

## Executive Summary of the EJP RD ERN-focused workshop 'Creating an Advisory Committee for Therapeutics (ACT) in new rare disease domains'

Between 7<sup>th</sup> and 8<sup>th</sup> July 2021, 30 experts participated to a workshop designed to explore the potential of creating Advisory Committees for Therapeutics (ACTs) in the rare disease community. The concept of an ACT originated within the neuromuscular field, in the form of the TREAT-NMD Advisory Committee for Therapeutics (known as TACT). First established in 2009, the TACT model centres on a multidisciplinary panel of experts who provide independent and objective advice on the development pathway of real therapeutic programs in neuromuscular diseases. This is a much-needed resource, as many manuscripts on potential therapies for neuromuscular diseases have been published, but few of these therapies actually move forward into successful clinical trials. TACT provides a unique resource and educational tool for the neuromuscular community, helping to bridge the gap between promising preclinical data and successful clinical trials, by optimising the planning and execution of early stage and later phase clinical research in this community.

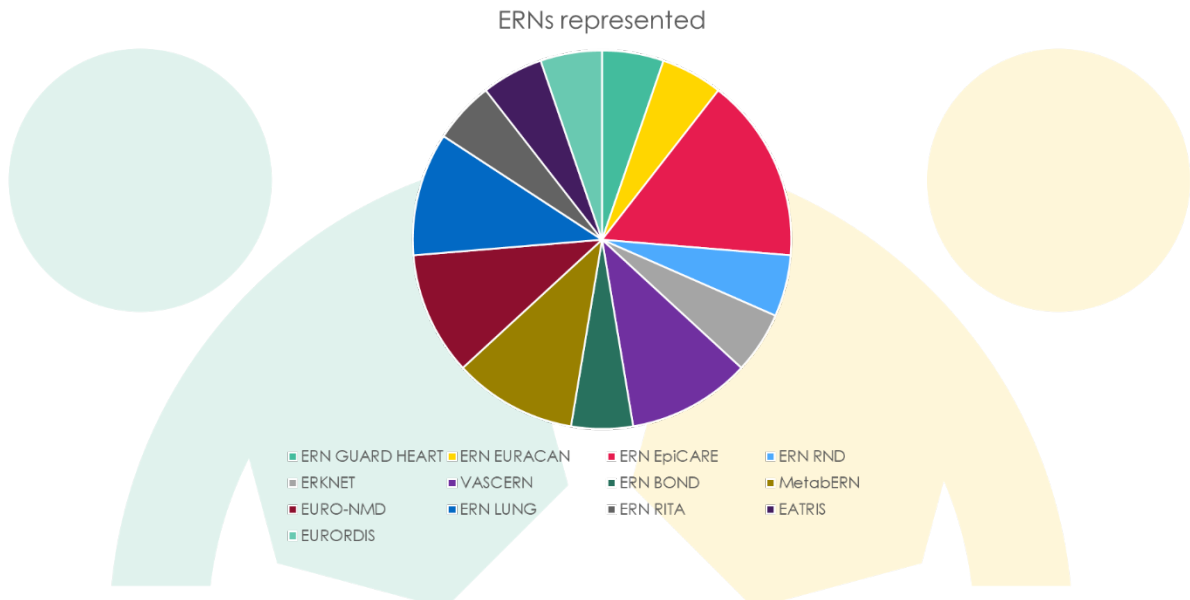
However, the model itself is readily transferable to many other rare disease areas, due to shared challenges in carrying out clinical trials. Newcastle University has therefore developed the Advisory Committee for Therapeutics (ACT) toolkit through the EJP RD, in compliance with the EJP RD mission of expanding good practices and innovative resources to other rare disease communities. The aim of the toolkit is to provide other rare disease networks with procedural advice and template documents to support them in the set-up their own ACT. The toolkit is part of the Innovation Management Toolbox, a virtual library of self-help resources, which will be made available to all on the EJP RD website.

