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REVIEW

Designing Clinical Trials for Dystonia

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Abstract With advances in the understanding of the pathophysiology of dystonia, novel therapeutics are being developed. Such therapies will require clinical investigation ranging from exploratory studies to examine safety, tolerability, dosage selection, and preliminary efficacy to confirmatory studies to evaluate efficacy definitively. As dystonia is a rare and complex disorder with clinical and etiological heterogeneity, clinical trials will require careful consideration of the trial design, including enrollment criteria, concomitant medication use, and outcome measures. Given the complexities of designing and implementing efficient clinical trials, it is important for clinicians and statisticians to collaborate closely throughout the clinical development process and that each has a basic understanding of both the clinical and statistical issues that must be addressed. To facilitate designing appropriate clinical trials in this field, we review important general clinical trial and regulatory principles, and discuss the critical components of trials with an emphasis on considerations specific to dystonia. Additionally, we discuss designs used in early exploratory, late exploratory, and confirmatory phases, including adaptive designs.

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Background

Botulinum toxins and surgical interventions, such as deep brain stimulation, have revolutionized the treatment of dystonia. Despite the effectiveness of these approaches in some patients, there remains a significant need to develop novel therapies. Botulinum toxin injections must be repeated every few months, are best suited for those with focal or segmental dystonias, and not all patients respond or maintain responsiveness, which may contribute to inadequate patient satisfaction [1, 2]. While surgical approaches can be quite effective for generalized and refractory segmental dystonias [3, 4], patient selection criteria are not well established, the benefit may be incomplete, the durability is not fully characterized, and there are inherent risks [5].

With advances in the understanding of the pathophysiology and etiology of dystonia, small-molecule therapies are being developed. Novel treatments may arise from optimization of currently available compounds, identification of drugs through screening, or development of approaches targeted at the underlying pathophysiology [6]. Such agents may be new molecular entities not yet studied in humans or drugs developed for the treatment of other disorders. Well-designed exploratory (learning phase) and confirmatory (efficacy) trials will be necessary to efficiently and rigorously evaluate the safety, tolerability, and efficacy of these agents in patients with dystonia.

To aid in planning trials, we discuss general principles of clinical trials, as well as special considerations for dystonia given its low prevalence, clinical heterogeneity, and currently available therapies. In addition, we review potential exploratory and confirmatory trial designs, including adaptive designs.

Clinical Characteristics of Dystonia and Associated Challenges

Dystonia encompasses a spectrum of complex and variable movements and postures, the distribution of which may be focal, segmental, or generalized, and the cause of which may be idiopathic, genetic, or acquired [7, 8]. Phenomenologically, the disorder classically is defined as "a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures" [9]. The movements may be brief, repetitive, irregular, or rhythmic, and the postures can be tonic and fixed or intermittent, prompting a refinement of the definition to capture these features [10]. In addition to the motor manifestations, nonmotor symptoms, including psychiatric, cognitive, and sensory abnormalities, are increasingly recognized as part of the clinical spectrum [11, 12]. Moreover, the clinical course is highly variable with respect to severity, as well as extent and time course of spread.

How can this clinical and etiological heterogeneity be addressed when designing clinical trials? It has been suggested that several forms of dystonia may have shared etiologies [13–15] and therefore may respond to the same therapeutic intervention. Although the primary cause for the signs and symptoms of dystonia may differ, there are several reasons to suspect a common underlying process [6]. Thus, treatments aimed at downstream targets might prove effective across multiple etiologies and allow for broader subject inclusion based on phenotype rather than etiology.

Such a phenotypic, nonmechanism-based approach is most applicable to evaluating a treatment that improves the symptoms of dystonia. Dystonia spreads in a significant portion of patients [16–18] suggesting that slowing or halting clinical progression may be of interest; however, developing such a disease-modifying therapy will probably require a better understanding of the disease mechanism. A trial aimed at slowing disease progression would require long-term evaluations and outcomes, or a validated, short-term surrogate outcome, which is currently lacking for dystonia. There is a relative paucity of natural history data for dystonia, and such data would provide valuable information regarding the rates of change of particular outcomes in the population of interest and help inform the necessary size and duration of the trials. For example, natural history studies may permit the identification of subtypes with distinct clinical courses; if factors influencing a more rapid clinical progression could be identified, then subject subtypes could be selected to "enrich" a study population [19]. Until such data are available, it is likely trials will evaluate symptomatic, rather than disease-modifying, agents.

