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REVIEW ARTICLE

Adaptive trial designs for spinal cord injury clinical trials directed to the central nervous system

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Abstract

Study design Narrative review.

Purpose To provide an overview of adaptive trial designs, and describe how adaptive methods can address persistent challenges encountered by randomized controlled trials of people with spinal cord injury (SCI).

Results With few exceptions, adaptive methodologies have not been incorporated into clinical trial designs of people with SCI. Adaptive methods provide an opportunity to address high study costs, slow recruitment, and excessive amount of time needed to carry out the trial. The availability of existing SCI registries are well poised to support modeling and simulation, both of which are used extensively in adaptive trial designs. Eight initiatives for immediate advancement of adaptive methods in SCI were identified.

Conclusion Although successfully applied in other fields, adaptive clinical trial designs in SCI clinical trial programs have been narrow in scope and few in number. Immediate application of several adaptive methods offers opportunity to improve efficiency of SCI trials. Concerted effort is needed by all stakeholders to advance adaptive clinical trial design methodology in SCI.

Introduction

Clinical trials in spinal cord injury (SCI) could benefit from adaptive design strategies to address challenges associated with conventional randomized controlled trials (RCTs). In 2007, an international consensus panel (International Campaign for Cures of Paralysis (ICCP)) published a set of papers [1–4] reviewing SCI clinical trial methodology and providing recommendations for future studies. The ICCP guidelines remain relevant and valid; however, the SCI research community has experienced persistent shortcomings and barriers to the successful testing of promising therapeutics through clinical trials. In recognition of the challenges identified based on by accrued clinical trial experience, The Spinal Trials Understanding, Design, and Implementation (STUDI) initiative was established to report on ways to improve upon participant recruitment, trial outcome measures, and trial design, through a series of papers [5–8]. This STUDI paper, which is the last of five STUDI papers, reports on selected adaptive design methodologies and considers both the immediate and future

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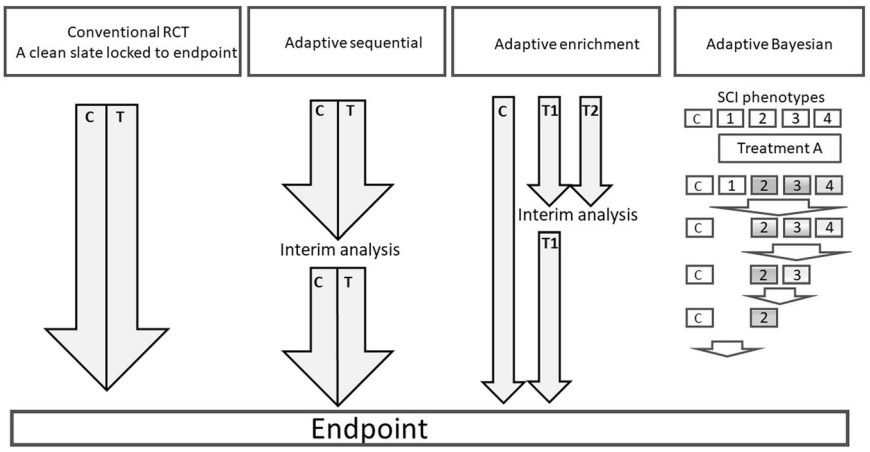

Fig. 1 Summary of comparison of conventional and adaptive clinical trial programs. C control group, T treatment group.

applications within SCI clinical trial programs to potentially address the challenges of standard RCTs.

The 2007 ICCP guidelines for SCI clinical trials promoted the use of prospective, double-blind RCTs as the most rigorous and valid SCI clinical trial design [4]. The rationale was that RCT designs mitigate bias and balance subject differences through randomization, blinded assessors, the use of a comparable placebo control group, prospective power analyses, and control of error rates, allowing a "true" treatment effect to be objectively demonstrated [4]. While the adaptation of an interim analysis for efficacy or futility is often built into the standard RCT study design, other planned and intentional adaptive methods are not commonly utilized in SCI clinical trials, with a few exceptions [9–11]. The importance of modernizing clinical trial methodology was highlighted in the 2004 Food and Drug Administration (FDA) Critical Pathway Initiative that addressed the causes of the low throughput of innovative medical products [12, 13]. Subsequently, the 2015 Clinical Trials Modernization Act stated the aim to "establish or clarify standards for using adaptive trial designs and Bayesian methods in clinical trials, including clinical trials that form the primary basis for approval, clearance, or licensure of the products involved" (https://www.congress.gov/bill/114th-congress/house-bill/1066/text). The essential problem of conventional clinical trial designs is that a number of uncertainties must be addressed before a conclusive or pivotal study can occur. These include whether a therapeutic is likely to be safe and effective, how to efficiently determine dosing, the therapeutic window, treatment duration, the treatment population, the likely effect size range, and its variability. While conventional RCTs are methodologically rigorous, they are expensive and lengthy, with high failure rates [14–18], and limited opportunity to use accruing information. Clinical trials in SCI have been affected by these challenges [19–21], such that no RCT program in North America or Europe has led to regulatory approval of a drug, biologic, or cell-based therapeutic to improve neurological recovery after SCI [18, 19]. In the past, conventional SCI RCTs have enrolled a diverse range of injury severities and large numbers of subjects. Because some injury severities have much more recovery potential than others do, this strategy has tended to require tolerance of large variances, increasing the necessary sample size.

