete the chain of evidence is encouraged. However, there are no specific guidelines regarding how to conduct or report such animal studies, nor an obligation to submit such data. In December 2015, the Committee for Orphan Medicinal Products (COMP), motivated by a high proportion of applications based on non-clinical data, established a Non-clinical Models Working Group that focuses on a systematic analysis of existing models in 28 neurology conditions (including neuromuscular diseases). The working group recognized the advantages of high quality non-clinical dossiers (with descriptions of methodology and statistical analysis) and that medical plausibility is supported by studies which include some disease relevant endpoints, preferentially in rodent models rather than in lower animal models, while mechanism of action studies *per se* may not be sufficient [34]. One of the limitations encountered was the limited availability of natural history data. The COMP Non-clinical Models Working Group therefore supports the efforts to standardize non-clinical studies, the development and further establishment of models and the improvement in reporting for the purpose of regulatory procedures.

The last talk was given by **Alejandra Clark**, senior editor at PLOS ONE, one of the peer-reviewed journals founded in 2006 by the Public Library of Science. The journal requires reproducibility and data sharing as publication criteria, next to originality of data and ethical standards. Reporting guidelines for different study types is part of the initial check, before manuscripts are seen by editors and peer reviewers. Mandatory are the CONSORT (Consolidated Standards of Reporting Trials) guidelines for clinical trial studies [35] and the PRISMA guidelines for meta-analysis studies [36], while for animal studies the application of the ARRIVE guidelines needs to be further encouraged. PLOS ONE has endorsed the ARRIVE guidelines since their publication in 2010 [11,37]. Committed to the 3R rules (replacement, reduction, refinement), PLOS ONE accepts the publication of negative results to reduce the risk of unnecessary animal research, and of replication studies to increase the availability of reproducible data.

Session 3: Presentation of draft consensus document on reporting guidelines. Miranda Grounds outlined a draft consensus document as the basis for group discussions by all stakeholders the following day. This focused on a pipeline to improve pre-clinical data and outcomes, including the need to use SOPs and adhere to the ARRIVE guidelines, confirmation of data by an independent group, and conducting a well-designed pre-clinical trial: such requirements address the fundamental issues of transparency and reproducibility in science. How best to implement, monitor and enforce the use of such guidelines and recommendations, along with the major concerns, obstacles and likely outcomes (all designed to improve future clinical trial efficiency and success) were discussed the following day.

2.4. Day two: Group discussions

On the second day, participants were divided into 3 groups representing the main stakeholder categories: clinicians and researchers, funding agencies, and journal editors, with about 8–10 participants per group.

2.4.1. Group 1 (clinicians and researchers)

This group discussion focused mainly on how to improve the cross-talk between experts of the different stages of medical development for the planning and evaluation of clinical trials. It was recognized that a closer contact between patients and academics would be useful for pre-clinical researchers; this can be increased when academic research is embedded in a university hospital, but is less possible in other settings. It was also observed that clinicians from minor or local health centers may not have enough experience in clinical trial planning and choice of appropriate outcome measures. In some countries, a strategy for improved cross-talk between researchers, academics and patients is in place, like the ALADIN (All Against Duchenne In The Netherlands) network in the Netherlands. The group proposed to take action to improve the education process and the cross-talk at the different stages by organizing teaching courses. It was proposed to use the expertise already available within the TACT Committee that

includes experts in pharmacology, biostatistics, regulatory experts, patient representatives, etc., and to organize a first course close to an international meeting with a potentially interested audience. It was decided to contact organizers of the **International Congress on Neuromuscular Diseases (**ICNMD), to be held in July 2018 in Vienna. Volker Straub and Kanneboyina Nagaraju will help lead the organization.

2.4.2. Group 2 (funding agencies)

Representatives of funding agencies discussed (i) how to increase the funding of pre-clinical confirmatory studies; (ii) how to require such applications to adhere to common guidelines; and (iii) how to fund studies of natural history, variability and animal model characterization. The group recognized that all of these aspects are essential to accelerate pre-clinical research and support decision making in the development of therapies for NMD.