Potential Sources of Novel Dystonia Drugs

Oral agents are often prescribed for the treatment of dystonia, including anticholinergics, benzodiazepines, drugs interacting with dopaminergic signaling, and "muscle relaxants" [20]. However, their use is rooted in decades-old empirical observations, none is approved by the US Food and Drug Administration or European regulatory agencies for the treatment of dystonia, and only one agent has been evaluated in a double-blind, placebo-controlled trial [21]. No new oral agents have been identified in decades; however, advances in understanding the pathogenesis of dystonia have led to several promising strategies for drug discovery and development.

One strategy is to improve on existing therapies. For example, anticholinergics seem to be effective in many different types of dystonia, both genetic and acquired. However, high dosages often are required and their use is limited by side effects. The significant advances in our understanding of the

role of cholinergic receptors in movement disorders, and specifically the identification of 5 distinct muscarinic receptors, has led to efforts to engineer subtype-selective agents that are more effective with fewer side effects [22]. Another strategy for identifying novel drugs for dystonia involves screening drugs in animal models of dystonia. A high-throughput screen conducted in a *Caenorhabditis elegans* model of DYT1 dystonia has revealed potential agents for further study, such as ampicillin [23]. Other promising agents have been identified through pharmacological studies of rodent models of dystonia, including the dystonic dt^{sz} hamster and *tottering* mouse models [6, 24]. Whether or not these agents are effective for patients with dystonia remains to be determined. A third strategy that has led to specific targets for therapeutic trials has come from studies of drugs that suppress levodopa-induced dyskinesias in Parkinson's disease or its animal models. Dyskinesias sometimes have a dystonic quality, and negative allosteric modulators of metabotropic glutamate receptor mGluR5 appear to specifically suppress dystonic dyskinesias in animal models [25, 26]. These observations raise the intriguing possibility that this category of drugs may suppress dystonia in other disorders, but further studies are needed.

General Prerequisites for Clinical Trials

When initiating clinical trials, it is important to carefully consider regulatory requirements, features of the investigational agent, and the primary study objective.

Regulatory Considerations

The regulatory requirements to proceed with a clinical trial depend, in part, upon the nature of the drug, the phase of the investigation, and the study proposed. Nonclinical pharmacology studies ranging from in vitro receptor-binding screens and functional assays to in vivo efficacy models may be useful to provide the rationale for a novel intervention [27–29]. Safety pharmacology and pharmacokinetic studies will be required, including studies that address absorption, distribution, metabolism, and excretion, as well as genetic toxicology and animal toxicology in 2 species for a duration similar to or longer than the planned human exposure. For trials evaluating a marketed product for a new indication, additional nonclinical studies may not be needed if the proposed trials are to be conducted at the same dosage, same duration, and via the same route as for the approved indication; otherwise, discussions with regulatory agencies will be important.

Additional studies may be required when conducting trials in pediatric populations [30]. Toxicology studies in juvenile animals may be necessary, and clinical safety assessments may need to evaluate effects on growth and development. It cannot be assumed that the dosage and the outcome measures appropriate for adults will be appropriate for a pediatric population.

Characteristics of the Intervention

There are certain properties of the drug itself that should be established in order to maximize the likelihood of successful development. Does the intervention reach the compartment of interest (e.g., cross the blood–brain barrier for a centrally-acting agent) and engage the intended target? Is the concentration sufficient to be biologically active? Target engagement should be demonstrated, if possible, and a downstream biologic impact should be measurable. If possible, a pharmacodynamic marker of target engagement should be included in any human study. It is important to determine the dosage necessary to achieve such effects, as well as any associated toxicity. Ideally, there also would be an endpoint, such as a blood test or other biomarker, that could be observed early and predict a long-term clinical response to allow for smaller and shorter duration studies. Yet, as for the majority of neurological disorders, no such biomarkers have been established for dystonia. Still, biomarkers of drug activity, as opposed to biomarkers of disease/clinical progression, could be very useful in identifying appropriate dosages for clinical trials.