Some of the multiple factors implicated in failure of conventional SCI RCTs [18, 21–23] may be resolved with more flexible adaptive methods to make trials "smarter." For SCI, clinical trial challenges include low incidence, high heterogeneity, lack of consensus on how to show a treatment effect, resistance to control group randomization, and high per participant study costs. Conventional RCT designs also limit the overall number of other SCI trials that can be undertaken, as conventional RCTs continue until preestablished enrollment is reached which can take many years. Given the limited research resources in some facilities and the relatively small SCI population, this may preclude other studies from being conducted in parallel. Thus, shortening the time for study completion may foster more studies and more rapid advancement of novel approaches. Below, we review the conventional phases of clinical trials and then discuss adaptations that can be applied in the near term to improve the efficiency of SCI clinical trial [24]. A summary comparison of conventional versus adaptive approaches to be discussed can be found in Fig. 1.

Phases of the traditional clinical trial design program

As discussed by Lammertse et al. [4, 19] and illustrated by Badhiwala et al. [21], conventional trial design programs are typically implemented in a serial manner with each phase defined by a primary focus. In a Phase 1 study, an experimental intervention that has undergone preclinical testing is administered in humans, usually healthy

individuals. For some agents where the therapeutic has already been used in people or where it may be unethical (e.g., invasive surgical administration) to dispense to healthy controls, then individuals with SCI are enrolled. Phase 1 studies often focus on pharmacokinetics, evaluation of safety, tolerability, and initial feasibility of the experimental intervention, and begin to refine the optimal dose and mode of administration. Phase 1 studies usually involve a small number of participants in a single active group (i.e., without a control group) and are often unblinded or "open-label," where both participants and investigators know what intervention has been provided. Because traumatic SCI is not typically a progressive central nervous system (CNS) disorder, risks must be minimized, particularly for more invasive routes of administration. Accordingly, Phase 1 studies are often limited to participants with a sensorimotor complete thoracic level SCI to mitigate the impact of a potential adverse effect or complication on neurological function.

Across all disorders, 63% of Phase 1 studies progress to Phase 2 [25] that continue to monitor safety, but also assess dose and therapeutic windows to establish "proof-of-concept" for the experimental therapeutic. The feasibility of future endpoints for Phase 3, including endpoints that can demonstrate a clinically important difference, must also be assessed. Often the progression from Phase 1 to Phase 2 is altered (i.e., temporally shortened or combined) because ongoing program funding is based on demonstration of possible clinical benefit in addition to the successful demonstration of therapeutic safety. Companies often need compelling early indications of beneficial outcomes to justify continued venture capital and other financial investment. Thus, many clinical trial programs incorporate an examination for the potential benefit of the therapeutic during the Phase 1 stage, which is then usually called a Phase 1/Phase 2a study. In SCI, demonstrating therapeutic benefit at this early phase is challenging due to the lack of a concurrent control group, lack of validated surrogate biomarkers, and the difficulties in demonstrating a benefit in sensorimotor complete thoracic injuries. Some Phase 1 SCI studies have used matched registry data as a comparison group in order to interpret a potential therapeutic impact and safety [25].

A "stand-alone" Phase 2 study is designed to track and extend information on the therapeutic response variability seen with given outcome measurements, in comparison to appropriate control participants. Phase 2 studies should provide a basis to define parameters for the subsequent definitive (confirmatory) Phase 3 trial, including the optimal dose, route and timing of administration, primary study endpoint, secondary outcome measures, and sample size.