Funding for confirmatory studies, to rigorously replicate initial efficacy findings before moving toward a clinical trial, is essential to inform go/no-go decision making in drug development. Too often, clinical trials have been launched without sufficient rationale to justify human studies, leading to numerous failed clinical trials. Yet, confirmatory studies can be hard for funding agencies and patient organizations to address, since their scientific review panels may not value repetition of work that appears to be already done. Similarly, even though such studies are essential, there may be insufficient incentives for scientists to participate in replication of prior studies. To address this gap, and ensure that the scientific premise underlying clinical trials is based upon rigorous pre-clinical data, the creation of dedicated funding mechanisms and/or a common fund to enable support for such essential studies was proposed. Continuing support for contract research organizations or academic labs dedicated to providing high quality replication studies is another potential option for funders to achieve this goal.

Ensuring the appropriateness of the animal models used in critical pre-clinical efficacy studies is another important concern for funders. The European Medicines Agency (EMA) considers knowledge of model organism natural history and endpoint measures in regulatory decisions. Funding the collection of natural history data in appropriate animal models is therefore essential. Funders should help develop and highlight animal/data sharing guidelines, standard operating procedures, and rigorous study design to ensure that such studies are informative.

It is also important to improve awareness of the standards needed for high quality pre-clinical research among patient organizations that do not have an expert scientific commission in place to evaluate project quality. The goal would be for all patient organizations to be able to triage which candidate therapeutics have established adequate scientific rationale, and thus are deserving of support to move into clinical trials, from those that require confirmatory studies to inform decisions for their further development. More experienced funding agencies could take a leading role in generating joint funding. The U.S. National Institutes of Health has developed rigor and reproducibility principles and guidelines (https://www.nih.gov/research-training/rigor-reproducibility) that could easily be adopted by patient organizations. Alternatively, patient organization funders could rely on the TREAT-NMD Advisory Committee on Therapeutics (TACT) to evaluate, and inform them of, the caliber of pre-clinical data and readiness of a company to move into early stage clinical trials.

Finally, the group proposed to use the leverage that patient organizations have on industry, to require strong pre-clinical data before engaging in a clinical trial. This leverage could take the form of industry engagement policies to be implemented by patient organizations. Under such policies, patient organizations would require that adequate scientific rationale be demonstrated for a candidate therapeutic before biotechnology and pharmaceutical companies could gain access to the organizations' resources (e.g., registries, recruitment/retention tools, etc.).

2.4.3. Group 3 (journal editors)

This group addressed 3 major issues:

(i) How to require adherence to reporting guidelines? An increasing number of journals have reacted to the criticism on transparent scientific reporting by requiring more rigor in submitted manuscripts; this necessitates inclusion of all experimental and statistical details that are needed to replicate the experiments and analyses reported [38]. In general, it was agreed that reviewers should not be the only people responsible for checking the submissions. A few journals (e.g. E-life, PLOS ONE, etc.) first screen the papers to ensure compliance before sending to reviewers and this approach was strongly recommended. Some journals pay a 4th reviewer to check statistical data in clinical papers but this is not affordable every time for pre-clinical studies: it is recognized that such additional expense can be a problem for journals that need to make a profit to remain viable.
It was proposed to build on the ARRIVE guidelines, to skip items related to animal welfare as this is already imposed by local ethical committees, to encourage the inclusion of checklists on the author instructions (that should also be useful to reviewers), and for more journals to consider screening the manuscripts before sending to reviewers. These all need to be more widely applied by journals [39]. It would also be advisable to link instructions to the TREAT-NMD standards, and to possibly have another specific workshop to agree on checklists and procedures.

(ii) How to encourage and support submission of negative results and confirmatory studies despite lack of novelty? All agreed that this is an issue of key importance with a need to proactively address, since it is critical that studies that do not support the use of a drug are also published to provide a balanced picture. Several proposals arose to encourage publication of negative or confirmatory results including: special section in journals ("no phenotype knock-outs", "missing pieces", etc.); encourage

