



**TREAT-NMD Advisory Committee for Therapeutics (TACT)
Terms of Reference**

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Overview

The TREAT-NMD Advisory Committee for Therapeutics (TACT) was established to provide the neuromuscular community with a unique drug development resource. TACT is staffed by a multi-disciplinary international group of internationally-recognized experts from academia, industry, patient foundations and government regulatory bodies who meet twice a year to review and provide guidance on the translation and development path of therapeutic programs in rare neuromuscular diseases with large unmet need. The confidential, comprehensive reviews and resulting recommendations emphasize a rigorous, milestone-driven approach enabling optimal use of funding and resources. The result of this is programs which are less likely to encounter common pitfalls in development, and more likely to be funded or partnered. TACT reviews are independent of funding streams.

Aim

To provide transparent and consistent guidance to the neuromuscular research community, from a drug discovery and development context, on the readiness of therapeutic programs to more effectively advance the treatment of neuromuscular diseases (NMD).

Context

TREAT-NMD was established in 2007 as an EU funded network of excellence aiming to advance treatments and care for patients with rare NMDs. Various network tools to accelerate clinical and, ultimately, therapy delivery have been developed including standard operating procedures (SOPs) for the assessment of animal models of disease, patient registries, definition of outcome measures, a trial co-ordination centre and a registry of trial sites. The network has expanded from beyond its original remit within Europe to represent patient registries and trial sites from around the world and to work with diseases beyond the original “flagship diseases” of Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA).

The pharmaceutical industry is increasingly involved in the identification and validation of new disease related targets and initiating development programs for NMD and also increasingly uses the TREAT-NMD tools in diligence and in planning trials. In addition, many potential therapeutic targets are being identified by academic groups including using drugs previously tested or already licensed for other indications. As many academic researchers are unaware of the requirements and complexity of drug development including human clinical trials, there is a pressing need to systematically evaluate these programs to enable a well-informed development path and transition to clinical trials. Similarly, pharmaceutical industry developers can benefit from a deeper understanding of the specific rare diseases and associated patient communities. For all of the above reasons TACT was formed to provide guidance on the translation of therapeutics programs in rare NMD.

Remit of the committee

The TACT review process is thorough, multidisciplinary and educational. It is aimed at helping researchers and drug developers navigate the full research and development process. TACT recommendations aim to facilitate human proof of concept (POC) trials, by generating preclinical and clinical data that will enable subsequent development decisions and potential registration. Through its comprehensive quality recommendations, TACT may act as an important diligence body and help stimulate funding opportunities.

Composition of the committee

The committee is a group run under the aegis of TREAT-NMD. However, membership of the committee is not limited to TREAT-NMD partners but rather is selected by the TACT chair together with the secretariat from the pool of experts nominated to represent the very best expertise available to address the issues pertinent to the TACT remit. The core committee covers a wide range of the expertise described below although it is not necessarily the case that patient groups are represented due to the disease-specific nature of their expertise. The core committee has responsibility for taking decisions about the running of TACT, strategy and direction along with the secretariat under the guidance of the chair. Core committee members are invited to attend all TACT meetings and convene together in advance of the wider group. Membership of the core is for 3 years after which a replacement will be sought to cover a similar area of expertise. The member will not stand down until a replacement is agreed, even if this extends their role beyond 3 years. When members leave the core committee they re-join the extended committee.

The chair of the committee is appointed by the TACT core group and serves for three years.

Additional experts are co-opted to an extended committee for assessment of areas not within the immediate expertise of the core committee. The extended and core committees are supported administratively by a secretariat provided by TREAT-NMD from the co-ordination office in Newcastle, UK. All committee members undertaking reviews and attending face-to-face meetings are reimbursed for reasonable, standard class travel expenses and are eligible to receive an honorarium for each meeting attended, with the exception of government employees acting in official capacity. All committee members sign a confidential disclosure agreement and complete a declaration of all potential conflicts of interest. Committee members are requested to update their conflict of interests before each review meeting. A short member's biography is published on the TREAT-NMD website. This includes a disclosure statement provided by the member declaring their commercial/potential conflicted interests.