The transition from Phase 2 to Phase 3 is the most vulnerable time in the clinical trial process, with slightly <31% of Phase 2 studies moving to Phase 3 [25]. At this transition, there are two critical challenges for SCI clinical trial programs: deciding the meaningful clinical endpoint and the criteria for enrolled participants. The purpose of the Phase 3 study is to produce the outcomes and safety data that are used by regulatory agencies to determine if the studied therapeutic should be approved for clinical practice. In most circumstances, two such trials are required by regulatory agencies to demonstrate the repeatability of the effects seen. Table 1 summarizes major SCI trials that are no longer enrolling participants [10, 26–31] and their advancement through clinical trial phases.

Considering interventional trials across all disorders, the average total time needed to progress from a conventional Phase 1 study to regulatory approval and market introduction is 12 years, with a success rate of 9% [24]. Given that the lack of success of conventional clinical trial programs is only evident late in the trials, there is a critical need to make earlier determinations of potential efficacy or lack thereof. In other clinical disorders such as oncology, stroke, Alzheimer's disease, and heart failure, adaptive clinical trial designs have been used to increase trial efficiency [32, 33].

Adaptive clinical trial methods for spinal cord injury

Adaptive trial designs [34] allow for planned data-driven modifications during the trial program that can potentially reduce costs, accelerate study timelines, address challenges with recruitment and heterogeneity, and mitigate inefficiencies associated with nonresponders. A key element of such designs is the use of existing information to model estimated outcomes, explore the statistical methods, and model the effect of adaptations on the operational elements of the trial without undermining integrity and validity [35–37]. Specific examples of these approaches for a variety of indications are provided in the 2019 United States FDA guidance on adaptive designs [38].

Chow and Chang [35], Dragalan [39], and Bauer et al. [40] provide extensive reviews of adaptive designs, and Meuer [41] illustrates their applicability to clinical trials of neuroprotection, including a trial modeled for SCI [42]. As shown in Table 2, general features of adaptive trial designs are different from those of the conventional RCT, but adaptive methods have been used within the RCT framework.

Planning phase

Both registry data and prior clinical trial data can be used to model the expected spontaneous neurological outcomes and time course, outcome variation, neurological patterns

Table 1 Summary of selected clinical trial progression for previous major SCI clinical trials.

Study	Phase I	Phase II	Phase III	Registered	Reason for lack of progression
Methylprednisolone (National Acute Spinal Cord Injury Study I, II, III) [26]	X	X	X	Off label	Completed Phase 3, but implementation in clinical practice is not currently widespread due to unclear results and associated complications
GM-1 ganglioside (SMASCIS–Sygen) [27]	X	X	X	No	Failed to meet primary endpoint (two grade improvement in the Modified Benzel Scale) at 6 months, although the difference was significant at 8 weeks
Fampridine (Acorda) [28]	X	X	X	No	Failed to meet primary endpoint (co-primary endpoint of Ashworth score and Subject Global Impression)
Autologous incubated macrophages (Proneuron) [29]	X	/		No	Trial was stopped for financial reasons. Analysis of enrolled participants demonstrated no treatment effect (ASIA Impairment Scale)
Small molecule with characteristics of basic fibroblast growth factor (SUN13837-Asubio) [30]	X	X		No	Failed to meet primary endpoint (total SCIM III score)
Neural stem cells derived from human fetal tissue (HuCNS-SC, Stem Cells, Inc.) [31]	X	/		No	A planned interim analysis was intended but the sponsor conducted an early, unplanned analysis, whereby the trial was halted for futility. Although the sample size was small the effect size was not considered large enough to continue (primary endpoint was ISNCSCI upper extremity motor scores)
Rho inhibitor (VX-210/Cethrin-Vertex) [10]	X	X	/	No	Phase 2b/3 study halted for futility at interim analysis (change in upper extremity motor score)

Current and ongoing studies are not included. X indicates trial phase was completed, / indicates trial phase started, but not completed.

Table 2 Cardinal features of adaptive clinical trial designs and comparison to the RCT.