submission of all data available from a study and not only the positive results; small publication grants by funding agencies; a specific note on the journal's website that negative or confirmatory results are encouraged, as already implemented by some journals including PLOS Currents, PLOS ONE, E-Life, and eNeuro. Several people remarked that the publication of negative results is not attractive to many journals, in part due to the quest for 'breakthrough newsworthy' results, commercial pressures, and the focus on impact factors. Some individuals considered that publication of negative results damaged the reputation of young researchers; however, negative papers can also be very well cited. These issues were quite strongly debated. All agreed that a change in the mentality is needed with regard to the community attitude toward negative results. The publication of a white paper on this issue may be helpful. It was also noted that while reproducibility is important, a confirmatory study may provide additional information that was not presented in the original study, and studies using other animal models or with other parameters than for the original publication may be also very valuable. In some cases, pilot trials in a few patients may be more informative than results confirmed only using animal models. The timing is also critical between confirmatory studies and commercial/clinical progress. There is a need for independent reviewers from other fields to evaluate the investments in time and resources on confirmatory studies; the role of funding agencies is therefore key on this issue.

(iii) How to deal with raw data? The storage and management of large data resources (e.g. microarrays and other 'omics', images) are becoming increasingly difficult, as these require much space and is often not feasible on the website of a journal or an academy. While this is considered obligatory by some journals, it is not enforced. Furthermore, compliance is not checked, since this is a time-consuming process. Both of these problems need to be addressed by journals (and others) since there is a compelling need for the original data to be available in a suitable form for scrutiny by others. There is also strong support for authors in the life sciences to share research materials used in their publications and this can be achieved using public and private tissue, mouse and other repositories, although how widely this occurs is unclear [40]. There is a need for more interdisciplinary discussions and action to improve access to the original data and materials for both interrogation and validation.

3. Conclusions

This workshop raised the awareness and emphasized the importance of a variety of issues related to the quality of pre-clinical studies, and their value in translation to facilitate effective treatments for neuromuscular diseases. Pitfalls and challenges were discussed for the first time with all stakeholders involved: clinicians, researchers, journal editors, industry, funding and regulatory agencies. Additionally, the use of appropriate biomarkers and the value of human pilot trials, to test a potential treatment efficacy on a few individuals, were mentioned as possible roads to improve the overall success of clinical trials for neuromuscular disorders. The main outcomes are:

1. A teaching workshop for clinicians and researchers interested in the planning and conduct of clinical trials, to be held in July 2018 at the ICNMD Conference in Vienna;
2. The common effort by funding agencies to promote rigorous scientific evaluation of grant applications and to enforce the requirement for strong pre-clinical data for clinical trials;
3. A white paper to encourage the publication of negative and confirmatory results by journals; and
4. A concerted effort by journal editors to implement the ARRIVE guidelines on their journals (with associated checklists for authors and reviewers).

4. Workshop participants

1. Jenny Versnel, Muscular Dystrophy, UK
2. Elizabeth Vroom, United Parent Project Muscular Dystrophy, Netherlands
3. Diana Ribeiro, Action Duchenne, UK
4. Anna Ambrosini, Fondazione Telethon, Italy
5. Grace Pavlath, Muscular Dystrophy Association, USA
6. John Porter, Myotonic Dystrophy Foundation, USA
7. Gustavo Dziewczapolski, CureCMD, USA
8. Victor Dubowitz, Neuromuscular Disorders, UK
9. Hanns Lochmüller, Journal of Neuromuscular Diseases, UK
10. Kevin Campbell, Skeletal Muscle, USA
11. Kay Davies, Human Molecular Genetics, UK
12. Kevin A. Roth, American Journal of Pathology, USA
13. Alejandra Clark, PLOS ONE, USA
14. Emilio Clementi, Pharmacological Research, Italy
15. Kanneboyina Nagaraju, School of Pharmacy and Pharmaceutical Sciences, Binghamton University, New York, USA
16. Nathalie Goemans, University Hospital Leuven, Belgium
17. Volker Straub, University of Newcastle, UK
18. Andrea Klein, Universität-Kinderspital Beider Basel, Inselspital Bern and CHUV Lausanne, Switzerland
19. Annemieke Aartsma-Rus, Leiden University Medical Center, Netherlands
20. Miranda Grounds, University of Western Australia
21. Raffaella Willmann, Swiss Foundation for Research on Muscle Diseases, Switzerland
22. Filippo Buccella, Duchenne Parent Project, Italy
23. Maaike van Putten (young researcher), Leiden University Medical Center, Netherlands
24. Maria Fries, Progena Foundation, Switzerland
25. Maria Sheean, European Medicines Agency (EMA), London, UK
26. Jon Tinsley, Summit Therapeutics, UK
27. Mahasweta Girgenrath, Pfizer, USA

