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Issues in SMA clinical trial design The International Coordinating Committee (ICC) for SMA Subcommittee on SMA Clinical Trial Design

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1. Introduction

Advances in preclinical SMA research have identified several candidate treatments. Early clinical trials evaluating these medications are underway or in the planning stage.

At the NINDS Workshop on SMA in September 2004 in Washington DC, discussions started within the international SMA community to identify features that should be common to SMA clinical trials [1].

Having a set of design features and outcome measures common to clinical trials would allow for

- Comparison of data across trials.
- Establishment of a data repository with placebo group data (for planning of future trials).
- Rapid expansion to additional sites in future Phase III trials (because sites will have experience with comparable outcome measures and procedures).

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Because early clinical trials are already underway or in the planning phase (in the USA and Europe), it is important that the different groups reach consensus on a core set of data elements and design features that would be common to all SMA trials.

2. Criteria to move drugs from preclinical or animal testing into human trials

The efficacy of experimental treatments should be evaluated in animal models when possible. Drugs intended to modulate the SMN2 gene transcription or splicing should be tested in animal models carrying the human version of the SMN2 gene (including its regulatory elements). For these presumed SMN2 modulators, markers of bioactivity include full length SMN transcript or protein (Western blot and immunohistochemistry) in different tissues including the spinal cord. The pharmacokinetics need to be taken into account when planning study time points relative to drug administration. However, it is possible that drugs may improve function or increase survival without measurably increasing SMN2 mRNA or protein levels. Independent of presumed drug mechanism, the following outcomes should be considered in animal testing: survival, motor function, body weight, motor unit number estimation, and histopathological findings related to motor unit loss. While animal models can be very helpful in assessing candidates, lack of an effect in a given SMA animal model should not be used to exclude a promising candidate in the presence of other data supporting potential therapeutic benefit. An extensive clinical trials experience in other neurodegenerative diseases, including ALS, has taught us important lessons about the benefits and drawbacks of animal models in translating treatments to human trials [2].

3. Shared database for SMA clinical research

The natural history of SMA is evolving. Function and life expectancy have improved with advances in medical and, in particular, respiratory care, and the effect of these interventions is particular evident in patients at the severe end of the clinical spectrum. We have relatively limited composite data on the natural history of SMA using comparable clinical outcome measures, and more information is needed to improve the planning of SMA clinical trials. This information could be collected in a repository for data from natural history studies, clinical trial placebo groups, and data from negative clinical trials. Data collected could include longitudinal observations of motor function, pulmonary function, and muscle strength. For use in planning or conducting clinical trials, it is most helpful if relevant data are systematically collected by well-trained personnel using standardized procedures (e.g. comparable outcomes, measurement procedures, visit intervals, and observation period).

The FDA has published suggested data elements for clinical datasets [3]. For potential data use in the regulatory approval process, detailed safety data are needed in addition to outcome data. These data should best be coded using one of the standard coding schemes (e.g., CTCAE [4]). Establishing a data warehouse will require funding for data management and statistical support, a steering committee that can oversee criteria for submission of data to the data warehouse and the dissemination of the data to SMA investigators. A data warehouse for SMA could be established independently or linked to an already existing database.

4. Biomaterial and cell line banking

If there were centralized biomaterial repositories, investigators could submit samples of SMA patients (collected from clinical trials placebo and treated groups). These samples would be useful to discover and to validate new biomarkers of disease progression, investigate modifying genes, study pharmacogenomic aspects, and to address future research

questions. Multi-center studies will likely require more than one repository given limitations in shipping samples, especially for protein assays and cell cultures. It will be important to have uniform specimen collection and processing as well as standardized assays between sites. Also, any tissue and cell repository would be enhanced if it was based on a phenotypically well described patient group and if the samples could be linked to a database of uniformly collected clinical information.

The investigation of tissue samples from autopsies might help progress in laboratory research. Even though this is a sensitive subject, it might be in the interest of the SMA community to consider asking research participants for post-mortem donations. This would allow research investigations that cannot be performed in blood samples alone (e.g., histological study of motor units in the spinal cord).