	Adaptive designs	
Traditional RCT	With or without Bayesian statistics	Platform trials
Fixed protocol that may have a preplanned interim analysis for futility. Prospectively defined inclusion criteria, intervention group (s), and control group(s)	Uses simulation and accumulating study data to make modifications to the study based on explicit and preplanned rules. Some, but not all adaptive trials use Bayesian statistics for conditional inference. Iterative and extensive modeling using preexisting and incoming data	Platform protocol involves multiple distinct treatment protocols with a common control group. There is shared administrative and statistical infrastructure, and usually more than one sponsor. Studies can be dropped or added (indefinitely)
Benefits: balances subject differences and reduces bias through randomization and use of a parallel placebo control group. Blinded treatment and assessment	How adaptive designs address challenges of traditional RCT: may identify early therapeutic benefit or futility for participant subgroups; reduces study inefficiencies by dropping nonresponders and altering allocation of responders; may decrease length of time to complete clinical trial program, thereby reducing costs	How platform address challenges of traditional RCT: common control group reduces number of placebo controls; accelerates testing of several therapeutics simultaneously; shared infrastructure offers efficiency
Challenges: within a study phase, limited or no opportunity to adjust participant criteria or treatment characteristics to better focus on most important beneficial outcomes; participants with low probability for benefit not dropped; high costs; long time needed to complete through to market approval	Challenges: methods are less familiar to regulatory bodies\ethics committees, funders \sponsors and SCI community; time and start-up costs are needed for pretrial simulation and protocol development; time and cost of repeated interim analyses and study logistics	Challenges: although well established in oncology, SCI does not have established genetic and molecular markers; shared statistical, administrative and financial infrastructure is a novel concept for SCI clinical trial programs; requires long-term financial commitment
Intent: efficacy/safety of intervention(s) in an intended homogenous group	Intent: efficacy/safety of multiple interventions in a potential heterogeneous group	Intent: efficacy of multiple interventions in different participant subgroups with common control group

RCT randomized controlled trial, *SCI* spinal cord injury, *PD* pharmacodynamics, *PK* pharmacokinetics.

associated with floor and ceiling effects [43]. An interim analysis is based on the assumption that accumulating data can provide some indication of treatment effect or lack thereof. A sequential clinical trial allows for planned interim analysis. If unblinded, the treatment effect magnitude can be determined, and the sample size can be re-estimated. If the blind is maintained, the observed variance in the key outcome measures guides sample size adjustments. An adaptive trial can allow further modifications based on the interim data [44], but in all cases, the trial design must control the Type 1 error rate [45].

The group sequential design is a type of adaptive design where the starting sample size is based on event rates (such as response to a drug, adverse events, or death), not the number of participants. An example is the estimated number needed to treat in order to observe a particular odds ratio or relative risk. Unlike the traditional fixed sample size design that sequentially enrolls participants in matched pairs for two different treatments until trial completion, the group sequential design enrolls participants until a prespecified endpoint such as, e.g., 50% enrollment occurs. At the interim analysis, the current "*Z*-score" that compares the difference in group mean values divided by the standard deviation is calculated to determine if the *Z*-value remains within the predetermined trial continuation boundaries. If the *Z*-score crosses either the lower or upper boundary (defined in the planning stage), the trial may be stopped for either futility or efficacy, respectively. Group sequential designs may be more practical in SCI than other adaptive options and have been used in recent studies, as described below and in Table 1. This design may facilitate earlier progression to the next trial phase, or identify futility earlier in the clinical trial, thus exposing fewer participants to risk.

Learning phase

"Learning phase" or exploratory phase adaptive options occur early in product development, are relevant to drug, biological, and cell-based studies, and include adaptive dose-response for toxicity or safety. Traditional dose range-finding is typically a 3 + 3 sequential design, in which three participants receive the drug at each dose level, starting with the lowest dose. If there are no dose-limiting toxicities for a given dose in three participants, the next highest dose is administered. If one individual has dose-limiting toxicity, three additional participants receive that dose. In many studies examining terminally progressive disorders, the maximum tolerated dose (MTD) is the dose at which <33% of subjects experience dose-limiting toxicities [46]. SCI is not a terminally progressive disorder, and investigators would not accept toxicity in as many as 33% of participants. As an alternative, an adaptive Bayesian approach (the continual reassessment method) [47] regularly assesses the MTD along a dose-response curve [48]. This method uses available information to create an estimated dose-toxicity curve that is updated sequentially with each subject's toxicity information. The dose-toxicity probability is first modeled based on the available prior information, and then subjects are dosed at close to the anticipated MTD. The method can increase the precision of the MTD estimate, reduce overall toxic events, and reduce exposure to ineffective doses [49].

Learning and confirmatory phase

Heterogeneity

Given the segmental organization of the spinal cord, there is heterogeneity in the level and severity of SCI. Even within the same level of injury (e.g., C5) and severity grade (for example, American Spinal Injury Association Impairment Scale [AIS] C), substantial heterogeneity impacts the range of neurological outcomes. In adaptive enrichment designs, the eligibility criteria of a trial are adaptively updated according to accumulating data during the trial to restrict entry to those participants most likely to benefit. This allows the determination of proof-of-concept in early trials that can later be more generalized. Without enrichment in early studies, the ability to discern a treatment effect may not be possible in a logistically feasible number of subjects.