This workshop was designed to give attendees the opportunity to become familiar with the ACT model and the lessons learned from its deployment over the past decade in the neuromuscular field, before shifting the focus to **explore the feasibility of adopting the ACT model in additional rare disease communities**. Any such expansion of the ACT model would ideally be overseen strategically, and European Reference Networks (ERNs) are perfectly placed for this, which is why an ERN-focused workshop was prioritised. The workshop had the following specific objectives:

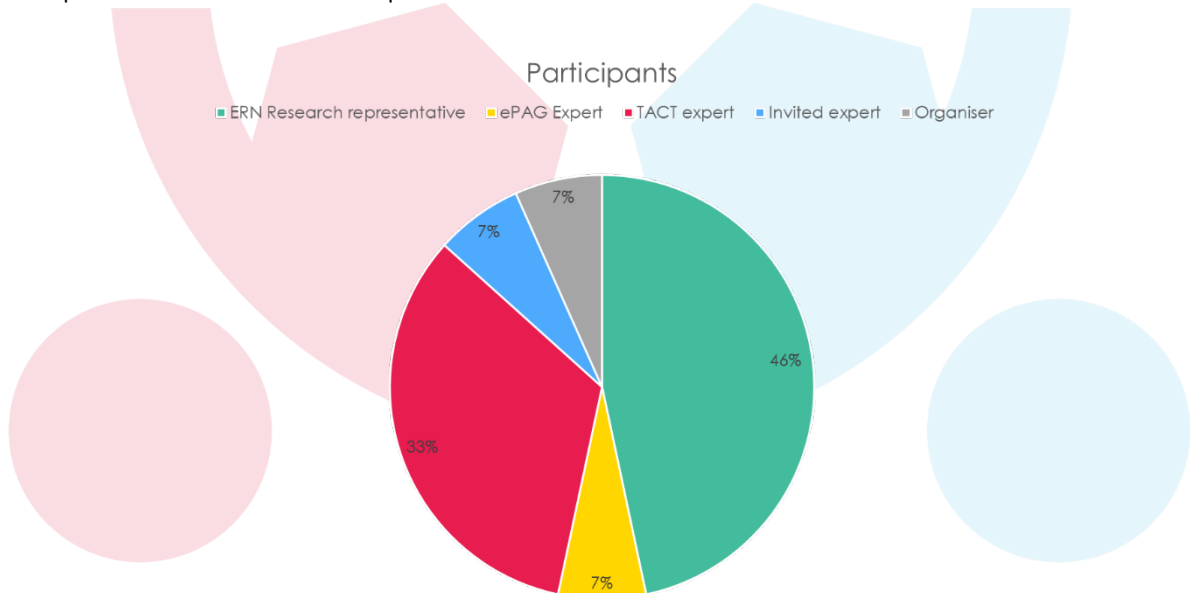
- Provide an in-depth understanding of the ACT model and show how the TACT model has served the neuromuscular community over the past decade
- Deliver a practical demonstration of a 'mock' review, to show how an ACT multi-disciplinary panel works together to provide objective and constructive recommendations
- Provide a forum for participants to engage with TACT reviewers, to gain an insight into the added value an ACT could bring to their field
- Encourage participants to scope-out opportunities and challenges in adopting an ACT within their network's disease areas and explore the practical steps they would need to take to do so

- Encourage participants to consider and scope-out the possibility of collaborating across and between disease domains

The following ERNs participated to the workshop:



To ensure a good mix of skills and experiences, from different stakeholder groups, the composition of the workshop was mixed, as below:



The full report of the 2-day workshop, including access to all presentations and a recording of a live mock review, can be requested by contacting [joanne.lee@newcastle.ac.uk](mailto:joanne.lee@newcastle.ac.uk).