Acknowledgments

This workshop was made possible, due to the generous financial support of the European Neuromuscular Centre (ENMC) and the ENMC main sponsors:

Association Française contre les Myopathies (France)
Deutsche Gesellschaft für Muskelkranke (Germany)
Muscular Dystrophy UK (UK)
Muskelsvindfonden (Denmark)
Prinses Beatrix Spierfonds (Netherlands)
Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland)
Telethon Foundation (Italy)
Spierziekten Nederland (Netherlands)
and Associated members:
Finnish Neuromuscular Association (Finland)

The authors are also grateful to Parent Project Muscular Dystrophy USA for funds to offset the travel costs of non-EU, non-industry participants.

References

[1] van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, O'Collins V, et al. Can animal models of disease reliably inform human studies? PLoS Med 2010;7(3):e1000245.
[2] Vesterinen HM, Sena ES, ffrench-Constant C, Williams A, Chandran S, Macleod MR. Improving the translational hit of experimental treatments in multiple sclerosis. Mult Scler 2010;16(9):1044–55.
[3] Prinz F, Schlange T, Asadullah K. Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov 2011;10(9):712.
[4] Benatar M. Lost in translation: treatment trials in the SOD1 mouse and in human ALS. Neurobiol Dis 2007;26(1):1–13.
[5] Willmann R, De Luca A, Benatar M, Grounds M, Dubach J, Raymackers JM, et al. Enhancing translation: guidelines for standard pre-clinical experiments in mdx mice. Neuromuscul Disord 2012;22(1):43–9.
[6] Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, Bradley EW, et al. A call for transparent reporting to optimize the predictive value of preclinical research. Nature 2012;490(7419):187–91.
[7] Begley CG, Ellis LM. Drug development: raise standards for preclinical cancer research. Nature 2012;483(7391):531–3.
[8] Shineman DW, Basi GS, Bizon JL, Colton CA, Greenberg BD, Hollister BA, et al. Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies. Alzheimers Res Ther 2011;3(5):28.
[9] Ludolph AC, Bendotti C, Blaugrund E, Chio A, Greensmith L, Loeffler JP, et al. Guidelines for preclinical animal research in ALS/MND: a consensus meeting. Amyotroph Lateral Scler 2010;11(1–2):38–45.
[10] Grounds MD, Radley HG, Lynch GS, Nagaraju K, De Luca A. Towards developing standard operating procedures for pre-clinical testing in the mdx mouse model of Duchenne muscular dystrophy. Neurobiol Dis 2008;31(1):1–19.
[11] Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. J Pharmacol Pharmacother 2010;1(2):94–9.
[12] Ting KH, Hill CL, Whittle SL. Quality of reporting of interventional animal studies in rheumatology: a systematic review using the ARRIVE guidelines. Int J Rheum Dis 2015;18(5):488–94.
[13] Amor S, Baker D. Checklist for reporting and reviewing studies of experimental animal models of multiple sclerosis and related disorders. Mult Scler Relat Disord 2012;1(3):111–15.
[14] Avey MT, Moher D, Sullivan KJ, Fergusson D, Griffin G, Grimshaw JM, et al. The devil is in the details: incomplete reporting in preclinical animal research. PLoS ONE 2016;11(11):e0166733.
[15] Smith MM, Clarke EC, Little CB. Considerations for the design and execution of protocols for animal research and treatment to improve reproducibility and standardization: "DEPART well-prepared and ARRIVE safely". Osteoarthritis Cartilage 2017;25(3):354–63.
[16] Heslop E, Csimma C, Straub V, McCall J, Nagaraju K, Wagner KR, et al. The TREAT-NMD Advisory Committee for Therapeutics (TACT): an innovative de-risking model to foster orphan drug development. Orphanet J Rare Dis 2015;10:49.
[17] Kimmelman J, Mogil JS, Dirnagl U. Distinguishing between exploratory and confirmatory preclinical research will improve translation. PLoS Biol 2014;12(5):e1001863.
