Advisory Committee for Therapeutics Toolkit
UNEW work is supported by the funding from the European Union’s Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP Nº 825575
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Within the European Union Framework Programme 6, funding was granted to build a network of excellence called ‘Translational Research in Europe for the Assessment and Treatment of NeuroMuscular Diseases’ (TREAT-NMD).

The purpose of the network was to shape the translational research environment for rare genetic neuromuscular diseases. TREAT-NMD partners collaborated to develop tools, services and infrastructure to support clinical trial readiness including the TREAT-NMD Advisory Committee for Therapeutics (TACT).

Established in 2009, TACT is a unique multi-disciplinary international group of basic scientists, healthcare professionals, patient advocacy representatives, regulatory experts and industry drug development experts, who meet twice a year to review and give objective advice on the development pathway of therapeutic programs in rare neuromuscular diseases.

Many manuscripts on potential therapies for neuromuscular diseases have been published, but very few of these therapies have moved forward into clinical trials. TACT provides a unique resource and educational tool to the neuromuscular community that helps to bridge the gap between promising preclinical data and successful clinical trials.

TACT was created to address a critical need to prioritise drug development in neuromuscular diseases, with large unmet needs and limited numbers of patients able to be enrolled into clinical trials. The aim of each TACT review is to help the applicant to position the candidate compound along a realistic and well-informed pathway to clinical trial and eventual registration, by identifying potential pitfalls in clinical trial design and giving independent and transparent advice.
It is a special privilege to be involved in TACT, as it is a unique advisory board based on independence, excellence, and multidisciplinary expertise and with no direct interest, other than to provide honest and constructive advice on the de-risking of therapy development in rare neuromuscular diseases. Efforts to advance drug development need to be balanced with expectations and safety of patients with these rare diseases. The best way is to reinforce excellent science and the highest quality of translational research at each stage, with the help of all stakeholders. After 10 years of activity TACT is a model advisory board for other rare disorders.

In 2016, TACT was endorsed by International Rare Diseases Research Consortium (IRDiRC) as a recognised resource. The vision of IRDiRC is to enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention. IRDiRC aims to contribute to the development of 200 new therapies by 2020. IRDiRC gives recognition to resources which contribute to this aim by accelerating the pace of translating discoveries into clinical applications. TACT contributes to the aim and vision of IRDiRC by giving comprehensive expert advice to researchers and industry on drug development programs for rare neuromuscular diseases.

"It is a special privilege to be involved in TACT, as it is a unique advisory board based on independence, excellence, and multidisciplinary expertise and with no direct interest, other than to provide honest and constructive advice on the de-risking of therapy development in rare neuromuscular diseases. Efforts to advance drug development need to be balanced with expectations and safety of patients with these rare diseases. The best way is to reinforce excellent science and the highest quality of translational research at each stage, with the help of all stakeholders. After 10 years of activity TACT is a model advisory board for other rare disorders.

Prof. Annamaria De Luca, - TACT Chair"
At time of production of this toolkit, 56 applications for advice have been reviewed by TACT in disease areas including:

- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Spinal muscular atrophy
- Limb girdle muscular dystrophy
- Myotonic dystrophy
- Congenital myopathies
- Pompe disease
- Facioscapulohumeral muscular dystrophy

Of the 56 applications reviewed, 38 were received from industry and 18 were from academia. Currently, 24 programs reviewed by TACT are still in development, including four programs in phase three clinical trials.

It is important to emphasise that the success of TACT should not just be measured by those reviewed programs still in development but by the systematic approach to identify the realistic prospects for a particular compound which, positive or negative, can help patients, the field and the applicant.

Members of TACT have produced a TACT 10th anniversary paper which demonstrates the impact of TACT, advice given and the progress made by previous applicants. In preparation for this paper, a survey was sent out to past applicants who reported that TACT had helped them to prepare for discussions with regulators, informed study design including selection of endpoints and go/no-go decisions, enrolment and dosing decisions.
Previous applicants have shared how they benefited from TACT’s multidisciplinary approach and from having a wide array of experts available during one meeting:

"The expertise TACT assembled in one room was unparalleled and greatly appreciated. The review provided us with an outside consensus regarding how to proceed in this uncharted territory as the first company working in this disease (Congenital Muscular Dystrophy)."

- Jodi Wolff, Santhera

"TACT provided a very accurate review of the protocol and useful suggestions on both the preclinical and clinical parts."

- Emilio Clementi, University of Milano

"We found the TACT report to be concise and well-organized. The committee put together a very thoughtful review and we intend to use the recommendations to augment our development plan."

- Dr Deborah Ramsdell, Valerion Therapeutics, LLC

"TACT comments highlighted relevant issues of the proposal and will surely help us to strengthen the final version of the project."

- Professor Giuseppe Vita & Dr Sonia Messina, University of Messina, Italy

TACT works closely with patient organisations in multiple regions to ensure that the review process meets the needs of the neuromuscular community as a whole. TACT would like to thank and acknowledge funding and support received from the following patient organisations:

Further reading: The TREAT-NMD advisory committee for therapeutics (TACT): an innovative de-risking model to foster orphan drug development.

