Clinical study protocols in neuromuscular diseases (NMD): objectives and points of attention for AFM-Telethon

The association's volunteer members (patient experts from groups dedicated to NMD or federations by disease) and employees are invited by clinical study sponsors or institutions to participate in the development or review of study protocols, patient information and consent documents. This activity is based on their disease knowledge, patient needs and expectations, the therapeutic drug development, and ethical issues. In addition to the sponsors, investigators and clinical experts (who focus on the medical aspects and the evaluation of the product efficacy and safety), the associations can propose protocol adjustments in order to facilitate patient adherence, which improves their inclusion and limits the risk of premature trial drop-out. They also promote more patient-centered assessment criteria, which can smoothen the regulatory treatment pathway (reimbursement stage).

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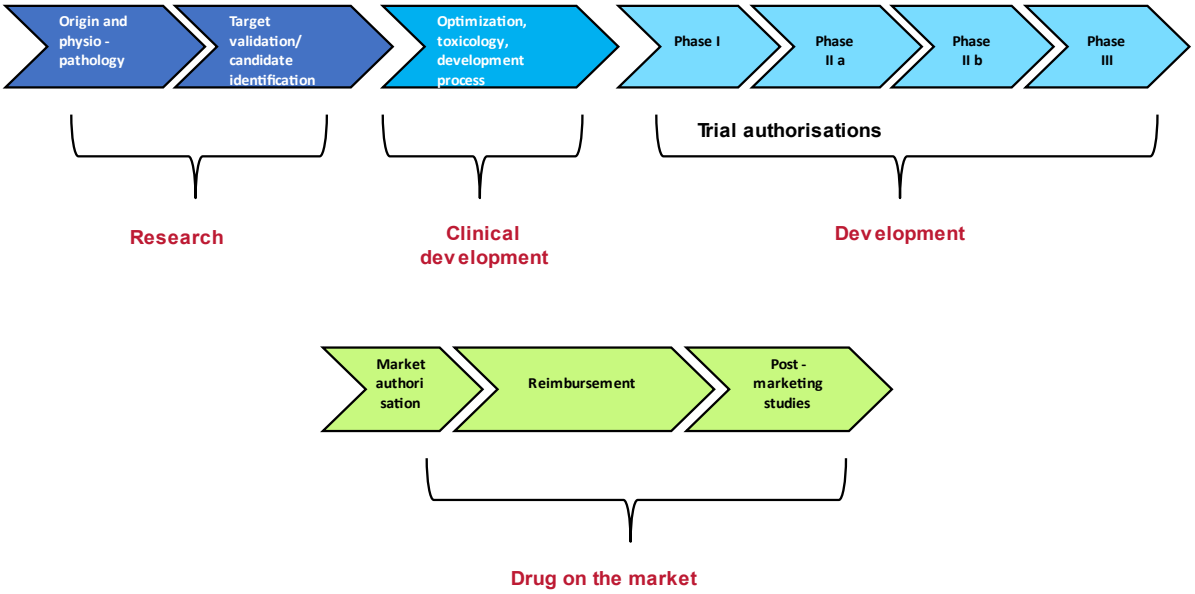
Method

AFM-Telethon wanted to formalise the objectives that clinical study protocols should pursue and the points of attention they call for concerning organisational and methodological aspects. This formalisation should help AFM members in their participation in protocols.

Experience sharing between members of AFM-Telethon and formalized feedback (based on a form developed by an AFCRO/patient association working group) were used. Here, the objectives and points of attention are classified according to topics. They will have to be updated with upcoming participations and according to the evolution of the stakes (new types of treatments, evolution in the methodology of studies, etc...).

The issues discussed here occur in the sponsors' study protocols or in organisational appendices intended for investigators or companies organising the trials (CROs).



How to work on the protocol and patient information documents

For patients: to be involved in the entire drug development process, as early as possible and to have full information

<u>Stage of product development.</u>

What are we talking about? A clinical trial, the entire clinical development (several studies), a pilot feasibility evaluation trial?