Trial Objectives

It is critical to define a focused research question, prioritize the outcomes, and ensure that the study design will answer the question of interest. The objectives for an exploratory study are generally focused on assessing bioavailability, metabolism, target engagement, safety and tolerability, and dosage selection. In early-phase exploratory studies, the primary aim is often identifying the maximum tolerated dosage (MTD). While identifying a signal of efficacy may be an objective in a later-stage exploratory trial, demonstrating efficacy generally is not feasible as the treatment effects observed with small sample sizes are imprecise. The objective of a confirmatory study is to evaluate efficacy definitively and to obtain additional data regarding safety and tolerability. There are many key components of clinical trials that affect the design and implementation, and the specific considerations may differ between the exploratory and confirmatory phases (Table 1). Furthermore, there are a number of trial designs that can be employed at different stages of therapeutic development to achieve the trial objectives (Table 2).

Considerations for Early- and Late-stage Exploratory Studies

As many confirmatory studies fail because of the lack of adequate exploratory studies, well-designed learning-phase

Table 1 Considerations for designing clinical trials

Objective	**Exploratory**	**Confirmatory**
	• Safety and tolerability	• Primary aim: efficacy
	• Dosage selection	• Secondary aims:
	• Preliminary efficacy	◦ safety
		◦ exploratory outcome measures
Subject population	• Inclusion criteria	
	• Exclusion criteria	
Trial design	• Treatment	
	◦ Dosing	
	◦ Duration	
	• Concomitant medications	
	• Blinding	
	◦ Drug	
	◦ Assessment and adjudication of endpoints	
	• Treatment assignment	
	◦ Treatment arms (e.g., single-arm, parallel groups, crossover)	
	▪ Should there be a control group? If so, what should it be?	
	◦ Randomization: Is it needed and what should the allocation ratio be?	
	• Primary outcome measure	
	• Secondary outcome measures	
	• Stopping rules: What are the safety concerns? What is tolerability?	
	◦ Stopping study drug in an individual subject	
	◦ Stopping the study	
Statistical considerations	• Number of subjects (feasibility); sample size justification	
	• Interim analysis plan	
	• Final analysis plan	

studies are critical. When considering a trial for a novel agent in dystonia, it will be helpful to identify what questions remain to be answered prior to initiating a confirmatory study and then to design the exploratory study to obtain this information (Table 1).

Objective

Demonstrating target engagement, determining the optimal dosing regimen, and showing proof of concept are often the primary objectives of exploratory studies. Exploratory studies also provide information about feasibility, including compliance, route of administration, delivery, cost, recruitment, and retention. First-in-human studies for a new molecular entity follow a general prescribed path of safety and pharmacokinetic evaluations [27–29]. However, the dosage of an agent that has been shown to be tolerated or efficacious in one disorder may not be the dosage to evaluate in dystonia as toxicity profiles and efficacious dosages may differ between disorders.

Table 2 Examples of trial designs

Phase	Objective	Outcomes	Design options*
Exploratory	Dose finding	Pharmacokinetics	Rule-based (e.g., 3+3)
		Adverse events	Model-based
	Safety	Adverse events	Single-arm, single-stage
	Tolerability	Compliance	2-stage with interim analysis
	Preliminary efficacy	Biologic activity	Futility
		Clinical efficacy	Selection
Confirmatory	Definitive efficacy	Clinical efficacy	Parallel group
	Safety	Adverse events	Factorial
	Tolerability	Compliance	Crossover

*See text for details.

Thus, it is important to conduct exploratory studies to ensure that the appropriate dosage is identified. While activity and efficacy outcomes might be included, such exploratory studies are not designed to draw conclusions regarding efficacy, but rather to inform a go/no-go decision as to whether a confirmatory trial should be undertaken.

Early exploratory trials are often focused on "dose finding" to establish a dosage or range of dosages with reasonable short-term safety to move forward to a later-phase study. This stage may involve estimation of pharmacokinetic parameters, assessment of tolerability and feasibility, or quantification of the toxicity profile, and the primary objective typically is to identify the MTD. Late-stage exploratory trials have several potential objectives. Most often, a major objective is to assess safety and tolerability in a moderate-sized cohort of affected individuals. One also may be interested in looking for "proof of concept" that the drug has its intended biological action and thus potential for efficacy.

Subject Population

When defining the eligibility criteria, the potential effect on the generalizability of the results should be kept in mind. The ability to recruit subject rapidly and to have generalizable results must be balanced with the desire to include only those deemed most likely to respond. Should subjects with different forms or etiologies of dystonia be included in order to facilitate enrollment and subsequent generalizability of the results, or would a more homogenous group of subjects be likely to yield a clearer answer? In the exploratory phase, it may be feasible to apply more restrictive eligibility criteria as the sample size will not be large. However, allowing enrollment of a diverse group may permit the identification of a responsive subset.