[18] Steward O. A rhumba of "R's": replication, reproducibility, rigor, robustness: what does a failure to replicate mean? eNeuro 2016;3(4).
[19] Perrin S. Preclinical research: make mouse studies work. Nature 2014;507(7493):423–5.
[20] Lynn S, Aartsma-Rus A, Bushby K, Furlong P, Goemans N, De Luca A, et al. Measuring clinical effectiveness of medicinal products for the treatment of Duchenne muscular dystrophy. Neuromuscul Disord 2015;25(1):96–105.
[21] Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JP, et al. Biomedical research: increasing value, reducing waste. Lancet 2014;383(9912):101–4.
[22] Ricotti V, Ridout DA, Pane M, Main M, Mayhew A, Mercuri E, et al. The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. J Neurol Neurosurg Psychiatry 2016;87(2):149–55.
[23] Bello L, Morgenroth LP, Gordish-Dressman H, Hoffman EP, McDonald CM, Cirak S. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. Neurology 2016;87(4):401–9.
[24] Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. Genomics 1988;2(1):90–5.
[25] Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. Muscle Nerve 2006;34(2):135–44.
[26] van den Bergen JC, Hiller M, Bohringer S, Vijfhuizen L, Ginjaar HB, Chaouch A, et al. Validation of genetic modifiers for Duchenne muscular dystrophy: a multicentre study assessing SPP1 and LTBP4 variants. J Neurol Neurosurg Psychiatry 2015;86(10):1060–5.
[27] Bello L, Flanigan KM, Weiss RB, Spitali P, Aartsma-Rus A, Muntoni F, et al. Association study of exon variants in the NF-kappaB and TGFbeta pathways identifies CD40 as a modifier of Duchenne muscular dystrophy. Am J Hum Genet 2016;99(5):1163–71.
[28] Hogarth MW, Houweling PJ, Thomas KC, Gordish-Dressman H, Bello L, Pegoraro E, et al. Evidence for ACTN3 as a genetic modifier of Duchenne muscular dystrophy. Nat Commun 2017;8:14143.
[29] Hobin JA, Deschamps AM, Bockman R, Cohen S, Dechow P, Eng C, et al. Engaging basic scientists in translational research: identifying opportunities, overcoming obstacles. J Transl Med 2012;10:72.
[30] Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol 2010;8(6):e1000412.
[31] Spurney CF, Gordish-Dressman H, Guerron AD, Sali A, Pandey GS, Rawat R, et al. Preclinical drug trials in the mdx mouse: assessment of reliable and sensitive outcome measures. Muscle Nerve 2009;39(5):591–602.
[32] Nagaraju K, Willmann R. Developing standard procedures for murine and canine efficacy studies of DMD therapeutics: report of two expert workshops on "Pre-clinical testing for Duchenne dystrophy": Washington DC, October 27th-28th 2007 and Zurich, June 30th-July 1st 2008. Neuromuscul Disord 2009;19(7):502–6.
[33] Willmann R, Dubach J, Chen K. Developing standard procedures for pre-clinical efficacy studies in mouse models of spinal muscular atrophy: report of the expert workshop "Pre-clinical testing for SMA", Zurich, March 29-30th. Neuromuscul Disord 2010;21(1):74–7.

[34] Sheean ME, Stoyanova-Beninska V, Capovilla G, Duarte D, Hofer MP, Hoffmann M, et al. Nonclinical data supporting orphan medicinal product designations: lessons from rare neurological conditions. Drug Discov Today 2017. https://doi.org/10.1016/j.drudis.2017.09.015.

[35] Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.

[36] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

[37] Muhlhausler BS, Bloomfield FH, Gillman MW. Whole animal experiments should be more like human randomized controlled trials. PLoS Biol 2013;11(2):e1001481.

[38] Teare MD. Transparent reporting of research results in eLife. Elife 2016;5.

[39] Baker D, Lidster K, Sottomayor A, Amor S. Two years later: journals are not yet enforcing the ARRIVE guidelines on reporting standards for pre-clinical animal studies. PLoS Biol 2014;12(1):e1001756.

[40] Sharing publication-related data and materials: responsibilities of authorship in the life sciences. Washington (DC): National Academies Press (US); 2003.