A decade of optimizing drug development for rare neuromuscular disorders though TACT
10 YEARS OF TACT IN FIGURES

The charts below depict the history of TACT by breaking down all 56 applications reviewed over ten years by disease area and class of therapeutic compound. The first chart shows development programs which were reviewed by TACT and are still in development.

APPLICATIONS CURRENTLY IN DEVELOPMENT

Of the 56 applications reviewed by TACT, 24 are still in development. The diagram below shows their current stage of development. The therapeutics are colour coded to the year that they were submitted to TACT for review. It is important to reiterate that the value of TACT is in its systematic approach to identify the realistic prospects for a particular compound which, positive or negative, can help patients, the field and the applicant.
Although the majority of applications (37) have been received for Duchenne muscular dystrophy, TACT accepts applications for all neuromuscular diseases including Spinal muscular atrophy, Limb girdle muscular dystrophy, congenital myopathies and Pompe disease.

APPLICATIONS BY DISEASE AREA

38% of applications reviewed by TACT were for small molecules, followed by 32% of applications being submitted for re-purposed therapeutics. Small molecules have the advantage of being easily able to administer orally.
WHY CREATE AN ACT?

The TREAT-NMD Advisory Committee for Therapeutics (TACT) was developed originally for the neuromuscular field and has proven to be a key resource in the quest to optimise the planning and execution of early stage and later phase clinical research in this community. However, the model itself is readily transferable to many other rare disease areas. Most clinical trials in a rare disease share similar challenges to those in the neuromuscular field, including:

- **Low Patient Numbers** - Further limited by clinical trial eligibility criteria
- **Lack of Clarity Around Outcome Measures**
- **Lengthy Trials**
- **Lack of Natural History Data**
- **Poor Pre-Clinical Data**
The European Joint Programme for Rare Diseases (EJP RD) is proposing that an ‘ACT’ - i.e. Advisory Committee for Therapeutics (ACT) - would add value to industry or academic-led research into new or repurposed therapeutics, in any rare disease.

Given the large number of rare diseases (6-8,000) and the heterogeneity of the conditions, some degree of strategic oversight in the creation of ACTs would be beneficial. The thematic groupings upon which the European Reference Networks (ERNs) are based, provide a logical framework for establishing ACTs in other rare disease areas and other highly specialised domains. The initial focus for a new ACT may vary according to the status quo of the field in question.

It may be preferable to initially create an ACT for specific diseases in which there is already a substantial level of basic research, or indeed for sub-domains of the overall ERN heading (i.e. for groups of clinically-similar conditions) which seem likely to be the focus of significant clinical research in the near future.

ERN-linked communities could establish an ACT in a harmonised manner by using the TACT model and resources as a blueprint. This toolkit has been created to support such an activity.

In summary, the main objective of any rare disease ACT would be as follows:
To provide a valuable resource and service to the rare disease community by giving transparent, unbiased, multi-stakeholder and multidisciplinary expert advice to optimise research, by either:

a) Steering studies along a realistic and well-informed plan to clinical trial/ later phase clinical activity;

or

b) Encouraging a change of direction or approach, to avoid failure further down the line.
HOW TO CREATE AN ACT

The following pages will provide you with guidance on how to create an Advisory Committee for Therapeutics (ACT), beginning with the required governance structure and detailed information on the important roles required to make an ACT fully functional.

GOVERNANCE STRUCTURE

A suitable governance structure needs to be in place before establishing an ACT. It is recommended that an ACT governance structure comprises of a core committee, extended committee and a secretariat. The level of commitment required differs between each group.

SECRETARIAT

The secretariat will coordinate each meeting and will invite applications for review, with guidance from the ACT chair and core committee. The secretariat will provide logistical support for each meeting, including selecting meeting venues, arranging accommodation for reviewers and processing travel reimbursements.

Commitment required: The suggested structure for the secretariat would be one project manager (full-time), one project assistant (part-time) and one academic lead to contribute time to review applications and select reviewers. The secretariat organises and attends each ACT meeting.
EXTENDED COMMITTEE

An ACT extended committee comprises of a large group of reviewers, with a wide range of expertise. Members of the extended committee will be invited to attend a particular ACT meeting depending on the expertise required for the applications due to be reviewed. Extended committee members will not be expected to attend all meetings but will be called upon when required. As members of this group are recruited to review, they remain on the committee indefinitely. The extended committee therefore grows over time. Members with experience and a track record in reviewing may be invited to join the core committee as places become available.

**Commitment required:** Members of the extended committee are not expected to attend all ACT meetings but will be invited to attend if their type of expertise is required.

CORE COMMITTEE

The core committee, guided by an ACT Chair, will make decisions on the strategic direction of the ACT and will review and provide feedback on all potential applications. The core committee should comprise of between 8-10 members, with wide and varied range of expertise covering all aspects of drug development. Core members will attend every ACT meeting and will review each application unless a conflict of interest has been identified. Members of the core committee will serve a term of up to three years before rotating off onto the extended committee.

Core members will have specific expertise and are expected to help to identify their own replacement before leaving the core group, usually from the extended committee. They will not rotate off the core group until a suitable replacement has been found.

The ACT chair is expected to govern the committee for three years. The core committee will vote upon a replacement when the chair’s term is due to end. The new chair will be selected from the core committee.