Trial Design Features

In exploratory trials, the dose–toxicity relationships are commonly investigated to identify the dosing regimen and treatment duration for later study. Typically, the assumption is made that the largest dosage that can be safely administered is the dosage to use in subsequent studies, and thus the primary aim of early exploratory studies is often to identify the MTD or a range of dosages to investigate further. It is important that such studies be carried out in dystonia subjects rather than assuming the dosage employed in other indications is optimal for dystonia.

The use of concomitant medications is particularly relevant to studies in dystonia given the wide use and effectiveness of botulinum toxins and the availability of other treatments of more modest benefit. Should oral medications and/or botulinum toxin be withheld during the course of the trial or should the novel therapeutic be evaluated as add-on therapy? Should enrollment be limited to those who do not respond to botulinum toxin, or would restriction to a treatment-resistant population not yield generalizable results? For a short-duration study, should subjects be evaluated during the time period when the effect of botulinum toxin is maximal and relatively stable, or would the benefits of botulinum toxin be so great as to mask additional benefit achieved by the add-on agent? Alternatively, should subjects be evaluated after the effects of botulinum toxin have begun to wear off, or would the negative consequences of wearing off confound the measurement of possible benefits of the new therapy?

Depending upon the study objectives, inclusion of a control arm, blinding, and randomization may be appropriate. For many types of exploratory trials, all subjects receive the active treatment and no control arm is employed. Yet, particularly when efficacy outcomes are being assessed, blinding of treatment assignment, assessments, and adjudication of endpoints is critical to minimize bias and control for factors that could influence outcomes. If there is more than one treatment arm, should there be a control group? If there is a control group, is a historical control acceptable, could subjects serve as their own control, or should there be a concurrent placebo arm? Are subjects to be randomized, and, if so, what is the randomization ratio? While a greater than 1:1 randomization to the treatment arm may enhance recruitment, with a fixed sample size, such an allocation will reduce the power of the study.

The primary outcome of an exploratory study is often based on safety and tolerability. For example, the objective of the study may be to determine the highest dosage tolerated by at least two-thirds of the subjects. Secondary outcome measures could include efficacy outcome measures such as clinical scales or potential biomarkers.

It is useful to prespecify stopping rules for both the investigational agent in an individual subject and for the study as a whole. What outcomes would indicate that the drug is not safe or tolerable in a subject? Are there interim safety/tolerability thresholds that would dictate that no more subjects should be enrolled?

Statistical Considerations

A common misperception is that exploratory studies can be based on an arbitrary, small number of subjects. However, any clinical trial must be adequately designed to achieve its primary objective. For example, when conducting an exploratory study based on safety and tolerability, the sample size might be calculated based on the number of subjects needed to achieve 90 % confidence that a particular dosage will be tolerated by at least two-thirds of the subjects.

Designs for Early Exploratory Clinical Trials

As discussed above, the primary objective of early exploratory studies is to identify the MTD (Table 2). There are 2 types of

dose-finding designs: rule-based and model-based. Both use the occurrence of some predefined dose-limiting toxicity (DLT) as the outcome variable of interest. However, the two approaches differ in how the MTD is defined based on the occurrence of a DLT. Rule-based approaches require prespecification of the dosage levels to be evaluated, escalation and de-escalation rules, and study stopping rules. Model-based methods do not require prespecifying dosage levels, but assume a functional form for the dose–toxicity relationship. After initial specification of a dose–toxicity curve, the curve is adjusted as data are accrued and used to determine dosage escalation or de-escalation.