Observers

In order to introduce new potential reviewers, educate patient organisations or other key stakeholders about the TACT process, observer status may be granted for review meetings. This allows individuals who have not been part of a TACT review previously to attend and observe a meeting under full CDA and Col agreements. Observers do not take part in the review but may view the applications and be present during discussions. They do not contribute to

the advice and report given to applicants. Funders of meetings do not necessarily receive observer status and individuals should only observe once.

Application process to TACT

Suggestions for programs that could benefit from a TACT review are solicited from the NMD community. Applicants can include principal investigators planning a study, preclinical investigators who wish to move to the clinical arena, industry sponsors or funding bodies seeking input on the feasibility of a given program considered for funding. All applicants are expected to complete a standard application and provide supporting data. The completion of this focused application form is in itself an educational tool. TACT proactively calls for nomination of drugs and approaches potential principal investigators to inform them on the role of TACT. All core and extended members of TACT as well as the secretariat, applicants, reviewers and observers are required to sign a confidentiality agreement.

Roles within the committee

Chair: to work with the TREAT-NMD secretariat on the following tasks:

- to agree on the therapeutics (with a predetermined maximum) to be appraised at a session
- chair the meeting
- oversee the preparation of the report and recommendations

Preclinical experts: to appraise critically the preclinical data either published or unpublished on the drug under study against the defined standards for preclinical assessments of animal models. Confidentiality agreements protect unpublished data.

Toxicology experts: to advise on the current status of human exposure to the drug in question including, if relevant, paediatric data.

Pharmacology experts: to advise on the current status of pharmacokinetic and pharmacodynamic data available for the product and to make recommendations for studies needed for regulatory approval.

Regulatory experts: to advise on the likelihood of regulatory approval for entering the clinic (and potentially subsequent registration) including acceptability of endpoints. Expertise covers both Europe and USA.

Clinical trial expert representation: to advise on the protocols likely to be necessary to test the drugs in the clinic, patient numbers and likely numbers of trial sites and potential sample costings.

Clinical representatives: clinic leaders from different geographical areas representing major clinical networks (e.g. Europe and USA). To advise on the practicalities of recruitment to a particular protocol in the context of other competing demands on clinic time and commitment and other general protocol issues.