5. Placebo controlled trials

The evaluation of new treatments for safety and efficacy requires prospective randomized, placebocontrolled clinical trials. Placebo controlled, double- blind trials can reduce bias when efficacy is studied. Open label designs can falsely suggest efficacy and fail to uncover harmful effects. Placebo controlled trials are considered ethical when there is no standard treatment better than placebo, and when participants are informed about the use of a placebo [5]. In Amyotrophic Lateral Sclerosis, a severe and progressive motor neuron disease mainly affecting adults, placebo controlled trials have been feasible and have resulted in drug approval [6–8]. The FDA Division for Neurological Drug Products has not approved a new drug without a controlled trial.

6. Collaboration between patient advocates and researchers during planning and implementation of clinical trials

Successful clinical trials require timely recruitment. A scientifically well designed trial is not feasible if patients are reluctant to enroll. SMA researchers and families have the same goal: finding an effective treatment for SMA as soon as possible. This goal could be achieved sooner if most patients with SMA participated in clinical trials. Patient advocacy groups can help investigators design trials that are likely acceptable to patients. Researchers and patient advocates can work together in educating patients on the necessity of clinical trials. Education may occur by word of mouth, publications and websites, or during support groups or family meetings. The following should be considered when planning trials and communicating with families:

- Centers participating in clinical trials will strive to provide expert care for SMA patients.
- Careful safety monitoring during a clinical trial helps to protect participants from possible adverse effects of new treatments.
- Other disease communities (e.g., AIDS, pediatric oncology, ALS) have found successful treatments by endorsing placebo-controlled clinical trials (after some initial resistance).
- There are multiple examples of new treatments that were actually found to be harmful in clinical trials. Many more patients might have been exposed if these harmful effects had not been identified in clinical trials [9,10].
- Physicians choose participation in clinical trials when they are in the patient role [11].

7. Recruitment and retention

Recruitment and retention in clinical trials may be facilitated by increasing the number of patients receiving active treatment (for example, 2:1 randomization). Trial designs that include interim analyses with the intent to make a new treatment available to all, if effective, as early as possible may enhance recruitment and retention. Similarly, trial designs that would uncover futility as early as possible would likely be more acceptable to families because they would minimize the exposure time to treatments deemed not effective.

To facilitate recruitment and retention, the visit schedule and study duration have to be acceptable to families. The tests planned for each visit cannot be too taxing for the participant.

8. Trial design issues in SMA

For new compounds with limited data on use in humans the drug regulatory agencies require Phase I testing. For compounds approved for indications other than SMA, limited Phase I testing may also be needed to determine the dose, pharmacokinetics and preliminary safety in the targeted population. Trial designs are typically dose escalation studies using fixed cohort size or adaptive designs [12–14] (e.g., continual-reassessment designs), and/or pharmacokinetic studies.

Phase II studies, usually examine one or multiple dosages in terms of safety, tolerability, and preliminary drug activity prior to exposing a larger number of patients to the new treatment in Phase III. Also, given the finite number of patients in a relatively rare disease such as SMA, and given the limited resources, Phase II trials can help in selecting the most promising candidate among multiple drugs for a future Phase III trial.

Phase II studies can include ranking and selection methods. Other than in formal hypothesis tests, in selection and ranking procedures the interest is not in guarding against commission of a type I error under the assumption of equal efficacy; rather, interest resides in making a required selection between drugs to move forward to efficacy testing [15]. These are typically more efficient in terms of sample size than hypothesis testing. Ranking and selection procedures are strategically important at a time when multiple treatments that have shown promise *in vivo* are awaiting clinical testing.

Other trial designs that can increase the efficiency of Phase II trials include non-superiority or futility studies [16]. Here, the error of declaring a new drug as ineffective is controlled by reversing the null and alternative hypotheses compared to a conventional Phase III design. The sample size can thus be relatively smaller compared to a conventional Phase III trial.

Two- or multi-stage designs allow for analysis at different stages of the trial and thus for early termination if the treatment appears ineffective. Generally, they would not allow early termination for efficacy [17,18]. They can increase efficiency in Phase II drug development because they may result in declaring futility at an earlier point during the trial when fewer patients have been exposed.