**Many important ideas, opportunities and challenges related to the creation of additional ACTs were generated throughout the workshop. These are presented below, grouped around 4 key questions.** These discussion points and conclusions should be viewed as highly relevant for any field wishing to explore the creation of an ACT in further detail:

The key discussion questions were as follows:

1. From what you've heard over the workshop so far, what are your initial views on the strengths of this 'ACT' model, currently deployed in the NMD field, and do you think it would be a useful asset if established in your community (why/why not?)
2. Can your group identify any particular ERNs/ disease areas in which setting up an ACT seems most feasible? Would any ERNs naturally share diseases/disease areas?
3. What do you think would be the main challenges in setting up an ACT in your field?
4. If we were eventually able to establish an ACT in a number of ERN fields/subdomains, can you envisage any opportunities for collaboration between them? E.g. do you think experts could be part of the core committees or extended committees for more than one ACT? What sorts of expertise might be cross-cutting to more than one community?

## **1. What are your initial views on the strengths of this 'ACT' model, currently deployed in the NMD field, and do you think it would be a useful asset if established in your community (why/why not?)**

### *Broad added-value of the ACT model to the RD field*

- There was strong consensus that the ACT model has major potential to help prioritise resources, to develop more high quality studies and to increase the chances of success for RD trials by identifying and correcting pitfalls in their trial design.
- The consensus-based approach of an ACT harmonises different opinions which could be highly valuable: the cross-disciplinary nature of the review panels assembled by an ACT is a major strength.
- The ACT model should be very valuable for many RD communities, as it is acknowledged that clinical trials are often extremely costly and resource-intensive. When RD therapy trials fail, it impacts the whole field. It is never possible to predict which trials will be successful and which will not, as there are so many variables – but a model which can remove some of the uncertainties and give a decent product its best chance of success would help to de-risk trials a little for companies.

- Although it may sound counter-intuitive, when we all want the greatest success in RD research, a key strength of the ACT model is the potential for research which really is not going to make the grade to avoid progressing to a clinical trial which then fails: if the foundational evidence is poor, it is better for the field for this study to 'fail fast' than for the study to go ahead and fail later. And indeed, we have responsibility to patients not to put them through unnecessary, risky studies (particularly where participation in a trial could debar that patient from future trials). This translational fail-fast paradigm is therefore something we should embrace across our RD communities and the ACT model could help to do this.
- It is acknowledged that the ACT model is less concerned with addressing a particular concern in RD research, which is the fact that many disease areas have very limited basic and preclinical research. One of our challenges in the RD community is how to stimulate and encourage research interest on the part of companies in the traditionally-overlooked disease areas (to-date, therapy development has focused on a number of core therapeutic areas, which now have multiple OMP authorizations, leaving many diseases with no therapies). The ACT model does *not* purport to address this particular challenge, but instead fulfils the vital function of ensuring that the studies which *are* being planned by companies and any other actor, now and in future, have the best possible chance of success.
- The successes of this model in the Neuromuscular field inspires a lot of confidence, and could be replicated in many other fields. The fact that a TACT review is seen in that field as a mark of quality (and is requested by some patient organization funders) is illustrative of its added-value in its home community. In fact, another advantage of the ACT model is the potential for ACT reviews to help funders of RD research to make better decisions.
- The ACT model capitalizes on –and reinforces– the benefits of seeking drug development advice early.
- An ACT could be useful for repurposed therapies, particularly from academic applicants.
- The ACT model could be particularly beneficial for gene therapy studies for RD in the future. In its neuromuscular incarnation (TACT), reviews of gene therapy trials have already taken place, but this could be an important avenue to consider in expanding the model to other fields.
- There are many advantages for those requesting an ACT review: not only is the advice received going to be valuable for the planning and execution of the research at-hand, but actually the experience of attending a meeting like this could help to prepare applicants for other meetings e.g. ethics committees.



- The existence of an ACT could actually help to drive standardization and harmonization across a particular disease area; for instance, in the neuromuscular field, TACT has indirectly led to far greater use of a set of pre-clinical SOPs, which means that a) trials are using the best, most suitable resources, but also b) there is greater harmonization of practice. When promoting more widespread use of robust outcome measures, for instance, the TACT experts noted the importance of seeking advice as early as possible from the experts who actually perform measurements of outcome measures, to see if proposed end-points are really feasible.