**Commitment required:** Each member of the core committee must be available to attend each ACT meeting. They will be required to provide a review for applications, six weeks before the meeting takes place. On an ad-hoc basis, they will be asked for their input on matters relating to ACT.
THE ROLE OF THE REVIEWER

A fundamental feature of the ACT model is that each application is reviewed by a multidisciplinary panel of leading experts. For each ACT meeting, the review panel will be selected by the ACT chair and the secretariat based on the needs of the applications submitted. The panel should comprise of approximately 15-20 members, although this can vary depending on the number and requirements of the applications being reviewed.

ACT reviewers will be expected to carry out the following activities:

Before an ACT review meeting:

• Sign a confidentiality disclosure agreement (CDA) - this will cover the reviewer for subsequent meetings, over an agreed time frame (e.g. five years, ten years).
• Declare any conflicts of interest for each application - this is to be carried out before every meeting.
• Complete a comprehensive review of each application (up to four per meeting), in their area of expertise, highlighting any missing information they feel would be useful to include. The secretariat will provide the reviewer with a form on which to do this.
• For each application, a lead reviewer will be selected from the review panel (this could be a member of the core or extended committee). A lead reviewer is expected to chair and lead discussions, as well as produce the applicant report, with feedback from the review panel.
• Reviewers are expected to submit their comments to lead reviewers within four weeks.
• Each reviewer should read the summary of comments from other reviewers in advance of the meeting.
During ACT review meeting:

- Pre-applicant discussion: The lead reviewer will give a presentation to reviewers which will summarise the application, highlight any areas of concern and suggest questions to the applicant. The applicant will not be present during this discussion.
- Pre-applicant discussion: Each reviewer will participate in the panel discussion before the applicant joins the meeting. Any further questions/clarifications required from the applicant should be raised during this discussion.
- Discussion with the applicant: The discussion with the applicant will be facilitated by the lead reviewer. Advice is not given during this meeting and questions should be constructive and positive. The purpose of this discussion is to gain more insight, clarify questions and discuss aspects of the application.
- Summary & recommendations: The applicant will leave the meeting and the review panel will aim to reach a consensus on the recommendations to be included in the final confidential report to the applicant.
- All reviewers are accepted to participate in each discussion.

After the ACT review meeting:

- Confidential report: The lead reviewer will draft the confidential report to the applicant after the meeting and forward to the secretariat for circulation to all the reviewers so they may review and add comments. The finalised confidential report is returned to the applicant within six weeks of the meeting.
- Non-confidential summary: This will be generated by the lead reviewer and the secretariat, to be agreed by the applicant and posted on your network’s website within eight weeks following the meeting. The purpose of the non-confidential summary is to inform the community that an ACT review has taken place. Interested parties and potential funders are encouraged to contact the researcher directly to request a copy of their full ACT report.
EXPERTISE REQUIRED TO FORM AN ACT REVIEW PANEL

This diagram illustrates the main areas of expertise that is required to form a TACT review panel. Although there will be common areas of expertise required to form an ACT review panel, your core committee should form and agree consensus on what type of expertise will be required, as a minimum, for each review meeting. The core committee attend every meeting so it is important that the committee includes key areas of expertise required for each meeting.

The type of expertise required can differ between applications, which is why we recommend that you form a large and varied extended review committee. Members of the extended committee do not have to attend every meeting, they can be called upon to attend any meeting depending on the applications to be reviewed and the expertise required.
It is essential to the success of an ACT that your new reviewers are adequately prepared to review an application for the first time. This will help to ensure that the applicant receives the best advice available to them. Each new reviewer should attend a short briefing before the review meeting begins.

We have provided you with detailed guidance on the different tasks a reviewer is expected to carry out. To complement this guidance, the next few pages include representative views from TACT members, including how they approach a review, common pitfalls and what the benefits are for becoming a reviewer.

### Pre-clinical

**Approach to reviewing an application:**
- Assess whether wild types were included to measure the deficit and control of a treatment.
- Assess if the work has been carried out in two separate laboratories.
- Have standardized operating procedures been applied?
- Has the applicant assessed multiple parameters, with a primary endpoint pre-defined?
- Have proof of concept and further preclinical studies been carried out (e.g. on dosing, timing, regimen etc.)?

**Common pitfalls to look out for:**
- No wild type controls used.
- Studies carried out in one laboratory only.
- Only few outcome measures included (sometimes handpicked).
- Only proof of concept shown and no pre-clinical optimization.

### Regulatory

**Approach to reviewing an application:**
- Has the applicant had contact with regulators?
- What endpoints will the applicants use in the trial? Are the end-points acceptable to regulators?
- Is there enough data to design a trial?

**Common pitfalls to look out for:**
- If the applicant has had no contact with regulators.
TACT REVIEWERS’ PERSPECTIVE

Clinical

Approach to reviewing an application:

- Evaluate the clinical trial eligibility criteria.
- Assess the suitability of the proposed outcome measures.
- Review the overall clinical trial design.

Common pitfalls to look out for:

- Insufficient sample size.
- Inappropriate outcome measures.
- Lack of biological rationale or supporting preclinical data.