Biomarkers

Adaptive designs can use emerging clinical trial data based on outcomes or biomarkers that are available relatively early following an intervention to guide trial modifications. Oncological trials have advantages that are well suited to adaptive designs, such as associations between biomarkers and objective outcomes. For many cancer types, genetic biomarkers aid prediction of effective therapeutic approaches; and may be incorporated into the prediction of objective outcomes such as a reduction in radiologically assessed tumor size and no evidence of the tumor on positron emission scanning. As an example, in the innovative I-SPY 2 breast cancer trial [50], tumors are categorized based on biomarkers, and patients are assigned to treatment groups based on probabilities of effectiveness using accruing trial data, with assignments favoring therapies that have been performing better for a given tumor category (https://www.ispytrials.org/i-spy-platform/i-spy2)

The multi-system complexity of SCI pathobiology has made it challenging to identify highly predictive biomarkers. Biomarkers that are strongly correlated with the neurological recovery prognosis are contusion length (including blood signal), an accepted acute magnetic resonance imaging (MRI) biomarker of SCI severity [51–53].

Additional biomarkers in the early validation stages include the axial MRI-based BASIC score [54], cerebrospinal fluid, and blood biomarkers [55, 56], possibly combined with MRI for some metrics [57]. Currently, other than MRI, there are no other validated biomarkers for SCI severity. Genetic biomarkers are a new area of exploration in SCI trials, with two intermittent hypoxia studies (NCT02323945, NCT04017767) incorporating screening for genetic polymorphisms that may influence responsiveness to the intervention. Development of these and other [5, 6] biomarkers for SCI may make the use of some adaptive models more feasible.

Confirmatory phase

Primary outcome measures

There is agreement that primary outcome measures should be correlated with meaningful functional change, but the magnitude of change that is sufficient in SCI trials has not been established. In diseases with objective biomarkers, such as cancer, it is possible to define response or no-response earlier in a clinical trial. Further "hard endpoints" such as recurrence are more straightforward to model than the discrete changes observed in SCI. This challenge cannot be addressed by adaptive designs, but advancements in this area improve opportunities to use adaptive models.

High study costs

The study costs for each recruited individual are often very high. Adaptive trial designs may potentially address high study costs by increased statistical efficiencies (seamless trials in which there is no break between study phases, futility stopping) and by platform trials (described below).

Slow recruitment

Given the relatively low incidence of SCI, recruitment of study participants to trial phases is slow, even when many study centers are involved. Recruitment into early phase trials has become even more challenging with the decreasing incidence of complete sensorimotor SCI in Western countries [58], as this type of injury is often required by regulatory agencies for early-phase, high-risk, safety studies such as cell transplantation and the implantation of biologics [59, 60]. The natural history of complete thoracic injuries is now well established and can be used to model expected outcomes [61]. In addition, safety studies for high-risk interventions such as intraparenchymal injection of cell-based approaches have been completed [62, 63]. Publication of these data may allow trials to progress to cervical SCI more rapidly than in the past. For therapeutics that are not directly invasive, incomplete subjects may be enrolled, and the challenge of greater heterogeneity is amplified.

In Table 3, we have provided simplified descriptors of the more fundamental adaptive methods and how they can be applied in different phases of SCI trials following the structure of Kairalla et al. [48].

In both conventional and adaptive randomization designs, the randomization allocation method is established prior to the trial, but adaptive randomization allows for planned modifications based on incoming information. The purpose of covariate randomization is to balance important baseline characteristics (age, injury severity, as examples). Specifically, covariate randomization chooses the allocation for the new study participant based on enrolled study participants' characteristics, such that the allocation minimizes the degree of imbalance across baseline characteristics. This strategy can be more efficient to balance covariates than enrollment to strata in which the final number of subjects in a given strata may be small. While the use of covariate randomization is increasing in clinical trial designs, care is needed to not introduce bias if an investigator observes sequential assignments that suggest the allocation group [64].

The anticipated variance of enrolled subjects may be difficult to predict and impacts the ability to compare the study groups according to the initial estimate. Adaptive sample size re-estimation incorporates new information about parameters determining sample size from within the trial data itself. There are several ways to use this adaptive approach in clinical trials, including blinded or unblinded analyses [65] that, respectively, examine the observed variance and effect size. One example is to set predefined enrollment-based interim analyses upon which the sample size may be adjusted according to incoming variance or event rate data, incorporating adjustments for a potentially inflated type I (false positive) error rate. Available clinical trial software such as nQuery and FACTS (Berry Consultants) is useful for both planning and conducting these estimates.