It is better to participate in the early stages of drafting projects, or failing that, to participate in protocol reviews. The discussion with the sponsor should start before meeting the agencies that authorise the trials.

<u>Working documents.</u>

Is the complete protocol available or just a synopsis?

It is recommended to have access to all the documents the sponsor can communicate. For this, a confidentiality agreement should be signed. In addition, even very technical information allows expert patients to respond better to the sponsor's requests.

Working method.

Is the work of the patients individual or will it be done in groups? Will they be able to participate in discussions with the sponsor/investigators? Do they have to provide written comments on an existing text? Who can help the expert patients?

Working on a protocol requires some individual work on documents. Sharing opinions then leads to a richer result for the construction of the protocol or in the synthesis of review opinions. Discussing with the sponsor /investigators/experts allows one to better justify one's point of view, listen other reasonings and identify new questions and possible solutions. For any meeting, it is necessary to have an agenda. It may also be useful to draft a written response to formalise the patients' position.
The appointment of a resource person (e.g. an investigator) to clarify technical points can be valuable. If this expert is external to the project, he or she will also have to sign a confidentiality agreement.

Possible conflict of interest of expert patients.

“Am I in a position of a conflict of interest?” (Example: I may gain an advantage over other patients/relatives because of this work).

Every expert patient must ask himself/herself this question before starting his/her participation. In case of doubt, the ethical aspects related to this situation should be managed as soon as possible.

What kind of training for AFM-Telethon expert patients?
AFM-Telethon expert patients are people affected by NMD or relatives. They are volunteers involved in the association, particularly through local branches and/or disease-specific interest groups. They are involved in listening to patients, accompanying them, representing them in the health and citizenship fields, and in therapy development. Patient experts have a deep knowledge of family needs and specific expertise in the therapy domain. They follow a general training course within the AFM-Telethon. In order to complete their own expertise in the disease, they also follow specific training courses on drug development (e.g. political and regulatory environment, elaboration of protocols, participation in the development of tools, participation in committees and regulatory bodies, understanding of international issues, etc.). Meetings between AFM-Telethon patient experts are organised to allow exchanges and sharing of experiences.

Study inclusion criteria

Inclusion criteria: cover all subgroups potentially concerned by the treatment in a study program.

Balance between access to treatment and demonstration of efficacy.

Does the trial population balance the objectives of demonstrating efficacy, safety, access to treatment through the trial and coverage of all potentially concerned patients (e.g. non-ambulatory population)?

National HTA agencies pay close attention to the population treated in trials when making their decisions. However, narrowing the target may facilitate the demonstration of efficacy. The methodology should outbalance these issues in different situations, for example, by scheduling different trials over time. Eg : open-label trial, with administration of investigational product, after the phase 3 study in an expanded population, with results known prior to review by the HTA agency.

Inclusion criteria and speed of inclusion.

Are the inclusion criteria likely to significantly lengthen the inclusion phase of the trial or the natural history study?

NMDs are rare diseases: if the inclusion criteria are restricted to have a perfectly homogeneous population, they may target a very small population, the same risk existing with a larger but stratified population. In general, the consistency between criteria, disease, and size of the target population in the trial should be analysed.

Doubt about efficacy or safety in a subgroup.

If there is doubt about efficacy or safety in a disease subgroup, that subgroup should be tested in the study program.

Treatments taken by patients prior to the trial.

If the inclusion and exclusion criteria contain information about the patient's current treatment, what medications does the protocol mention?

Medical and drug management is not the same from one country to another. Furthermore, beware of the wording of certain drug criteria which may exclude a large proportion of patients.

Impact of geographic criteria.

Is there a geographical area of inclusion?

As NMDs are rare, the largest possible areas should be chosen, and appropriate measures should be taken to access the investigating centres. The trial documents must specify whether overseas territories are part of the recruitment perimeter. They should detail the various costs related to the distance.