Physiotherapy

Approach to reviewing an application:

- Assess what the mechanism of action of the drug is. This is crucial to understanding if the right outcome measures will be used.
- Does the applicant understand the disease area and the nature of that condition, such as its complexity and components of progression (muscle weakness, respiratory, learning issues etc.).
- Is the mechanism of action reflected in their choice of inclusion and exclusion criteria? Do these make sense both clinically and practically or will they make recruitment difficult?
- Are the clinical endpoints feasible, fatiguing, appropriate and are they measurable?
- Are the outcome measures valid and reliable?
- What is the frequency of assessments?
- Is the length of the clinical trial appropriate for the mechanism of action?
- Have they included Patient Reported Outcome Measures (PROMS) and Quality of Life (QoL) measures that are appropriate?

Common pitfalls to look out for:

- Poor understanding of outcome measures.
- Not linking outcome measures with mechanism of action.
- Too many outcome measures proposed.
- Problematic inclusion and exclusion criteria.
- No draft schedule of events.
TACT REVIEWERS’ PERSPECTIVE

Statistics

Approach to reviewing an application:

Pre-clinical
- If only pre-clinical data is provided, assess that the data was analysed and used properly. It is crucial that the applicant provides summary statistics and the statistical methods used, rather than only text statements of the findings, which cannot be critically reviewed.

Clinical
- If preliminary clinical data is provided, assess if the data is adequately described in order to review the statistical methods used and the conclusion made.
- Has a power or sample size analysis been carried out on the proposed clinical study, to ensure that there will be adequate data to test the hypotheses proposed?
- If provided, review the statistical analysis plan for the proposed clinical study. Critically thinking about and writing the analysis plan helps to define the primary hypothesis of the study.

Common pitfalls to look out for:
- Inadequate or incorrect analysis of pre-clinical data. Pre-clinical data can be rather complex in certain experiments, however, the statistical analysis of that data is often very rudimentary or incorrect.
- Including the conclusions from non-published pre-clinical data but not providing details of the data within the application.
- Proposing a very complex clinical study (i.e. multiple drug doses, multiple time points, multiple endpoints) without consideration of how complex the statistical analysis will be, often leading to a proposed analysis that cannot test the primary hypothesis proposed.
- Lack of appreciation of the sample size required for complicated studies. This is particularly true if the proposed study is pre-clinical in nature. Often pre-clinical studies are planned with a sample size of 10 or smaller, without regard to whether or not that sample size is adequate.
- Lack of appreciation for the difficulty in patient recruitment for rare diseases.
- Lack of appreciation for the patient burden for clinical studies. Clinical studies can often propose to collect large amounts of data from patients without considering the burden of a long clinical visit on a patient.
TACT REVIEWERS’ PERSPECTIVE

Approach to reviewing an application:

- Understand if the rationale is solid where the application is at the pre-clinical stage. It is important at this stage to evaluate if the product is relevant to patients - what will the landscape look like when this product is marketed? Will the product still be relevant?
- Review trial feasibility.
- Assess if the patient burden is too high.
- Review aspects that matter to the patient including travel burden, assessment schedule, invasive procedures such as biopsies, use of placebo, availability of open label extension, inclusion/exclusion criteria, etc. This information helps to answer the question of whether the trial will be able to recruit or not.
- Has the applicant provided a regulatory plan and how do they plan to demonstrate evidence of benefit to risk?
- Has the applicant talked to patients/families and/or patient advocacy organizations to understand the disease, the burden, the needs and the landscape overall?

Common pitfalls to look out for:

- If it is not clear what the product will do, how it will be used and administered and who it is for.
- If an applicant has not discussed their project with a patient group, or does not have a strong understanding of the community and how the patient voice can help.
- If aggregate data summaries are used rather than the individual level data.
- If the trial design is hard to follow and not enough detail is provided. It is essential to include detailed information on the patient journey - how will the patient flow through the trial from screening to end?
WHAT ARE THE BENEFITS OF BECOMING AN ACT REVIEWER?

The diagram below includes feedback from TACT reviewers about what the benefits are to them for participating in a TACT review:
THE ROLE OF THE SECRETARIAT

The secretariat are integral to inviting and coordinating applications for review, as well as organising all logistical aspects of ACT review meetings. The following information will help you to understand the activities carried out by an ACT secretariat and will help you to build your secretariat accordingly.

Before an ACT review meeting:
- The secretariat must regularly and actively seek applications for advice. There are a number of suggested sources to elicit applications:
  - **Newsletters** - Include ‘call for applicant’ articles in your network’s newsletter and/or affiliated newsletters.
  - **Patient Organisations** - Contact relevant patient organisations to ask for recommendations of potential applicants. Patient organisations regularly receive requests to support research. An ACT report could help them to make decisions on whether to support and fund a particular request.
  - **Conferences** - Raise awareness of your ACT by attending conferences in order to communicate the purpose and benefits of an ACT review. You can do this by submitting an ACT poster and networking with both industry representatives and researchers.
  - **ACT committee** - Contact both your core and extended committee members to recommend potential applicants. As drug development experts, they are best placed to identify applicants who could benefit from an ACT review.

- When an expression of interest has been received, the secretariat must send the applicant a pre-application form. Once the pre-application form has been submitted, the secretariat and the TACT chair will review the application for suitability.
Before an ACT review meeting (cont.)