Adaptive enrichment designs seek to identify individuals who are most likely to respond to a given therapeutic and can adjust the inclusion criteria. For example, in the discovery phase of a study, one might identify which subgroups are most likely to benefit from the intervention. In later phases, individuals from these subgroups are randomized to preferred arms, and those who are likely to be nonresponders are not. In oncology trials, the assignment to preferred arms and the elimination of subgroups is often based on the presence of genetic tumor biomarkers. When groups of SCI participants can be identified and categorized with valid early biomarkers linked to potential treatment efficacy, this strategy may be feasible. For those SCI protocols requiring functional outcome measures that take

Table 3 Methods used in adaptive trial designs that have immediate advantages for SCI clinical trials.

Adaptive methods	Immediate opportunities for SCI clinical trials
Adaptive sequential analysis (group sequential design): preplanned sequential analyses (interim analyses) based on incoming data, to determine if the study continues or stops for efficacy or futility. This is the most common adaptive feature in clinical trials	Readily integrated into studies based on modeling prior to the study. Multiple interim analysis can occur as long as stopping/continuing rules are prespecified and error rates are controlled. Decision-boundaries are prespecified
Learning/exploratory phase (Phase 1\2)	
Adaptive dose response for toxicity or efficacy: change in dose \treatment window to identify the minimum effective dose and the maximum tolerable dose	An alternative to standard 3 + 3 design for determining maximum tolerated dose, based on incoming trial data
Learning and confirmatory (Phase 2\3)	
Adaptive seamless design: trial phases are combined, decreasing the time needed for regulatory approval of "new" protocols. Learning and confirmatory data are sometimes used in the final analysis	Combine initial dose range-finding protocol with determination of efficacy, decreasing the "white space" for regulatory approvals between protocols
Confirmatory phase (Phase 3)	
Adaptive randomization: Covariate randomization allows for balancing of covariates (severity, age) during the enrollment phase Response adaptive randomization (RAR) allows for modifications of randomization schedules in order to increase probability of efficiency based on interim analysis of accumulating data on potential benefit. Participants who are enrolled later in the trial have higher probability of being assigned to treatment arm that was more efficacious than participants who were enrolled early in the trial	Covariate randomization improves the covariate balance between controls and treatment but does not increase trial efficiency. It can increase the validity of the group comparisons. Prior to study, modeling recovery rates for potential participants can assist with identifying target population most likely to benefit, as well as appropriately powering endpoint values For early trials 2:1 randomization (emphasis on allocation versus size)
Adaptive sample size: sample size adjustment or re-estimation based on interim analysis. Allows for adjustments based on incoming data on variance or event rate. Number within each subgroup or overall	Although variance can be gleaned for common endpoints, by mining historical databases, for less frequently used endpoints, adapting sample size based on incoming data would be particularly beneficial
Adaptive participant population (adaptive enrichment): initial trial enrollment is broad but based on interim analysis subgroups with the most opportunity to benefit from a given intervention are identified, based on factors such as genetic or physiological markers or demographics. (severity\level)	Modeling prior to and throughout the study to identify responders and nonresponders and alter enrollment of certain subgroups (age, severity of SCI, pattern of recovery, physiological markers, pathological characteristics based on imaging, future reliable biomarkers) such that subgroups that respond have higher rate of enrollment and subgroups that do not respond have lower rate of enrollment or are dropped
Adaptive treatment arms: inferior arms are dropped based on prespecified criteria, and additional arms can also be added	Interim analysis to carry out prespecified rules or actions regarding dropping, for example different treatment doses, arms, etc.
Evaluating multiple therapies or doses simultaneously and use planned modifications to allocate more participants to optimal treatment dosages and to reduce number of participants allocated to treatment dose that is less effective	

longer to be observable, this would be more challenging. Although adaptive enrichment may increase efficiency, these studies are more complex, may have limited generalizability, and may lose information about groups who were not included. Per Kairalla et al. [48], this design may be best for later stage learning trials.

Adaptive seamless designs may be utilized in the learning and confirmatory phases. Seamless designs can combine trial phases into a single protocol, decreasing the time needed for protocol advancement and regulatory guidance between phases. They may be, respectively, operationally or inferentially seamless or both, and do pose some limitations. Incoming data can inform decisions about the enrollment of future groups within the same protocol. For example, identification of the best dose and timing (learning phase) may be combined with a trial using the identified best dose and assessing efficacy (confirmatory). In this scenario, data from individuals receiving the optimal dose in the learning phase may be combined with data from the confirmatory phase, leading to smaller sample size requirements. Two primary concerns are related to bias and error rate inflation, which can, in part, be addressed by using adjusted estimates and simulations to examine the extent of bias. An unlikely limitation of Phase 2/3 inferentially seamless designs is that unblinded study data may not be available to the sponsor before study completion [49].