Study Inclusion Criteria: Spinal muscular atrophy, Spinraza versus Evrysdi

Negotiations in European countries for the reimbursement coverage of these two drugs have had a rather different course.

Spinraza was put on the market without any prior study of the adult population. It obtained a European marketing authorization for the entire affected population. However, to this day, in several European countries such as Spain or Denmark, there is still no reimbursement for the adult population, five years after the launch. In France, AFM-Telethon and clinicians have had to argue with national authorities for reimbursement to cover SMA types 2 and 3 regardless of age.

Conversely, for Evrysdi, the company developed, after patient requests, a trial for a population aged 2 to 25 years, as well as an open trial up to age 60. There have been discussions about the relevance of reimbursement but based on clinical data and in almost all European countries, coverage by the health insurance systems is independent of age.

It should be noted that since no trial has been conducted in SMA type 4 patients, they are not included in the MA and therefore do not have access to this treatment, which could potentially be effective for them.

Evaluation criteria

Evaluation criteria: meet both study objectives and patient needs

Evaluation criteria and study purpose.

Are the criteria in line with the purpose of the study? Are they not too numerous or too frequent? Does their collection cause pain?

A natural history logically follows many parameters: clinical, muscular, respiratory, cardiac assessment, quality of life, adverse events, etc... A therapeutic trial will focus on evidence of efficacy and side effects. The evaluation criteria and the duration of the study may vary depending on whether the trial wants to show rapid efficacy (e.g. gene therapy in children) or stabilisation or even a slowing down of the disease progression.

To measure the effectiveness of a symptomatic treatment, it is possible to have a PRO as the primary evaluation endpoint. These criteria, which were rarely used in the past, are now accepted by the regulatory authorities and are valued in the reimbursement evaluation.

A too long a list of tests and/or frequent assessments will hinder recruitment and lead to dropouts during the course of the protocol: the impact on daily life and the need for each assessment must be considered.

Choice of the primary endpoint.

Motor function is often the primary endpoint: is this choice relevant?

In neuromuscular diseases, motor function is often chosen by the sponsor as the primary endpoint. However, depending on the disease, other functions may be more critical from a patient perspective, such as cardiac or respiratory function. In relation to the specific objective of the study and the knowledge of the disease and its evolution, it is possible to discuss this choice.

Biomarkers, if they exist, are often highly prized by sponsors, but authorising and HTA agencies require, as a priority, positive clinical results or the prior demonstration of a link between biomarkers and clinical parameters.

Relevance of motor function criteria.

Is this measure sensitive enough to show a change?

For ambulatory patients, the 6-minute walk is an outcome with strong limitations: difficulty in maintaining attention and understanding the duration for young children, tolerance of the test due to the weakness of patients, substantial variations according to fatigue and low sensitivity. It is better to use other, more elaborate scales such as MFM or Hammersmith (HFM-SE).

For non-ambulatory patients or young children, scales such as Upper Limb or Chop Intend are most often used.

Upper-limb assessment.

Should an upper-limb assessment be planned?

The upper limb plays a significant role in the daily life of ambulatory and non-ambulatory patients, and its assessment is important for

people affected by NMD and agencies to evaluate the patient benefit.

Performance of motor function tests.

Are motor function tests performed according to good practices?

Fatigue is one of the limiting factors of motor function in NMD. In order to get a reliable evaluation of the evolution of motor function, the tests must be performed under the same conditions (schedule, fatigue, etc.). Moreover, the tests are subject to the assessment of the evaluating physiotherapist, so it is important to train him or her and, if possible, to keep the same evaluator throughout the trial to guarantee comparable data.

Secondary endpoints.

In view of the disease and the patients' expectations, are other criteria measured?

Vital criteria such as breathing or cardiac function must most often be analysed because their dysfunction is a major stress factor for patients and families. Other criteria such as ease of eating, pulmonary aspiration, constipation, fatigue, ability to memorise represent important quality-of-life criteria and are useful to monitor.