- The secretariat will inform the applicant if their pre-application for advice has been successful. If their pre-application has been accepted, they will be asked to sign a CDA, complete an applicant agreement and complete a full application form. If the applicant is from industry, they must include in the applicant agreement the number of employees their company employs. This number will allow the secretariat to advise a suitable request for a donation towards meeting costs.
- Advised by the ACT chair and core committee and based on the information provided in the pre-application, the secretariat will contact suitable reviewers.
- Reviewers will be sent a CDA (if not already in place from previous meetings) to sign and a conflict of interest declaration to be completed for all applications they have been asked to review.
- The secretariat must select and secure a suitable venue for the meeting and arrange accommodation for reviewers within budget.
- Once the applicant agreement has been signed, the secretariat must raise and send an invoice for the appropriate contribution amount to the applicant. - Please note this is only relevant to industry applicants.

- Applicants will be sent the full application form to be completed six weeks before the meeting. Once all applications have been received, they will be sent to all reviewers along with a template to provide their review. The reviews will be collated by the secretariat and circulated to all reviewers. The reviewers written comments will not be shared with the applicant.
- An agenda will be produced by the secretariat and circulated to all reviewers. The agenda will include information on meeting venue and accommodation, as well as timings for each application and a list of reviewers.
- Each applicant will be provided with an agenda for their particular review meeting and this will include a list of reviewers.
- The secretariat will prepare the following documentation for the meeting:
  - Name plates for reviewers and applicants
  - Copies of the agenda for all reviewers
  - Copies of applications and summary of reviewers comments, if requested by reviewers. Reviewers should be encouraged to view these documents electronically during the meeting.

- The secretariat must contact the applicant and ask them to provide slides summarising their application, no later than one week before the review meeting.
THE ROLE OF THE SECRETARIAT

During an ACT review meeting:

- The secretariat will regularly liaise with the hotel to ensure all arrangements are in place including catering, accommodation and audio visual requirements.
- The secretariat will be responsible for displaying all presentations.
- If microphones are required, the secretariat will distribute them when required.
- The secretariat will meet the applicant in advance of their meeting and bring them into the room when required.

After an ACT review meeting:

- Lead reviewers will produce and circulate their report to reviewers, with support of the secretariat. Once the final version is agreed, the secretariat will add the report to the ACT report template.
- All reports must be sent to applicants within six weeks of the meeting.
- The secretariat will work with the applicant to produce a non-confidential summary to be added to your network’s website.
- Information on the reimbursement and honorarium process (if applicable) should be sent to reviewers. The secretariat will coordinate this process and will make sure that reimbursement payments for travel are made in a timely manner.
THE ROLE OF THE APPLICANT

Within the ACT model, an applicant is classed as a sponsor/researcher from industry or academia who submits a request for advice for a proposed therapy that they are developing.

It is essential that the applicant fully understands what is expected of them and fully understands what the ACT process entails. This will ensure that they get the most out of the review process and that the reviewers will have the necessary information they require to successfully review their application. When first engaging with the applicant, the process below should be communicated to them:

Before an ACT review meeting
- The applicant must submit a pre-application form. This form will allow the secretariat to evaluate if the application is at an appropriate stage for review. The applicant should include information on:
  - Proposed therapy
  - Proof of concept
  - Stage of development
  - Relevance to disease
  - Links to relevant papers
- The completed pre-application must be comprehensive. The form will be used by the secretariat to select appropriate reviewers.
- The secretariat will send the applicant the proposed list of reviewers. The applicant will have the opportunity to identify any conflict of interests which have not already been identified. **Important: applicants cannot suggest or choose their own reviewers, only identify possible conflicts of interest.**
- The applicant must submit their full application three months before their review meeting is due to take place.
- The full application form gives the applicant an opportunity to ask specific questions about their proposal. Reviewers will include responses to these questions in the report to the applicant, which will be issued after the review meeting. Reviewers will not provide answers to these questions during the review meeting.
- Reviewers may ask the applicant additional questions and for clarifications about their application, via the secretariat.
- The applicant must inform the secretariat who will be attending the review meeting. A maximum of four people may attend and they must all attend in person.
Before an ACT review meeting cont.

• During the face to face meeting the applicant will be given the opportunity to give a 10 minute presentation. The presentation will be a summary of their application and an opportunity to present any new data received after their application was submitted. The applicant must submit their slides to the secretariat one week before the review meeting.

During an ACT review meeting

• The review panel will meet first, without the applicant present, to discuss the application and agree questions to the applicant.
• The applicant will then join the meeting and will begin by giving their presentation. If the applicant exceeds 10 minutes, they will be stopped by the lead reviewer.
• The lead reviewer will lead the discussion with the applicant and reviewers will have the opportunity to ask the applicant questions. This discussion is for the reviewers to gain further information and clarifications to help form the final report. No recommendations will be given during the meeting. The discussion, including the applicant’s presentation, will last an hour and a half.
• The applicant will leave the meeting after this discussion and the review panel will discuss and form their recommendations, without the applicant present.