Information gained from exposure of patients in Phase II studies may not always be optimally used when drug development follows the discrete steps of conventional Phase II and Phase III trials. Treatment is discontinued at the end of the Phase II follow-up period so that the opportunity to obtain longer-term exposure data is lost. In addition, there is typically a time lapse of several months between a completed Phase II trial and start-up of the subsequent Phase III trial due to funding, regulatory and other issues. Adaptive, seamless designs can reduce delays and increase efficiency in time as well as sample size. These are

designs that allow participants to seamlessly roll over into the next phase of the trial, for example from a preliminary Phase II efficacy test into a Phase III trial. However, seamless Phase II/III trials are often logistically complex. Also, regulatory approval may be easier when a trial is planned in two separate steps with data from phase II available by the time of phase III approval. Conducting efficacy trials in a rare disease is challenging. However, there is precedent for relatively small efficacy trials leading to regulatory approval in orphan diseases (e.g., alpha glucosidase in Pompe disease [19]).

Phase III studies evaluating efficacy and longer-term safety are needed before a medication is approved and recommended for the treatment of SMA patients. Phase III studies test the null hypothesis that the new treatment and placebo are equal, controlling the error of falsely declaring a new drug efficacious. Phase III studies are typically large and will require a multi-center and possibly international effort.

Phase III trials should be randomized, double-blind, and placebo-controlled, and all should require the primary statistical analysis to be performed according to the intention-to-treat principle. An unbalanced randomization scheme (2:1 active to placebo) can be considered to facilitate recruitment. In trials with a reasonably short follow-up period, or a time-to-event outcome, group sequential or fully sequential designs can similarly be more efficient than designs requiring a fixed sample size. Sequential designs aim to limit the number of subjects in a trial once there is sufficient evidence of superiority or futility and have been used in motor neuron disease trials [20,21]. Cross-over designs can increase efficiency in Phase III but have several limitations including the possibilities of a non-linear disease course, or carry-over of drug effects. Factorial designs can increase the proportion of subjects randomized to one of the active treatments and accelerate the testing of more than one experimental compound.

9. Study population

To be inclusive, individuals across the spectrum of disease severity and age should be offered clinical trials participation when possible. Studies involving patients with Type 1, Type 2 or Type 3 SMA can be carried out in parallel. However, different trial designs may be necessary for each of these different entities.

Inclusion criteria should be simple and allow as broad a patient group as possible to participate while maintaining the trial's scientific integrity. Complicated and overly restrictive criteria can impede recruitment. The inclusion criteria define the age range and disease stage of the targeted population and will depend on the age range for which the outcome measures can be reliably administered, and on the presumed mechanism and safety profile of the study intervention.

The SMA phenotypes are primarily clinically defined based on the highest motor function *ever* achieved (i.e. never sat = Type 1, ever sat = Type 2, ever walked = Type 3). SMN2 copy number may be used to determine inclusion based on the association between clinical phenotype and SMN2 copy number. However, this association is not perfect. If SMN2 copy number is needed as inclusion criterion (such as in young SMA 1 patients), copy number assays have to be available reliably and with reasonable short turnaround time. Exclusion criteria should be carefully considered and justified by patient safety considerations. Patient advocates ask that we exclude as few patients as possible from the opportunity of participating in a clinical trial. For example, one should carefully consider excluding SMA 2 patients who had spinal fusion surgery in the past, even if the surgery limits the performance range on motor function measures.

Medical care, including nutritional and respiratory interventions, influences prognosis and should be standardized when possible. Uniform standards of care would be expected to reduce variability between subjects and thus possibly reduce the sample size required for studies. However, cultural circumstances and parent choices have impact on management and prognosis and cannot be equalized. The likelihood that differences in care between sites will affect results of a randomized trial can be minimized when randomization is stratified by site. Also, a trial that does not attempt to strictly "regulate" standard of care is closer to the reality of SMA patients, more feasible and will have results that are more applicable to the general SMA population. Any intervention or treatment that is medically indicated during the follow-up period should not be prevented by the patient's clinical trial participation.

10. Phase III trial design issues for SMA Type 1

10.1. Study population

A fairly wide clinical spectrum is included under Type 1 (sometimes termed Types 1a, b, c), with differences in age at onset and prognosis, although the neonatal onset (1a) and the mildest form (1c, closer to Type II SMA) are less common than the typical SMA Type I (1b). A decimal classification ranging from SMA 1.0 to 1.9 has been suggested for SMA1, and, similarly, for the milder SMA variants [22]. The SMA Type 1 study population may need to be further defined or stratified, for example by age at onset and/or SMN2 copy number. While inclusiveness is important, it is currently difficult to design a trial targeting the most severe end of the clinical spectrum, in particular neonatal onset SMA. If universal newborn screening for SMA was instituted, then clinical trials for the most severely affected type 1 patients as well as pre-symptomatic treatment for other patients could be considered.