Patient-related/reported outcome (PRO).

Is there a patient-related/reported outcome measure? What is its degree of validation (and translation)? Has it been developed with patients?
These PROs are often necessary to report quality of life, symptoms experienced or functional capacities. However, they are often not validated for the relevant NMD(s). Some not (yet) validated PROs can be interesting to add to validated PROs, with the protocol analysing their correlation to other parameters.

Generic quality-of-life scales.

Is there a generic quality-of-life questionnaire? Is it relevant to the disease?

This evaluation is necessary for the medico-economic modelling requested by the reimbursement agencies (alternative: the existence of a correspondence between a specific scale and generic quality of life values). This assessment must be adapted to the trial population; for example, vigilance is necessary for paediatric diseases.

Study of previously identified adverse events.

If the toxicology study has identified an adverse event in humans or animals, does the trial identify the exact impact in humans so that clear recommendations can be made?

The control group

Control group: disease management according to the best "standards of care"

Rationale for the existence and size of the control group.

Does the protocol give statistical reasoning to define the smallest possible control group? Are there natural history data that can serve as control group?

There are techniques to reduce the size of the control group such as statistical modelling or pooling of control groups over several trials.

Natural history data sometimes makes it possible to dispense with a control group, especially if the expected efficacy of the treatment is high (eg. certain approaches in gene therapy).

Natural history information is often based on the pooling of a large number of data: retrospective data, existing prospective natural histories, data from clinical trials, etc. Their development and use are desirable in order to limit the use of the control group, which is often not appreciated by patients.

Care in the control group.

If the trial requires the use of a control group, is the control group treated according to the best standard of care?

If there is an effective, agency-approved treatment available for the condition, its administration to the control group follows an ethical principle and the expectations of the national HTA agencies that evaluate the comparative effectiveness of the products.

Example:

A study in one NMD is testing an indication expansion for a symptomatic drug with a marketing authorisation (MA) for another NMD. A placebo group protocol was developed. However, it turns out that off-label use in the disease targeted by the extension of indication is established in the country where the trial is to take place. Official recommendations even exist on this use. Patients are treated and should stop treatment momentarily during the trial if they are in the placebo group. This situation does not follow the best standard of care in the control group and makes recruitment very complex. This trial should not take place in the country initially envisaged.

Medical procedures used in the study and the well-being of the patient

Medical procedures in the study: limit heavy, invasive and tiring examinations to what is strictly necessary

Cumbersome tests and exams

Do the tests and examinations seem too numerous or too concentrated in time? Does the number of scheduled biopsies seem too high? Is it necessary to take all the scheduled walking tests? Are fasting blood tests on the evaluation day necessary, or can they be advanced? Is the possible pain associated with the tests well managed?

If patients are unable to perform part of the test, is this part excluded in advance to avoid unnecessary testing?
Do not hesitate to question the choice and the number of assessments to be performed, to study all possibilities to reduce pain (painkiller patch, light anaesthesia, etc ...). Tests can have iatrogenic effects. For example, there is a risk of hypoglycemia if the patient remains fasting for too long (and of distorted measurements) ...

Local adaptation of examination organisation

Do the centres have the flexibility to adapt to the needs of the patients in terms of grouping examinations?

The protocol must define the exhaustive list and schedule of examinations. However, the investigating centre is responsible for organising these examinations and should be able to adapt to the patient's needs.

For example, on a single day for some patients, or on two days to better distribute the examinations if requested by the patient.

Welcome conditions.

Are the time and comfort aspects (dedicated space, etc...) adequately addressed?

Ideally, visits should follow the standards of a multidisciplinary visit:
- Patients should be welcomed by the health care team as soon as they arrive: for example, plan for staggered arrivals, present the day's schedule, and adapt it, if possible, to the patient's specific needs (e.g., a moment of rest at mid-day)
- If possible, have a private room or place to stay
- Possibility to be accompanied by a caregiver throughout the day…

Psychological support.