The most common rule-based design is the 3+3 design, a type of "up-and-down" design widely used in cancer trials where the objective is to identify a dosage with a DLT rate slightly below 33 % [31]. While there is no standard trial design for this purpose in neurological disorders, the 3+3 design, or one of its variants, can be utilized. With this approach, a starting dosage is selected and administered to three subjects. The dosage employed in subsequent cohorts is the next highest or lowest dosage depending upon the outcomes at the current dosage and simple decision rules. For example, a particular dosage of the drug is administered to 3 subjects; if no DLTs are observed, then the next highest dosage is given to a subsequent cohort of 3 subjects. If one DLT occurs, another cohort of 3 is administered that same dosage. If 2 or more of the 6 total subjects at this dosage experience a DLT, then the dosage must be decreased for the next cohort. Dosage escalation continues until at least 2 subjects in a dosage cohort experience a DLT; the previous dosage level is then deemed the MTD and is employed in subsequent studies. The 3+3 design may be inefficient as it requires prespecification of the dosage levels to explore and it tends to underestimate the true MTD [32]. Furthermore, the decision rules do not use all the available data to guide dosage changes. However, this approach is simple to implement and does not require specialized statistical software. In the 3+3 design, the assumption is made that a 33 % DLT rate is unacceptable; if the acceptable DLT rate is lower than 33 %, different decision rules can be applied [33].

The continual reassessment method (CRM) is a more sophisticated and efficient model-based approach to finding the MTD [34]. As in the 3+3 design, DLTs and study stopping rules based on target toxicity rates are predefined. Typically, a dosage range is decided upon, and an initial hypothesized dose–toxicity curve is developed based upon preclinical data, experience with similar compounds, or experience with the agent in another disorder. As data on DLTs are accrued, the curve is re-estimated and a statistical algorithm determines what dosage the next cohort of subjects should receive. The next cohort is then treated at the current estimate of the MTD, or the dosage closest to the current estimate of the MTD, and the process is repeated until a prespecified stopping rule or sample size is reached. While model-based designs are comparatively complex and require more statistical input, they introduce efficiencies by utilizing all cumulative data, and the MTD is typically identified more accurately than in the 3+3 design. With the original CRM, there were concerns about the potential to expose subjects to high and potentially toxic dosages as a result of making too large of a dosage change based on outcomes observed in a small number of subjects. A number of modifications have thus been proposed, including choosing a low starting dosage, using small incremental increases in dosages until a DLT has been observed, and treating a small cohort of subjects, rather than a single subject, at each dosage. Other similar approaches include escalation with overdose control [35] and the time-to-event CRM [36].

Designs for Late Exploratory Clinical Trial Designs

There are several designs to assess activity and preliminary efficacy in addition to safety and tolerability in the late exploratory stage (Table 2). A single-arm, single-stage study can treat all subjects with active drug to determine if there is any signal of efficacy. Response rates with treatment greater than an expected response rate based on a historical control would suggest the agent might be efficacious. Yet, in the setting of unblinded, uncontrolled observation, a placebo effect and evaluation bias cannot be excluded. Another approach is Simon's 2-stage design [37] where interim data are analyzed and the study stopped early and the drug deemed ineffective if fewer than a prespecified number of responses (or number of subjects with a prespecified level of improvement on an outcome measure) is observed; if the prespecified number of responses is observed, then additional subjects are enrolled in the second stage of the study. Preliminary evidence of efficacy is then assessed through the proportion of positive responses over the 2 stages of the study. This design also suffers from a lack of blinding and absence of a concurrent control group, although a randomized control group can be included [37]. Another design, which has recently been utilized in trials for neurodegenerative diseases, is the futility design [38–42]. The objective of a trial with a futility design is not to demonstrate that an intervention is efficacious, but rather to demonstrate that it is futile and not worth further study. If the intervention does not achieve a specified minimum level of benefit, the agent is deemed futile. The basis of comparison could be a historical control group or a concurrent control arm. If a historical control group is utilized, it is important to ensure that these data are still applicable and that potentially confounding factors, such as diagnostic criteria, treatment, and evaluation methods, are comparable in the two sources of data [40].

If there are several interventions or dosages of interest, and the objective is to decide which should be investigated further,

a selection design can be employed [43]. The "best" agent or dosage to study is selected as the one that has the superior effect (e.g., has the highest group mean or highest percentage of positive responses); formal statistical comparisons are not performed. The sample size is determined to yield a high probability of correct selection when there are truly superior choices. When making selections among equally effective treatments, it may be unimportant which treatment is selected. Because no formal hypothesis testing is performed, the required sample size is much smaller in selection designs than in conventional parallel group designs that formally evaluate the statistical significance of group differences. Selection designs can also be used in a sequential manner, where in an initial stage the "best" agent or dosage is chosen and then used in a superiority or futility design in the second stage of the trial [41]. Such adaptive designs are discussed below.