Use of adaptive designs in SCI trials

Although the majority of SCI trials have not integrated adaptive methods into their designs, some examples exist.

Two recent trials, the Stem Cells, Inc [31]. and the Vertex Rho inhibitor (VX-210) [10] studies, included preplanned interim analyses. The Stem Cells, Inc. interim analysis occurred earlier than the preplanned analysis, while for Vertex, the interim analysis occurred as planned; both studies were stopped for futility based on the interim analysis [10, 31]. It is essential that the impact of interim analysis on the study power associated with accepting the null hypothesis is given careful attention in the planning phases. An NIH sponsored adaptive clinical trial program (ADAPT-IT) formulated several adaptive clinical trial designs to address acute neurological emergencies [41, 42]. One study design to test hypothermia for neuroprotection in acute SCI was developed. The design was for a seamless Phase 2/3 trial, which incorporated duration response modeling to determine the optimal duration of cooling for the most significant benefit. In this case, subsequent participants would receive the optimized cooling duration, based on accumulating study data, while sub-optimal cooling periods were dropped. Longitudinal modeling was also incorporated whereby the strength of the correlation between proximate outcomes to the primary outcome measure would be assessed and, if meaningful, could be used during the trial to predict the most effective neuroprotection paradigm. Proximate outcome variables are not validated surrogates but are intermediate outcomes that may be linked to the primary outcome measure and warrant further study. In traumatic brain injury, an example is a measured reduction in intracranial pressure [66]. For SCI, a potential acute proximate variable that might be impacted by hypothermia could be the extent of T2 signal propagation above the initial acute MRI injury signal [67].

A current study, Riluzole in Spinal Cord Injury Study (NCT01597518) is a double-blind, multicenter RCT that incorporates a sequential adaptive design in a placebo-controlled study [11]. Included in the study design is a planned modification to terminate the study for futility or efficacy at the time of interim analysis using predefined boundaries based on *Z* scores, as described previously. A recently initiated trial of an anti-Nogo decoy (AXER-204, sponsored by ReNetX Bio) (NCT03989440) fusion protein is using an adaptive seamless approach in a Phase 1/2 trial. Part 1 is a multicenter, open-label, single ascending dose in four chronic SCI cohorts. Part 2 is a multicenter, randomized, double-blind, placebo-controlled, repeat dose study, using the dose level and frequency identified in Part 1.

Adaptive designs using Bayesian analysis

Bayesian analysis is a powerful statistical paradigm that provides a formal mathematical method for combining data from previous studies with accumulating data from a current study [68], to predict the likelihood of a future event [35]. Bayesian adaptive clinical trials rely heavily on prediction models to inform study modifications based on prespecified rules and iterative analysis of preexisting and accumulating study data. The advantages of Bayesian designs include flexibility in addressing complex relationships via ongoing modeling and estimating prediction probabilities. Inferences are made based on data that are actually observed, while prior and accumulating knowledge is used to adjust study methods rather than accepting uncertainties for the duration of the study. Another advantage of Bayesian analysis is that the results can be expressed on probabilities that are more readily interpreted by clinicians than *p* values.

The role of simulation/modeling

Simulation has an important role in the design of adaptive trials. Simulation and modeling are conducted iteratively to explore different study designs and components such as interim analyses. Simulations can help select the statistical and procedural properties of the trial, and to understand type I and II error rates, study power and accuracy of estimated treatment effects, and rates of adverse events across a wide range of population characteristics [69]. The necessity for simulation in adaptive designs underscores the importance of access to high-quality clinical data sets and registries that track standard of care outcomes after SCI. Several relatively large-scale SCI clinical data sets are available where neurological and functional changes have been obtained at various time points after SCI (Table 4) [70–72]. These databases have provided valuable estimates of variance and may be used to simulate control groups [73, 74] and to examine potential study endpoints such as motor scores, recovery of levels, AIS grade change, and Spinal Cord independence Measure scores.