Is psychological aid provided?

Trials generate stress for patients. The presence of a psychologist is an important plus to help them better understand the trial and also to manage the wait and possible negative effects (for example, following a change in their usual treatment).

Pre-existing treatments.

How are the person's current treatments taken into account?
Some patients have ongoing treatments that are not directly related to the NMD. Those that cannot be continued due to a possible interaction with the trial must be listed. By default all other treatments will be continued. A positive list of treatments that can be continued may unnecessarily exclude patients taking treatments that have not been considered.

Decentralisation of trials and use of telemedicine.

Does the study make sufficient use of the possibilities offered by telemedicine or home care ?

Patients with NMD are often very tired, so limiting unnecessary travel is essential. The use of health professionals at home or in a local hospital and telemedicine avoids losing school or work days, and allows the inclusion of patients far from the reference centres. Examples of examinations possible remotely: intermediate consultations, measurement of muscle strength at home, blood tests, sending the treatment by specialised carrier, etc...

Choice of centres and geographical distribution.

What is the trade-off between centralisation of procedures/minimisation of cost VS equity and ease of geographic access?

A large number of centres means greater equity for patients (probability of being included, distance to the centre). It can lead to higher costs, more complex logistics, and even lower trial quality if inconsistent procedures are used. Question the choice of centres and the geographic area of recruitment.

Trial and usual patient care.

Ensure that there is a link between the investigating centre and the patient's usual care centre.

If the trial site is the same as the care site, does the organisation ensure that the patient can also receive his or her usual care when moving to the centre?

Practical aspects

Costs of participating in the trial: aiming for zero out-of-pocket expenses for the patient

Reimbursement of medical expenses and other costs.

Is the principle of reimbursement of all medical expenses respected? Are there any plans to cover other costs related to missed working days or childcare?
Legally, the medical costs of the trial are covered by the sponsor. It is possible to add an appendix to the protocol for other costs covered by the sponsor. This document should be as complete as possible. For example, it may contain the conditions (and sometimes maximum amounts) for coverage of: transportation costs (in relation to the geographic area of recruitment), accommodation and meals for the patient; caregiver costs (travel, accommodation, meals); days not worked (waiting days) for the patient or family caregiver; costs related to siblings (childcare costs, possibly hospital visits); costs of locating the family near the investigating centre, etc.

Organisation to minimise fatigue and facilitate the family's organisation.

Are the necessary precautions taken to avoid unnecessary fatigue? Do they allow the patient to participate in a serene manner and to organise daily life beforehand?

The organisation should include adapted transportation (cab from the hospital to the train station, compensation for personal vehicle, etc.), nights in hotels before and after visits and in adapted rooms, and the possibility of specific meals (mixed meals, etc.). The travel and accommodation arrangements must allow the patient to undergo motor function tests at the same time of day. For example, the patient systematically arrives the day before (hotel night planned) and is thus more rested for the measurements the following morning.

Impact on family life.

Can the appointment schedule be adjusted to facilitate the family's organisation?
A provisional schedule of all visits is communicated at the screening visit (or patient selection visit) and should be discussed with the patient in light of family life (postpone a visit for reasons of vacation, school exams, etc.). It is also important for patients to understand when the last visit is.

Single point of contact for the physical organisation of the trial.

Is a single contact person planned?

The identification of a single contact person is desirable. Ideally, he/she will be able to answer questions or direct the participants to the right person, manage reimbursements, organise transportation and accommodation, meals with their specificities, etc...

It is important to ensure that at least one member of the medical team is fluent in a language spoken by the patient and his/her family.

What is planned after the study?

Protocol content: describe how patients will access post-trial treatment.

Receive treatment after the last visit.