### *The added-value of an ACT could depend upon the scope and research pipeline of a community*

- The ACT model may be more appropriate, in its current form, for some fields compared to others. For instance, the ACT model is intended to add value for communities where clinical trials are either taking place already or are on the horizon. It could be viewed as particularly useful for fields with quite a strong research pipeline, as it enables them to focus investments on the studies most likely to succeed: resources are finite and it is frustrating for all involved when studies fail for probably-avoidable reasons.
- It is also worth noting that the ACT model deals with therapeutics, first and foremost. It was conceived initially to optimise trials of medicines/ drugs. And not all ERNs are equally concerned with medicinal products. Some are more focused on surgical and other procedures, for instance. We would need to consider how applicable an ACT would be in these sorts of setting. Indeed, the 'T' in ACT stands for 'therapeutics'. Industry applicants are important for the sustainability of an ACT, and we would need to consider whether Industry would request a review for something that does not pertain to medicines. Perhaps medical devices would be an interesting avenue to explore.
- Similarly, for some disease areas, 'treatment' may consist largely of a combination of therapies. The ACT model could still be advantageous to this sort of study, assessing optimum treatment regimes, as the advice a panel could provide in terms of design, patient preferences, endpoints, etc., would remain valuable. However, if most studies under a given ERN's domain were of this kind (i.e. around optimum combination therapies) there would likely be limited Industry involvement, which would make sustainability of the model difficult perhaps (ideally, an ACT needs a mixture of industry and non-industry applicants to fund the central services and cover costs of the review meetings)

### *Patient centricity of the ACT model*

- A key strength of the ACT model is the fact that it is so patient-centric. Having patients involved in all review panels is a really important element of the ACT model, and allows patients to really shape the way in which a trial is planned and delivered. There are issues that patients raise e.g. the size of a tablet, that may not be considered by the other experts. Furthermore, COVID has taught

us that not all assessments need to be done in a clinic, some can be done at home and the patient voice is important to advocate for these changes.

- Besides involving patients in the reviews undertaken by an ACT, it would be important, strategically, to include patients in the development of an ACT in a given community. Patients should advise in the setting-up of an ACT, recommending types of expertise and suggesting individual experts to populate the core committees and extended committees (which are key parts of the ACT model). The ePAG advocates could be a logical starting point for this, in any given ERN.
- An ACT allows patients/patient representative to advocate for changes specific to a certain review but also to convey certain messages across reviews, directly to the sponsor, concerning things which really make a difference time and again e.g. ability to do assessments at home, size of a tablet, the mechanism of action.
- ACTs could also provide an opportunity to highlight the concerns of the health care professionals, who work regularly with patients, to the sponsor.

#### *ERNs should play a strategic role in establishing an ACT*

- ERNs, with their strategic oversight of rare diseases, grouped into clinically-relevant subdomains, are ideal entities to oversee and stimulate the creation of ACTs in other areas. An important benefit of an ACT is the fact that it is tied to a disease community but not a specific institution. Funding would need to be channeled through a legal entity but the ACT itself would act as an independent third party for a whole community.
- ERNs have already facilitated the identification of expertise related to very broad disease and procedure-based groupings, through their operations to-date. They naturally unite multiple stakeholder groups, which is something the neuromuscular group had to really work at, when starting to create their ACT over a decade ago. Therefore, the ERNs have an advantage here already. The community buy-in was very important for the success of TACT, and having ERNs play a role in overseeing -strategically at least- the creation of ACTs in other areas would be very valuable.
- Once you have someone in mind who can oversee the creation of your ACT (a coordinator) and support from someone able to handle the administrative and logistical tasks, a key task would be setting up the Core Committee and Extended Committees. The composition of the Core Committee, in particular, is key as this should include key opinion leaders who are well-connected. This is another area in which the ERNs are particular well-placed to establish their own ACTs, as the ERNs have done a lot of work to map what kind of expertise exists in their field, and to identify field leaders.