After an ACT review meeting

• The final report will be sent to the applicant six weeks after the review meeting has taken place. No amendments can be made to the final report.
• It is entirely the applicant’s decision as to whom they distribute the report to (e.g. patient organisations, funders, regulatory authorities). If the applicant does decide to share the report with anyone, they must do so in its entirety. ACT reserves the right to investigate if a report has been altered.
• ACT will not distribute the full report to anyone other than the applicant.
• The secretariat will contact the applicant two months after the meeting to agree a non-confidential summary, which will be made publicly available.
• Once the report is issued, the applicant will not normally receive any ongoing advice or support from ACT.
• ACT will only consider reviewing the same programme again if substantial new data is available or the programme has significantly changed.
• Applicants are welcome to come back to ACT with applications for new programs.
THE ROLE OF THE APPLICANT

To ensure that applicants provide reviewers with adequate, clear and concise information, they should be asked to consider including the following information in their full application, where possible, thus allowing reviewers to give a well informed review of their application.

Hypothesis:

- What is the biological support for the drug to be considered as a potential therapy?
- If a clinical study is proposed, a clear primary hypothesis is to be tested. This hypothesis must be specific about the intended outcome (i.e. “strength will increase with treatment” is not a clear hypothesis).

Preclinical:

- Provide detailed information on preclinical studies including the number of mice, how they were treated and how they were evaluated.
- Evidence that the sample size proposed is adequate.
- Have preclinical data been reproduced in more than one laboratory?
- Are the preclinical studies supportive of the route and dosage of administration required for a clinical trial?

Drug Substance:

- What is it? Is it available? Could it be commercialized?

Pharmacology:

- Drug potency, selectivity, proof of concept, advantages over competitive approaches.
- Pharmacokinetics (time course upon administration) and pharmacodynamics (intensity of effect).

Formulation and administration:

- Provide information on the relationship between dosing in the preclinical studies and subsequent clinical trials. Is there appropriate justification for the scaling up of dosing?
- Is the route of administration compatible with clinical trials?
### Evidence of Safety:
- Where the target population is paediatric, what previous paediatric regimes have been used? If there is perspective for long term use, do previous studies reflect this or would further studies be needed to extrapolate to different populations or duration of dosage?

### Plans for clinical trials:
- Have the applicants considered all relevant aspects of trial design for the disease under consideration?
- Would patients be available and recruitable based on actual estimates at intended sites and data available from established international patient registries?
- Are outcome measures well understood and have they been used in previous studies?
- How would a trial for this drug fit with ongoing or planned studies in the disease under consideration?

### Patient Perspective:
- Do patients/patient representatives agree that a trial with this drug would be an acceptable burden on the target population?
- Have the researchers fully addressed the risk/benefit balance for these plans?
- If marketed would the drug make a clinically meaningful contribution to the existing standards of care for the condition?

### Regulatory:
- Does the applicant understand the process for seeking advice (such as orphan drug products) and registration? e.g. FDA and EMA.
- Have regulatory issues in different countries been considered, relevant to this treatment?
In order to allow you to plan effectively for your first ACT meeting, you will find below a detailed timeline that shows the process that should be followed after an expression of interest from a potential applicant.

**ACT TIMELINE**

**MONTHS PRIOR TO MEETING**

- **-4**
  - Receive expression of interest and completed pre-application forms

- **-3**
  - Receive completed full application
  - Confirmed proposals invited to submit a full application

- **-2**
  - Distribute complete applications to reviewers
  - Collate reviews and circulate to all reviewers involved in the review of a specific application

- **-1**

**At least 4 months before meeting**

A potential applicant will contact the ACT secretariat to discuss their proposed application and to gain an understanding of the ACT process.

An applicant will be invited to complete a pre-application form, which will be reviewed by the core committee, secretariat and ACT chair for suitability.

If deemed appropriate, the applicant will be invited to submit a full application to the ACT Secretariat, using the form provided.

The secretariat, advised by the ACT chair and core committee, will invite reviewers with suitable expertise to review the application and attend the meeting.

The secretariat will secure a suitable venue to hold the meeting and will arrange all logistics relating to the meeting.

**3 months before the meeting**

The full application is due to be submitted to the ACT secretariat by the applicant.

**2 months before the meeting**

The secretariat will circulate the full applications to the review panel. Reviewers will provide their comments and feedback to the secretariat. A lead reviewer will be selected for each application. The secretariat will compile all feedback and circulate to the lead reviewer and review panel.
During the meeting
The meeting will convene and each application will be allocated half a day for review. Each application will be discussed for 1 hour by the panel, before the applicant will be invited to join the meeting for discussion and questions, which will last 1 hour and 30 minutes. The applicant will leave and the panel will discuss their recommendations for 1 hour.

After the meeting
The lead reviewer will write a report to the applicant, using a template provided by the secretariat. The report will include an overview of the proposal, strengths and limitations as agreed by the panel and responses to the questions asked by the applicant in their application.

Six weeks after the meeting
The report must be sent out to the applicant six weeks after the meeting. A PDF version of the report will be sent to the applicant with the disclaimer that if they chose to share the report with anyone e.g. patient organisations, funders, regulatory authorities it must be sent out in its entirety. The ACT committee reserve the right to investigate if a report has been altered.

The applicant and the secretariat will agree a non-confidential summary to be made public on the network’s website. Examples of non-confidential summaries can be found on the TREAT-NMD website here.