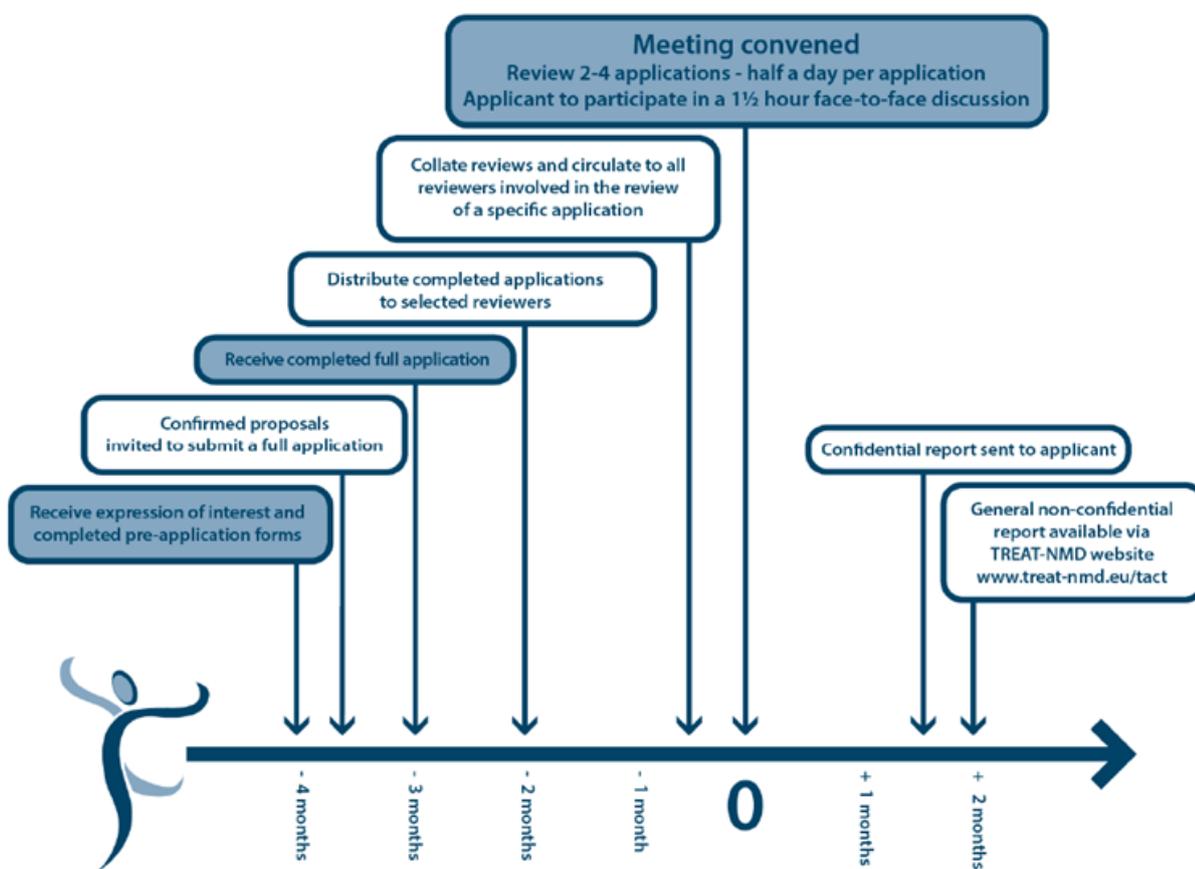
Ethical input: to advise on the ethical dimensions of the proposed studies.

Patient organisation representation: to provide the patient perspective on the proposed studies.

TREAT-NMD secretariat: provides perspective on the broader TREAT NMD mission, expectations and key issues, and supports all logistical aspects of planning, conducting and follow up from review meetings. The secretariat also helps identify additional expertise or individuals that could contribute to the TACT reviews.

Relationships with funders: funders can enter into a contract with TREAT-NMD to perform work in partnership or on their behalf. Funding a TACT meeting does not imply that funders will be granted attendance to the TACT meeting.

Process and timing



Pre-application

Potential applicants complete a pre-application following expression of interest for a TACT review. Pre-applications are reviewed by the chair and secretariat to assess their suitability for a full review.

Full application

Full applications are completed via an online system approximately 3 months prior to the review meeting. Completing the application focuses the applicant on a number of important considerations including: scientific

rationale, the appropriateness and interpretation of the preclinical studies performed, safety and toxicology issues, drug distribution and kinetics, feasibility and cost of drug manufacturing and supply, context of the project in the clinical development plan and regulatory consideration critical to advancing a compound into the clinic. A lead reviewer and additional multidisciplinary reviewers are selected for their specific expertise as it relates to each application. Patient representatives also complete written reviews, according to standardized forms, in advance of the meeting. These reviews are distributed to the full core committee and all reviewers prior to the meeting.

Meetings

Meetings are scheduled twice a year - generally one in Europe and one in the US, to review two to four applications. A half day is devoted to discussion for each application including a session with the applicant to provide clarifications as needed and ensure the subsequent committee report is as relevant as possible.

Report generation: is driven by secretariat and lead reviewer reports are sent to the applicant within 6 weeks of the meeting. The report includes an objective assessment of the project plan and recommendations for the program. Typically, the applicant poses important questions in writing to TACT, and these are addressed in the written review. The applicant receives this full report and then a non-confidential summary of the report (which is agreed with the applicant) is detailed on the TACT website.