## 2. Can we identify any particular ERNs/ disease areas in which setting up an ACT seems most feasible? Would any ERNs naturally share diseases/disease areas?

### *Setting-up an ACT would make more sense in 'trial-ready' areas*

- The most logical criterion in terms of identifying an appropriate ERN field – or indeed subdomain – for a new ACT would surely be the maturity of the research pipeline. Fields with multiple trials ongoing/coming up would be the most obvious areas in which to prioritize the creation of an ACT. The concept of an ACT may be less relevant for some ERNs (see above). But generally, the best targets are 'trial-ready' communities.
- It is important to understand what 'trial ready' actually means. A logical focus would be disease areas which have agreed standards of diagnosis, fairly homogeneous populations and well-characterised cohorts, and ideally some end-points agreed, amongst other aspects. Having patient registries and an established standard of care are advantageous but not a pre-requisite for trial readiness.
- The ERN representatives overwhelmingly favoured the creation of an ACT addressing a particular subdomain/sub area under their broad general headings. Specific Proposals from ERN representatives were as follows:
  - ERN RND is keen to begin creating an ACT for Ataxias (a subset of the rare neurological conditions the ERN focuses on)
  - EURACAN covers 300 solid rare tumors. They could begin an ACT with Adrenal cancers, as there are few treatments available.
  - ERK-NET could look to prioritise one area, such as nephrotic syndromes and then expand the ACT into other diseases
  - VASCERN could prioritize lymphatic AVM (Arteriovenous malformation) as this area is ready for many clinical trials.
  - In ERN-LUNG, there are many studies in the pre-clinical stage which could benefit from the ACT model.

### *Defining the coverage of an ACT*

- An important operational question is whether it would be advisable to create a new ACT at the level of the ERN (e.g. rare metabolic diseases) or to focus on clinically-relevant subdomains. Perhaps strategically the best approach would be to think in terms of creating an ACT at that higher level, with the understanding that it would concentrate in the first instance on applications relating to a particular subset of diseases (which might be represented by a certain subdomain of the ERN). This is how things evolved in the Neuromuscular

field: the ACT is in theory open to reviews from any and all neuromuscular diseases, but in reality these reviews were, in the early years, primarily focused on DMD (as the focus of most research activity at the time). If you explicitly created an ACT for merely a subset of say metabolic diseases, e.g. Lysosomal Storage Disorders, and focused on eliciting applications in that sphere, should the group wish to expand to other rare metabolic diseases they would not need to create a new ACT. All that would be needed is a record of which experts cover which subdomains- if an ACT targets LSDs initially, someone will draw up a list of experts for the core and extended committees (especially the latter, as this is the large expert body upon which ACT reviews would draw) based upon those conditions, and expand the list/database as request arise from other disease areas

- It is important to consider the fact that an ACT may not be directly an activity OF an ERN, exclusively, but rather could be a tool of the rare disease community which is strategically created along ERN lines. Thus a rare neurological diseases ACT would not be exclusively an ERN-RND venture, but would involve the wider rare neurology community.
- It is acknowledged that some specific conditions could be classified under more than one ERN – e.g. Fabry Disease, Ehlers Danlos Syndrome, Scleroderma. When establishing an ACT it would be important to think about where such conditions might naturally sit. If we reach a point where rare skin diseases have an ACT, as well as rare autoimmune diseases, would an application from a Company or academic seeking to launch a study in Scleroderma approach one or the other? These strategic overlaps in conditions are increasingly being recognised by the ERNs concerned and they could probably agree how to handle some of these multi-ERN conditions. But indeed, the fact that the ERN disease coverage does not have hard borders could be an asset to communities establishing an ACT: and requests for reviews in these particular conditions might be addressed by involving experts from more than one ERN, on occasion, to cover different aspects of the same condition.