Does the protocol provide for the patient to receive treatment after the last visit?
For example, access in an open-label trial can be arranged as soon as possible after the active phase of the trial and as soon as any risk of toxicity has been ruled out. This open-label study also provides long-term data on treatment toxicity and efficacy.

Trial following natural history.

If the study is a natural history followed by a therapeutic trial, are we aware of the conditions for linking the two?

It is desirable that patients in the natural history are given priority access to the trial if they so wish, according to the inclusion criteria.

Negative result and support.

What measures are foreseen in case of a negative result (no demonstration of efficacy and safety)?

It is possible to include in the protocol the procedure and the information conditions in case of trial failure or a major adverse event (leading to the suspension or stopping of the trial). This procedure can include the medical and psychological follow-up of the patient after the trial.

Information for patients/families and patient organisations

Patients and patient organisations: having all legally available information in understandable language

Protocol information sheet.

Is it consistent with the protocol? Is the procedure for informing minors described? In what language is it available?
It is important to ensure that the information leaflet includes the essential points of the protocol, and if necessary that the French translation is of good quality. The documents should not contain acronyms or undefined medical terms.
The document for informing a minor must be adapted to the comprehension capacities and seek the personal adherence of the minor concerned.
There must be a translated version in one of the languages that the patient can read.

Decision support for participation in the trial.

What information is given to the patient? Is the (potential) collective benefit of the trial in terms of knowledge clearly explained? Is psychological or peer support provided to help the family and the child make their choice?

In addition to the package insert, the trial should be explained to the patient in a simple verbal manner, with its benefits and potential risks, the expected benefit to the community, the practical conditions of the trial, and, if the duration of the trial is long, an explanation of the commitment required (especially if the trial is a "one-shot" trial with the possibility of a large benefit at the beginning of the trial). For trials that test different doses, the possibility of reduced benefit due to the dose received should be addressed. In paediatrics, some trials offer a simplified document to help the child understand the trial. The patient should also have the opportunity to discuss the trial with a qualified person outside the investigating team prior to inclusion.

It is vital to have expert patients involved in the development of the checklist documents

Respect for confidentiality by patients.

Is it clearly explained to the patient what he can or cannot say about the trial?

In a trial, information on efficacy or side effects is held by the sponsor; in most cases the patient is not allowed to communicate anything about his/her condition. It is preferable to clearly state the limits of the dissemination of information to the outside world (social networks, various organisations, etc.).

Information on the opening of centres.

If centres are scheduled to open gradually, will patient organisations be kept informed regularly?

Patient organisations disseminate information about the trials, which encourages inclusion. It is possible to ask the sponsor if they are assisting the centres with the administrative procedures for opening and to be kept informed of any problems.

Dissemination of information during the trial.

How will legally authorised information about the trial be disseminated?

Some information can be communicated by the trial sponsor, and it is sometimes important to be able to disseminate it widely and quickly: practical information (investigating centres, start of inclusion, end of inclusion), communication in a crisis event (major adverse event, death of a patient, etc.). For crisis communication, the participation of expert patients in the crisis unit is beneficial. It is also useful to inform the sponsor of "rumours" about the trial so that it can clarify its communication.

Information on treatment/control group membership.

Is it planned to inform patients whether they received the experimental treatment or were in the control group?

Special case of genetic screening pilot tests.

If negative results are not expected to be reported, the maximum time frame for receiving a positive result should be given to limit the stress of waiting for the result.

Feedback on the overall study results to patients.

Are there plans to communicate these results to patients? In what form and at what date?

General information in simple language to all participants as soon as (or just before) the results are published is a good practice, in addition to information delivered by the investigators. Rapid information to patient organisations in the form of a dedicated press release.

A support tool.

In their work to participate in clinical research protocols, AFM-Telethon members who promote the patient perspective will be able to rely on the objectives and points of vigilance outlined in this document.

The document helps to ask the right questions, to discuss with the different stakeholders: sponsors, investigators, experts. Different and adapted answers are to be given depending on the study and the disease.

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