Considerations for Confirmatory Clinical Trials in Dystonia

The information obtained from exploratory studies is critical to informing the design of the confirmatory study. Typically, it is assumed that previous studies have demonstrated safety, tolerability, and proof of concept regarding efficacy for the agent. It is also assumed that earlier studies have identified an appropriate dosage or small number of dosages and route of administration.

While the trial design components are similar to those incorporated in exploratory trials, several features may vary given the different trial objectives (Table 1).

Objective

The primary objective of a confirmatory study is to evaluate efficacy of the agent with respect to a clinically meaningful outcome measure. Additional data are also collected on safety and tolerability.

Subject Population

Similar to exploratory studies, enrollment criteria should be carefully considered to ensure they are not overly restrictive. It must be decided if the subject pool should be more homogeneous and comprised of a single form or specific etiology of dystonia, or if broader eligibility criteria are desirable to enhance generalizability. If the goal of treatment is to alleviate symptoms, then the etiology of the dystonia might be less important. However, if the therapy is directed at a specific biological mechanism, more restrictive enrollment criteria may be appropriate. For a trial evaluating a potential disease-modifying agent, the sample size would be based on achieving a clinically meaningful change from the natural rate of progression. However, natural history data are limited in dystonia.

When evaluating a novel symptomatic agent, the concomitant use of botulinum toxin must be carefully addressed given the magnitude of its effects. In addition to the aforementioned considerations for exploratory trials, a confirmatory design could accommodate the use of botulinum toxin by evaluating a time-to-event outcome, such as the time to the loss of botulinum toxin effectiveness.

Trial Design Features

The dosing paradigm of a confirmatory trial should be extrapolated from the exploratory studies in the disorder and not from findings in other indications. Prior to initiating the confirmatory study, the MTD should be identified. Typically, this dosage will be evaluated in the confirmatory study, and data from preliminary efficacy or activity outcomes may also guide the decision regarding dosage. The duration of treatment should be sufficient to allow a treatment effect to become detectable with a feasible sample size.

As described below, there are various confirmatory study designs. Randomization and blinding are critical components of efficacy trials in order to address the placebo response, minimize bias, and protect against the influence of the knowledge of treatment assignment on known and unknown factors affecting study outcomes. It is important that a placebo indistinguishable from the active agent be formulated and that outcome measures be assessed and adjudicated by raters blinded to treatment assignment.

The primary outcome in a confirmatory trial should assess a clinically meaningful treatment effect. In the absence of a biomarker that has been validated as a surrogate for the clinical outcome, valid, reliable, and responsive instruments are needed to evaluate meaningful clinical outcomes. For dystonia, a variety of scales have been developed, yet important limitations exist, and not all types of dystonia have validated instruments [44, 45]. The Burke–Fahn–Marsden Scale, Unified Dystonia Rating Scale, and Global Dystonia Rating Scale were developed to evaluate generalized dystonia, but are also used for other dystonia types [44, 46]. The Tsui score [47], the Cervical Dystonia Severity Scale [48], the Cervical Dystonia Impact Profile [49], the Craniocervical Dystonia Questionnaire [50], and the Toronto Western Spasmodic Torticollis Rating Scale [51] have been developed for cervical dystonia; the Jankovic Rating Scale [52] is used for blepharospasm. These scales vary in their ease of use in the clinical setting and appropriateness for use in clinical trials [45]. The nonmotor aspects of dystonia are currently not completely assessed, and there are no validated rating scales for several dystonias, including spasmodic dysphonia, as well as task-specific, limb, oromandibular, and trunk dystonias.

Development of such scales will be necessary for clinical trials in these disorders.

Another important aspect of an outcome measure in a clinical trial is the minimal clinically important change, i.e., how large the change in the proposed outcome measure must be in order to be clinically meaningful to patients. Generic global, activities of daily living, or quality of life scales may be included as secondary outcomes to confirm that the changes demonstrated with the dystonia rating scales are associated with a meaningful improvement for patients. For the dystonia rating scales, the minimal clinically important change has yet to be characterized, and knowledge of this parameter will aid in determining the appropriate sample size.

In confirmatory trials, secondary aims include evaluating safety and tolerability. In fact, no treatment can ever be proven to be entirely "safe", as adverse events occur, and are monitored, postmarketing. Each step in the development process examines safety in additional detail. For example, although an assessment of safety is usually a major emphasis of exploratory studies, these studies tend to be small. Confirmatory studies permit the assessment of safety of the agent in a larger sample over a longer period of time. As a result, important, but infrequent, adverse experiences might be uncovered. Additionally, novel outcome measures or biomarkers are sometimes included in order to gain additional experience with these measures. However, as they are secondary outcomes, definitive conclusions cannot be drawn from them.