10.2. Outcome measures

10.2.1. Primary outcome measures—Survival time (from randomization) or the time to an equivalent respiratory outcome is a possible primary endpoint for an SMA type 1 clinical trial. The definition of respiratory insufficiency that would be equivalent to a survival endpoint requires agreement on a specific definition. Respiratory insufficiency is generally defined as the inability to maintain adequate alveolar ventilation and gas exchange. SMA patients typically present with an acute deterioration of underlying chronic respiratory compromise (respiratory muscle weakness, ventilatory restriction, insufficient cough). Factors other than disease progression may influence the time point when respiratory insufficiency occurs (e.g., seasonal differences in the incidence of respiratory infections, use of preventative measures such as influenza vaccine and RSV prophylaxis). To account for acute, temporary worsening in the setting of infection, a respiratory insufficiency endpoint could be further described by its persistence. However, including persistence in the definition of an endpoint can introduce uncertainty and needs waiting time before the outcome can be ascertained.

In clinical trials for Amyotrophic Lateral Sclerosis (ALS), investigators have chosen as respiratory endpoint the time when more than 18 hours of mechanical ventilation were needed. When considering a similar endpoint for SMA, it will have to be defined such that a sufficient proportion of the study population reaches the endpoint during the trial period. Also, respiratory status and interventions are influenced by the pulmonary care provided with practices varying between sites, including the use of partial diurnal ventilatory support.

In addition to chronic diurnal respiratory insufficiency, symptomatic nocturnal hypoventilation should be considered [23]. This is important because the use of non-invasive

nocturnal ventilation in patients with chronic nocturnal hypoventilation may delay the onset of diurnal respiratory failure.

The definition of a respiratory endpoint has to carefully balance the need to have a clinical trial endpoint that can be reliably and feasibly ascertained against the need to have a clinically meaningful pulmonary measure. The specific definition will depend on the study population targeted in a given trial.

10.2.2. Secondary outcome measures—Possible secondary outcome measures are respiratory measures, motor function measures, electrophysiological measures (including motor unit number estimation – MUNE), and biological markers of SMN gene expression.

Establishing reliable infant *motor function measures* for SMA 1 is complex because the measures have to account for developmental maturation, the level of cooperation and other confounding factors.

Pulmonary function testing in infants and young children is limited by their inability to fully cooperate. Pulse oxymetry and end-tidal carbon dioxide measurements are feasible and reproducible in young children and reflect the effectiveness of alveolar ventilation. Respiratory outcomes can include the frequency of respiratory infections with hospital admission and/or hypoxemia, the presence of daytime hypercapnia, or presence of nocturnal hypoventilation (for example, mean, nadir, and percent of sleep time with oxygen saturations below 90% and/or mean, maximum, and percent of sleep time with carbon dioxide tensions above 50 mmHg).

Motor unit number estimation (MUNE) is a quantitative assessment of the number of functional motor units and thus relevant to the disease process underlying SMA. It is feasible in infants and children with SMA, correlates with the clinical severity, and can demonstrate a decline in motor units before clinical symptoms or signs emerge [24–26].

Biological outcome measures might include the level of full length SMN transcript or protein and should be evaluated prior to the first dose and at different intervals relative from the dose (interval depends on the pharmacokinetics of the study drug). Additional biological measures that have been proposed by laboratory researchers (e.g., 3-2 snRNP assembly in leukocytes) or other future biomarkers might be included in a trial. This will allow comparing the sensitivity of new tests with more established methods (such as western blotting). The ideal biomarker would be one that can be reliably measured in a blood sample of reasonably small volume, that is sensitive to change, and that reflects biological activity in the spinal cord.

10.3. Duration of follow-up period and frequency of visits

The duration for a study in Type 1 SMA will depend on the event rates. However, any placebo controlled study of long duration may not be easily acceptable to families. The visit schedule has to be acceptable to families and the evaluations at a given visit have to be planned with consideration to patient and family burden.

11. Trial design issues for SMA Types 2 and 3

11.1. Study population

Inclusion criteria require a specific clinical definition for the SMA phenotype (SMA Type 2 may be defined by the subject’s ability to ever have sat independently for at least 30 s when placed. SMA Type 3 may be defined by the subject’s ability to ever walk 4 steps unassisted).As with type I, type III can be divided into IIIa (diagnosed by age 3 years) and

IIIb (diagnosed over age 3 years). These groups have been shown to have different natural history as to age when independent ambulation is lost.