### 3. What do you think would be the main challenges in setting up an ACT in your field?

- One major strength of the ACT model, as deployed in the neuromuscular community, is the ability for self-sustainability, which comes from the Industry reviews: the fees paid by Companies cover the small amount of core coordination staff time, as well as the costs of future meetings, and essentially means that the model can provide free research reviews for non-Industry applicants. However, an initial source of funding is needed ideally to start things off; specifically, to pay for some person-time to establish and coordinate the



model (e.g. to find experts to populate the review panel, to find and liaise with the first prospective applicants, and to organize the first review meeting).

- One challenge with ERNs playing a key role in setting up ACTs in their communities would be the fact that the Networks themselves are not legal entities. The key to making the ACT model self-sustaining in the neuromuscular field is the ability to attract applications for ACT panel reviews from Industry, who pay fees for this extremely valuable service. Those funds then go back into the ACT 'pot', to cover the costs of the next review meetings (where up to 4 applications are reviewed over a couple of days) and also to cover staff time for someone to coordinate the ACT and manage the logistics and administrative side. In the neuromuscular field, these funds from Companies are paid into a bank account of a single HCP which takes responsibility for the ACT secretariat (and in which the funded staff are also based). The HCP is a University/Hospital and thus is a legal entity. Therefore, other fields would probably need to think similarly, i.e. of nominating one HCP to take the lead in setting-up and coordinating the ACT model for their field (and ideally, the staff they manage to dedicate to working on their ACT, even if part time, would be based in that same centre). This would ensure the funding can flow properly and be managed appropriately.
- Ideally an ERN/ERN subdomain would be able to nominate a person (or a part time person) to coordinate an ACT in their field, as well as a portion of administrative time. It is easier to find dedicated person time if you have a pot of initial funding you can use, until the model becomes self-sustaining. (Through the funding received from EU FP6, to establish the TREAT-NMD network, the neuromuscular community was able to fund a project manager to set-up TACT.) The main challenge then, for all ERN-organised communities, would be to find that initial pot of funding to get things rolling.) But perhaps some ERNs could begin with some time of a person already working within one of the ERN HCPs, to get through those initial applications (the fees from which then make it easier to become self-sustaining and have those key salaries covered)
- The ERN Board of Member States has traditionally been reluctant to allow ERNs to engage with Industry, despite the absolute necessity of this to advance rare disease research (which is an ERN expectation). The latest statement from the Board recognises some engagement will be important, but the guidance over what kinds of interactions are 'approved' does not yet exist, and ways of working with Industry are still being agreed. In reality, therefore, engagements with Industry are carried out by leading RD centres and researchers on a more 'one-to-one' basis, as they have been, in some cases, for many years. Naturally, researchers have not ceased to engage with Companies simply because they now coordinate an ERN or are based in a centre which is part of an ERN. The activity – whether participating to clinical trials, collaborating on registries, providing trial feasibility data, etc - is simply not badged as activity 'of the ERN' per se. It is proposed therefore, that until there is a change in the policy of the

Board of Member States, that engagement with Industry in the course of operating an ACT in a new ERN field would follow this pattern, which avoids any potential issues. By implementing the disclosure templates etc. developed and deployed in the neuromuscular ACT for the past decade and more, ERN communities can be assured of the ethical and legal safeguards surrounding Industry engagement via an ACT.

- The lack of biomarkers in a specific disease area could pose a problem in establishing an ACT.
- For some ERNs, the creation of an act would be hampered by the lack of basic research and clinical trial (see sections above): it would be difficult to establish an ACT in a disease area with little clinical trial activity.
- The participants discussed the need to avoid conflicts of interest, which it is acknowledged, can sometimes be difficult in rare diseases. In the TACT model, all reviewers are asked to declare their interests but are only considered conflicted if they are working directly with a company on the program with which the application is concerned, OR if they stand to gain financially. This actually allows TACT to use industry experts on the panels, from time to time.
- Deciding on frequency and medium of meetings could potentially be a challenge, at least if ACTs are established in the current climate: face-to-face meetings are more beneficial for reviewers to work together and develop as a team but virtual meetings may be preferred by some patient representatives, even after the pandemic. The regularity of review meetings is also perhaps something to consider: TACT holds meetings twice a year and reviews up to four applications per meeting. This may be too frequent for disease areas with less activity, which might only need a single meeting a year, until they get established.