As with exploratory trials, it is important to prespecify stopping rules in the event that safety issues arise. For an individual subject who experiences adverse events associated with drug administration, should the dosage be reduced or should the drug be discontinued? Can a subject be rechallenged with the drug, and when should a subject no longer continue treatment? Under what safety concerns would the study be terminated?

Statistical Considerations

For a confirmatory clinical trial, the sample size should be chosen to provide adequate power to answer the primary question. This power calculation should be based on a clinically meaningful effect size, and the feasibility of achieving this sample size should be ensured. The analysis plan should account for missing data and subject withdrawal. Confirmatory studies typically employ an intention-to-treat analysis in which all randomized subjects are included regardless of compliance or completion of the treatment regimen. Outcome measures should be collected and analyzed on subjects who withdraw from treatment, if possible. In many instances, it may be useful to include an interim analysis for efficacy and futility. While an interim look at the data may have a small effect on power, such analyses can allow a study to be prematurely stopped if the agent is unlikely to be of benefit (futility) or if efficacy is clearly demonstrated in a smaller sample than expected. In all situations, the final analysis plan should be clearly defined and approved by all relevant parties (e.g., sponsor, Data and Safety Monitoring Board) before the data are examined in an unblinded manner.

Designs for Confirmatory Clinical Trials

The usual confirmatory trial design is the randomized, double-blind, placebo-controlled, parallel group study in which subjects are randomly assigned to either an active intervention or placebo (or some other type of control agent) (Table 2). Depending on the outcome variable and the effect size of interest, this design may require a relatively large sample size that may not be feasible in a rare disorder such as dystonia. If there are several interventions to study, possibly given in combination, a factorial design can be conducted. For example, in a factorial design with two agents, subjects are randomized to receive either treatment A alone, treatment B alone, both treatments, or placebo. It generally is assumed that all treatments can be given simultaneously and that the effect of one treatment does not depend on the presence of the other. Under this assumption, a level of efficiency is introduced as two questions can be addressed in the same trial without an increase in sample size. In the above example, the effect of treatment A is estimated by comparing those receiving treatment A (alone or in combination with treatment B) with those not receiving treatment A (treatment B alone or placebo). However, if there is a possibility of an interaction between the two agents, the trial must be designed with a sample size sufficient to make comparisons among the individual treatment conditions or to examine the effect of each treatment in subgroups.

An alternative to the parallel group design is a crossover design where within-subject comparisons are made for the active intervention versus placebo. In this design, subjects are randomized to different sequences of treatments (e.g., active treatment followed by placebo or vice versa), with a washout period between the treatment periods. This design is advantageous for heterogeneous disorders as each subject is his own control. All subjects receive the active agent at some point during the study which may enhance recruitment. Moreover, the required sample size is much smaller than that for parallel group designs, which may be advantageous for rare disorders like dystonia. While this design may be considered when an agent is known to have only a short-term benefit, it is important that the washout period is sufficiently long to ensure that there is no carryover effect of treatment from one period to the next. The crossover design is not appropriate for rapidly progressive disorders where the effect of time may confound the results.

Regardless of the study design, many confirmatory studies utilize group sequential methods [53] to conduct interim analyses for efficacy or futility. Repeated interim looks at the data

can inflate the risks of a type I error (false-positive result) and a type II error (false-negative result), and a number of approaches control these error rates.

Adaptive Designs

There may be limited information to guide the initial study design, particularly in the setting of a rare disease. As more knowledge will accrue as the study progresses, adaptive designs allow these elements to be reviewed during the trial and for the trial to be modified based on cumulative information [54, 55]. The Food and Drug Administration guidance document defines an adaptive design as "a study that incorporates a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study". Importantly, such changes must be prospectively planned and prespecified in the protocol; otherwise, bias may be introduced and the validity and the integrity of the trial cannot be ensured.

There are many types of adaptive designs including the group sequential design, the CRM exploratory design, and Simon's 2-stage design discussed above. Additional approaches include adaptive randomization, which allows for modification of the scheme for randomizing subjects to treatment arms during the course of the study. For example, with response adaptive randomization, the allocation probability is based on responses observed in previous subjects and is chosen to maximize the number of subjects on the treatment that appears to provide the most benefit. With covariate adaptive randomization, the allocation probability is chosen to reduce covariate imbalance between groups [56].