The full report will be circulated to reviewers for their reference. Under the terms of each reviewer’s CDA, the report is solely for their own viewing and must not be shared.
FUNDING AND SUSTAINABILITY

Through donations from industry applicants towards meeting costs and ad-hoc funding from patient organisations, the ACT model has the potential to be self-sustaining. However initial “seed” funding will be required to set-up your ACT. Initial funding for the TACT model came from the European Union’s Framework Programme 6.

When requesting funding it is crucial to be able to demonstrate both the need for and the potential benefits of this resource. In order to do this, consider the following:

THE NEED IN YOUR DISEASE AREA

To make a case for the need for an ACT in your disease area, you may consider collating the following evidence:

- **The number of treatments available in your disease area:** It is estimated than only around 5% of rare diseases have a treatment, see the EMA Orphan Medicines pages [here](https://www.ema.europa.eu/en/medicines/human/orphan). EURORDIS also highlights recent approvals [here](https://www.eurordis.org/). The lack of treatments in a disease area is good evidence of need.

- **The number of trials currently available in your disease area:** [ClinicalTrials.gov](https://clinicaltrials.gov) and [Clinicaltrialregister.eu](https://www.clinicaltrialregister.eu) have search tools that allow you to search for trials by disease. The website includes information about trials that have terminated, which can generate statistics about the number of unsuccessful trials. This information could support the need to have a resource which provides independent and object advice on the development of therapeutic programs in your disease area.

- **The current drug pipeline:** Having a knowledge of potential drugs in development is important. Companies with therapies in development are your potential applicants. Regular horizon scanning opportunities can help you keep up to date with your field (horizon scanning involves actively looking to see what the future might look like). In the field of medicine and healthcare, this is about investigating to see what medicines are in the “pipeline,” that is, in development in clinical trials but also in pre-clinical research. By systemically investigating the evidence, a clearer picture can be presented, as to what is in development in a given disease or sub-group. Earlier identification of potential medicines can facilitate greater collaboration between industry, academics, patient organisations and disease networks.
• **The current drug pipeline cont.**: There are various ways to conduct this sort of horizon scanning: for instance, many patient organisations publish drug pipelines on their websites. In terms of pre-clinical research it is best to check company websites, such as their pipeline sections, press releases and investor presentations (as this is early stage, it is unlikely to be included on clinical trial registers but note pre-clinical research may be published in an academic journal). There are also websites available to carry out pipeline searches.

**WHO IS THE USER COMMUNITY?**

The user community of an ACT will include:

• **The applicant**: An ACT review provides the applicant with advice, which is independent of any funding stream, to inform their clinical trial design including recommendations on go/no go decisions, selection of endpoints and outcome measures. A subsequent ACT report could help an applicant to secure additional funding from other sources. Whilst industry applicants will be asked to make a suitable donation towards meeting costs, academic applicants can have access to this resource free of charge.

• **Reviewers**: To be able to offer such a high-level of multidisciplinary advice, it is essential to engage with the key opinion leaders in your field. Their support and input is imperative to the success of an ACT. There are many benefits to reviewers participating in such a review panel including learning from experts in different areas of the same disease field. Reviewers can also be best place to identify applicants who can benefit from an ACT review.

• **Patients**: The overall aim of an ACT review is to examine the realistic prospects of a compound, and provide objective advice to support the development of a compound through to eventual registration, which will benefit patients. Patients and/or patient representatives will always be included on each review panel and will have the opportunity to give the patient perspective on the risk/benefit and potential burden of a clinical trial, as well as advising on the relevance and significance of expected outcomes of a therapeutic to patients.

• **Patient organisations**: Whilst an ACT report is confidential, interested parties can contact an applicant to ask to view a copy of the report they received from ACT. This report could help patient organisations (and other funding bodies) prioritise requests for funding.
WHAT IS THE VALUE OF AN ACT?

An ACT review meeting is significantly different to an advisory board used by industry. The ACT secretariat will form a bespoke, independent, multidisciplinary, objective panel of drug development experts, especially for each application under review. The independent aspect of ACT is key to ensuring that each applicant receives objective advice.

Each reviewer completes a conflict of interest declaration prior to being selected. The applicant does not have any influence over the selection of reviewers. At the face-to-face meeting, the applicants are the guests of the reviewers, rather than the other way round.

To form a panel of this standard would be significantly costly, as well as logistically difficult to bring together a group of highly valued and key opinion leaders. For academics, such an advisory board is not typically a resource available to them.

An ACT can provide academics with multi-disciplinary advice free of charge. An ACT is a unique resource available to both academics and industry to utilise twice a year, every year. Thus providing a long term resource to support the development of therapeutics in rare diseases, where there are few or no treatments available.

ONGOING FUNDING

In order to support each ACT review meeting, you may wish to consider the following examples of sources for funding:

**Patient Organisations**

Support and funding from patient organisations has been crucial to the TACT model, particularly for providing funding for the TACT project manager role. Many neuromuscular patient organisations have financially supported TACT meetings, where only academic applications have been submitted. Without their support it would be difficult to cover the costs of academic applications, which are free for the applicant.