#### **4. If we were eventually able to establish an ACT in a number of ERN fields/subdomains, can you envisage any opportunities for collaboration between them?**

For example, do you think experts could be part of the core committees or extended committees for more than one ACT? What sorts of expertise might be cross-cutting to more than one community?

- It is likely that there will be certain types of expertise that could be considered cross-cutting i.e. are not especially disease-specific. In particular, skills such as regulatory expertise and statistics would be good. We know from the experiences of the neuromuscular ACT that there are certain pitfalls many applications (i.e. many research proposals) tend to attract, and the advice is often disease-agnostic. These kinds of specialist skills are much in demand, and

perhaps individuals who possess that kind of expertise could be invited to review panels for multiple ACTs, acting as and when required.

- An important area to consider –in terms of expanding the ACT model into different ERN areas – will be gene therapies. Although the disease expertise will be bespoke to each condition (with disease specific expertise needed to understand the mechanism of action, to advise appropriate outcome measures and end points) there are probably some commonalities across gene therapy trials which would appear in all reviews of a prospective gene therapy product. Examples would be in regulatory expertise, and in logistical and manufacturing advice related to trial planning and delivery. If this were to become a key area for future ACTs, we would probably need to consider whether it would be beneficial to engage with projects/groups dedicated to gene therapy specifically, to integrate that expertise.
- There may also be cross-disease area interest in applications concerning the repurposing of therapies for rare diseases. Regulatory expertise and insights from groups which have successfully repurposed drugs for a rare disease/a different rare disease, could also be shared between ACTs (e.g. when different ACTs receive an application concerning repurposing, they could ask the same person/group of people to serve on that review panel, in view of the cross-cutting applicability of the expertise)
- To keep track of which experts are involved in different ACTs (and whether these people are part of the smaller Core Committee – which is changed every few years – or the much broader pool of experts making up what we call the Extended Committee), it would perhaps be helpful to somehow centralise this list of names and areas of expertise. Some participants suggested that a database or registry of ACT experts could be developed, as ACTs develop one by one, which could be used by all ERNs as they set up their ACT. So when seeking some of these cross-cutting expert profiles, a new field just getting started with an ACT could approach some of these experienced individuals (and in turn, add their own experts).
- Notwithstanding these excellent suggestions, capacity of experts could be a limiting factor. We would need to think of more than one expert with statistical experience, for instance, to work across multiple ACTs, as one or two people would probably be overstretched (in the Neuromuscular ACT, TACT, these individuals would be invited to a maximum of two review meetings per year, and this is probably as much of a time-commitment as most experts could manage. Thus we would need to grow this pool).



## Key Conclusions and Next Steps for ERNs interested in establishing an ACT (Advisory Committee for Therapeutics)

After the workshop took place, each participant was asked to complete a satisfaction survey. The responses to the survey were incredibly valuable to the organisers, as they helped to gauge interest in the ACT model and the development of future ACTs. **The key finding of the survey is that 11 participants said that they expect to explore further the possibilities of establishing an ACT within their disease area/ERN grouping.**

The strategic propositions, opportunities and challenges, detailed in the responses to the questions above, should form the basis of next steps, both for the organizers and the participants themselves. To support the participants in developing their thinking further, the ACT toolkit was sent to all participants after the meeting, which provides concrete resources and practical steps. During discussions on day 2 of the workshop, it was suggested that the organisers should look into applying to future EJP RD calls, specifically the networking call, to hold another workshop to pilot an ACT in on 1 or 2 disease areas. If able to secure funding, the organisers will contact participants to identify suitable disease areas to pilot an ACT.

For more information about the ACT concept, to request the ACT toolkit or to further explore the creation of an ACT in your field, please contact [joanne.lee@newcastle.ac.uk](mailto:joanne.lee@newcastle.ac.uk).