When selecting between several agents or dosages, a biomarker adaptive design can be employed where drug or dosage selection is based on short-term markers of target engagement or clinical status. Such biomarkers allow for earlier and more frequent assessment than the gold standard clinical endpoint. However, use of this design is often limited by the lack of validated biomarkers.

A sample size re-estimation design refers to an adaptive design that allows for an adjustment of sample size based on a review of the interim data. Re-estimation of sample size based on re-estimated nuisance parameters (variance, control group event rate, etc.) is well accepted, while re-estimation of sample size based on estimated treatment effects is more controversial [54, 57].

A seamless design combines objectives traditionally addressed in separate trials into a single trial. For example, an adaptive seamless phase 2/3 design is often a 2-stage design that involves dosage selection in the first stage and confirmatory examination of efficacy in the second stage, using data from subjects enrolled before and after the adaptation for the final analysis. Such designs have the potential to improve the drug development process by reducing the timelines for approval. However, the data analysis requires specialized methods to correct for bias introduced because data from the first stage are used for both decision making and final analysis. Hence, extra planning is necessary for an adaptive seamless design, and the potential benefits should be carefully weighed against the challenges of implementing such designs [58].

Adaptive trials require significant planning for design and simulation to avoid the potential biases discussed above. Adaptive designs are not always better [59], and the time required to perform the simulations needed to justify an adaptive design may offset any time saved by the adaptations. Although adaptive designs have received a great deal of attention, their use has not been consistent with that interest. This is particularly true in the academic clinical trials environment, where substantial operational and logistical issues may preclude such extensive planning [60].

Clinical Trial Implementation

Beyond defining the clinical question of interest, determining what data are needed to answer the question, and designing the trial, there are the many facets that are critical to successful trial implementation.

In the planning stages, it is important to consider how sites and investigators will be selected. Training procedures will need to be developed to ensure investigators assess outcome measures in a consistent manner across sites. Study materials, including the manual of procedures, the data system, and adverse event reporting methods will need to be developed. From a data management standpoint, the type of data collection (paper forms or electronic data capture) must be determined and training approaches considered. Prior to study start-up it is necessary to assess the resources that will be needed for database management and statistical support. Furthermore, the source of drug supply and matching placebo, if needed, must be identified. In addition, the process for drug distribution and accountability should be determined. Study supplies and central laboratories may need to be identified. Regulatory paperwork at the federal and local institutional review board levels will need to be filed prior to study initiation, and contractual arrangements established with participating clinical sites.

During the course of the study, it will be important to direct efforts toward subject recruitment and retention, as well as data quality. Site monitoring often will be necessary, and it will be important to ensure that quality assurance/quality control measures are in place. Regulatory filings may be required including, for example, annual reporting and reporting of unexpected adverse events. In addition, regular reporting to a Data and Safety Monitoring Board may be necessary.

At the completion of the trial, the study, sites, and subjects will need to be closed out. In addition, it is important to consider how subjects will be informed of the study results and their treatment assignment, if applicable.

Conclusions

The evaluation of novel treatments for dystonia will require well-designed exploratory and confirmatory trials. The time and costs associated with clinical trials are substantial, with the average cost to develop a drug estimated at $1.2 billion and the time ranging from 10 to 15 years [61], and the low prevalence of dystonia can introduce special challenges to developing a therapeutic agent, implementing a clinical trial, and achieving drug approval [62]. Nevertheless, there is significant interest in developing therapies for rare neurological conditions, and the clinical development timeline is similar to that for more common diseases [63]. While the evidentiary standards for regulatory approval are the same for rare and common diseases, the sample sizes for pivotal trials in rare disorders are generally smaller, and a design other than the standard "randomized, double-blind, placebo-controlled" trial is often employed [64]. Recognizing the limited patient pool, it is important to consider various approaches to design trials efficiently. To minimize the chance of a false-negative confirmatory trial result, it is critical to optimize dosage selection in the exploratory phase. Several aspects of the trial design must be considered (Table 1) and close collaboration among clinicians, statisticians, and data management personnel will facilitate defining the clinical question and designing, implementing, and analyzing an efficient trial.

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