Patient organisations understand the crucial role that patients can play in improving the design of clinical trials. The ACT model allows patient representatives to be involved at the earliest stages of clinical trial design in an independent and structured environment.
The ACT model can bring additional advantages; some patient organisations who have worked with TACT now require that applicants for research grants must first complete a TACT review. Supporting a multi-disciplinary committee, which objectively reviews developing therapeutic programs, can be of huge benefit to patient organisations when making funding decisions. In addition, when patient organisations see the value of the process to translational research and the benefit to the patients that they represent, they are often keen to offer support.

Industry applicants

In the TACT model, industry applicants are asked to pay a contribution towards meeting costs depending on the size of their company. TACT operates on a not-for-profit basis and all funding supports meeting costs. TACT uses the boundaries below to decide a contribution amount to ask of industry applicants:

- ≤9 employees
- ≤50 employees
- ≤250 employees
- ≥250 employees

Academic applicants are able to submit an application free of charge. If you receive more academic applications than industry, you will need to seek alternative funding to support the costs of the meeting.

Utilisation of other meetings

Meeting venues, travel and accommodation will account for the majority of expenditure in your ACT budget. Explore the opportunity of utilising a meeting room at an upcoming conference or large meeting, at which many of your potential reviewers will already be present.
COSTS TO CONSIDER

In order to properly support an ACT meeting, the following costs should be considered within your proposed budget. Based on the TACT model, a meeting can cost between €20,000-€40,000. Costs vary depending on location, venue, number of reviewers and reviewers’ location.

**Venue**

A suitable venue will need to be identified to hold the meeting. Consider utilising university/hospital meeting rooms which will likely be free or little cost to hire. If these type of rooms are unavailable to you, consider contacting patient organisations with whom you may be engaged to ask if they have available meeting space. If none of these options are available, you will need to budget for a hotel or conference-centre venue. Patient participation is essential when forming an ACT panel of reviewers so you may need to consider accessibility to, and any specialist equipment required to ensure participation at any chosen venue.

**Staffing**

You will need to create a secretariat in order to run and organise ACT meetings. It is advised that a project manager (full-time), one project assistant (part-time) and the time of one academic lead will be required to support and run an ACT. In addition to organising and running the review meetings the secretariat must promote ACT, recruit potential applications and support the committee.
Reviewer Costs

In advance of the meeting you must decide on and budget for reviewers’ costs. Depending on the applications being reviewed, between 12-20 reviewers will be invited to attend the meeting. For each reviewer’s participation, depending on your available budget you may consider offering the following:

- **Honorarium for attending the meeting and reviewing applications.** It is advised that the honorarium is a fixed amount for all reviewers, including patient representatives.
- **Reimbursement** for reasonable travel costs.
- **Accommodation** - to control costs it would be advisable to make a block booking at a hotel and you will likely receive a preferential rate by doing this.
- **An evening meal for all reviewers** - this is also important for bringing the panel together as a team in a social setting.

Promotion Costs

You may wish to budget for costs for the design and printing of leaflets, brochures and posters for promoting your ACT to potential applicants and at conferences and for travel to attend such conferences.
The intention of these documents are to provide you with guidance and structure, when creating documents to be used by your own ACT. These template are based on documents used by TACT. Neither TACT or the EJP RD are responsible for the use of these documents by other networks or individuals. For further information and guidance or to report misuse of these documents, please contact joanne.lee@newcastle.ac.uk.

**Pre- Application form**

The pre-application form should be issued to potential applicants when they enquire about an ACT review. This form is designed to gain more information about their intended drug development plan and to allow the ACT chair and secretariat to decide if their application is at a suitable stage for review. If accepted, this form will also be used by the secretariat to identify potential reviewers.

[DOWNLOAD HERE]

**Full application form**

Once the pre-application form has been accepted, the applicant will be asked to submit a more detailed application form. This will ensure that the review panel will have sufficient information to be able to comprehensively review the application for advice. Depending on the disease area, the core committee should agree consensus on the questions to be included as part of an ACT application form. For guidance, an example of the TACT application form can be found [here](#).

[DOWNLOAD HERE]

**Applicant agreement form**

Once the pre-application form has been accepted for review, an applicant agreement form should be issued to the applicant to ensure that they are committed to attending an ACT review meeting. The agreement will include a request for donation. Please note that this agreement is only to be completed by industry applicants. You may wish to create a modified version for academic applicants.

[DOWNLOAD HERE]
Conflict of interest form

To ensure that a review panel includes independent and objective reviewers, each reviewer is required to complete a conflict of interest form for each application they review. The conflict of interest form must be submitted when a reviewer agrees to provide advice at a particular ACT meeting. Each form will be reviewed by the secretariat, in consultation with the ACT chair. If a conflict of interest is identified for a specific application, they will not be able to review the application form or provide advice on the application.

Download Here

Review meeting agenda

This template includes a suggested schedule of timings, based on the TACT model. This agenda is intended for reviewers, observers and the secretariat. A modified version should be created for each applicant informing them of timings of the review, venue and a list of reviewers on their review panel. The modified version for each applicant will not include information about other applicants.

Download Here

Report to applicant template

After the review meeting, the lead reviewer, with input from the review panel, will create a report to the applicant which will include recommendations, advice and answers to the applicant’s specific questions. The lead reviewer will send the report to the secretariat to be formatted, reviewed and added to the report template before being sent out to the applicant.

Download Here