One or more of these phenotypic groups may be included in a given trial. Additional age limitations to the study population will likely be determined by choice of outcome measure (for example, some motor function measures may require a minimum age of 30 months, and most respiratory measures or muscle strength measures may require a minimum age of 5 years).

11.2. Outcome measures

The *primary outcome* may be the change from baseline to end-of-study in a motor function measure, respiratory measure, strength measure or other functional measure. Given that most patients are in a phase of relative clinical stability at the time of trial entry, studies will likely be designed to demonstrate improved muscle strength or function rather than slowing of disease progression [27]. However, disease progression may be noted over longer observation periods [28].

Motor function measures used in SMA include the Gross Motor Function Measure (GMFM), a non-disease specific measure. It has been validated in SMA [29,30], but can take more than 30 minutes to be completed. The Hammersmith motor function scale for SMA is an alternative motor function measure and is disease specific [31,32]. The Hammersmith measure is shorter and easier to administer, but may be limited to a moderate phenotype within the SMA Type 2 spectrum due to floor and ceiling effects. The MFM motor function scale has been developed to assess motor function in several neuromuscular diseases including SMA [33,34]. Spinal fusion can influence motor function scores as it interferes with some tasks, e. g. rolling.

Possible respiratory measures include spirometry (FVC, FEV1), peak inspiratory pressures, and peak cough flow. Nocturnal oxygen saturation and end-tidal carbon dioxide tensions can be studied.

Possible motor strength measures include manual muscle testing, myometry using a handheld dynamometer, or quantitative muscle testing using a fixed system [30].

The *secondary* outcomes may include additional functional measures not considered as primary outcome as well as MUNE, DXA or biological outcome measures (see above).

Quality of life and caregiver burden measures should be included among the secondary outcomes. General QoL measures have been used in SMA, e.g., PedsQoL [30]. Disease-specific QoL measures are under development [35].

11.3. Duration of follow-up period and frequency of visits

Generally, an SMA trial should be as short as possible. For SMA Type 2 or 3 trials it seems less likely that a meaningful change in motor function could be observed over a 3 month period than for example over a 9–12 month period. Also, a somewhat longer duration of follow-up than for SMA Type 1 trials may be acceptable given the more benign phenotype. However, any study duration of greater than 12 months may likely be less acceptable to families.

The duration for a study of Type 2 SMA will depend on the outcome measure, the anticipated mechanism of action of the study medication, and the magnitude and time course of the expected effect. The visit schedule has to be acceptable to families and the evaluations at a given visit have to be planned with consideration to patient and family burden.

12. Summary/Conclusion

Several compounds are currently available for SMA clinical testing and more are expected to move along the “pipeline” of SMA drug development. To evaluate these new treatments in a timely fashion, the following issues should be considered when designing clinical trials:

Researchers and patient advocates should collaborate starting in the planning stages of a clinical trial to design studies that will be acceptable and supported by families. More education of physicians, patients and families is needed regarding the benefits of participating in a randomized controlled clinical trial and the virtues of randomization, blinding, and appropriate controls. These steps will enhance recruitment and support for research in the SMA community.

As many SMA patients as possible should have access to clinical trials to expedite evaluation of new treatments. Trials should target a broad spectrum of the SMA population and minimize patient exclusion, as long as this does not threaten the scientific integrity of the trial. In a relatively rare disease with a limited number of possible trial participants, clinical trials that can collect data of sufficient quality while being performed outside of major academic medical centers would allow patients from a larger geographic area to participate.

Study groups should aim for consensus on a minimum core set of common design features and outcome measures so that data can be compared between trials. This would likely facilitate the expansion to additional sites as needed in future Phase III trials. Data from completed trials could be submitted to a data warehouse and be made available to investigators for meta-analyses and for the planning of clinical trials.

All Phase III trials should be randomized, double-blind, and placebo-controlled, and all should require the primary statistical analysis to be performed according to the intention to treat principle.

Given that there are a number of potential treatments for SMA based on *in vitro* studies, and given the relative rarity of the disease and thus the limited patient pool, efficiency and investigator collaboration are key in SMA clinical trials.

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