Master protocols

It is acknowledged that to achieve neurological recovery after SCI, several mechanistic approaches will need to be combined. The oncology field has influenced the development and implementation of adaptive clinical trial programs using master protocols. Rather than conducting single biomarker-based trials, many oncology clinical trial programs are able to use master protocols to investigate distinct multiple treatments within and across tumor types successfully due to tremendous advances in genomics, imaging, and computational science. Master protocols and their associated clinical trial designs have been addressed by the FDA [75] and others, including Saville and Berry [76], Berry et al. [77], Redig and Jänne [78], and Simon et al. [79]. A master

Table 4 Summary of the most widely used SCI registries.

	N	Data collection range	Location	Available uses
Spinal Cord Injury Model Systems	27,836	Acute—death or dropped participation (longest is 40 years)	United States	Has been used to track patterns in demographics and natural recovery
European Multicenter Study About SCI	4700	Entries at 5 time points during of First-time Rehabilitation—48 weeks	Europe	Has and is being used to identify: (1) participant inclusion/exclusion criteria, (2) potential study cohorts (e.g., responders versus nonresponders), (3) useful study endpoints
Rick Hansen Spinal Cord Injury Registry	7196	Acute—10 years	Canada and Aust., Israel	Is being compared to other registries to determine comparability of outcomes
North American Clinical Trial Network	990	Acute—48 month	United States and Canada	Has been provided to several studies as a comparator group to aid clinical trial design

N number enrolled in registry at time of writing.

protocol is an adaptive clinical trial design that contains multiple embedded studies involving a variety of therapeutics across one or more disease types. Three oncology trial designs using master protocols include basket, umbrella, and platform trial designs.

Basket oncology clinical trials are typically early phase trials that enroll patients who have tumors at various anatomical locations that share the same molecular mutation [79]. In contrast, umbrella oncology clinical trials enroll patients with the same cancer type, perform molecular and genetic testing, then allocate patients to a study arm based on detected molecular\genetic mutations that are matched to a potentially effective therapeutic. Common to both the basket and umbrella trial design is the process of allocation to study arms by matching targeted therapies to genomics, and molecular mutations [78]. Basket and umbrella trial designs as conceptualized in oncology are not currently applicable in SCI because there are currently insufficient validated molecular and\or genetic biomarkers for SCI. However, as the role of gene expression, gene networks, and RNAs on the ability to respond to rehabilitation, secondary damage, and/or recovery patterns following SCI becomes better defined [80, 81], methodologies similar to basket and umbrella designs may become more relevant.

In contrast to the basket and umbrella approaches, a platform trial is an adaptive design that tests distinct multiple interventions and hypotheses and can add and remove study arms based on accumulating trial data and data from sources external to the study. Platform trials explicitly assume that treatment effects will differ across groups of participants [68, 69], which is particularly attractive to SCI trials owing to the heterogeneity of the population.

The advantages of platform trials include shared sponsorship of infrastructure costs across experimental treatments, a coordinated statistical plan, and accelerated testing of therapeutics in a larger number of persons with a disease or subgroups of the disorder. Evolving information leads to the preferential assignment of therapeutics to probable responder groups. Adoption of master protocol clinical trial designs would require a fundamental shift from a single sponsor/single investigator perspective to a collaborative paradigm defined by cooperative and trusting relationships among multiple companies, agencies, foundations, universities, as well as clinical and community stakeholders [82].

Challenges with adaptive trial designs

Adaptive designs are not without significant challenges [48, 82]. In general, significantly more time is needed for study start-up for discussions between study investigators and expert methodologists. Time and funding are also necessary to implement and review simulations of the trial. For investigator-initiated studies, upfront funding for these planning activities is lacking, or at best difficult to obtain. Frequent analyses and study modifications add many operational complexities to study protocols, which require careful oversight for adherence to the pre-specification of all adaptive parameters. With adaptive trials, the concept of clinical equipoise (uncertainty about the benefits and risks of the therapeutic intervention) still requires the need for objective, independent oversight [83, 84]. There have been other criticisms of adaptive designs, including premature termination of studies of promising therapies, increased risk of falsely detecting treatment effects, and statistical bias, all of which can also occur in conventional RCTs. Lack of training and knowledge in adaptive trial designs, inadequate infrastructure (including funding) for preplanning activities, and a lack of involved trialists and biostatisticians with expertise in adaptive trials and Bayesian statistics on the trial team have all been implicated in the slow uptake of adaptive clinical trial designs. Adaptive designs themselves

cannot solve the problem of limited numbers of subjects that meet enrollment criteria, and the time lag between the treatment and the determination of the endpoint. However, increased trial efficiency and the validation of early treatment response biomarkers will likely mitigate these problems.

In this paper, we discuss opportunities and outline future possibilities that have the likelihood to address some persistent challenges faced by SCI RCT programs. Specifically, we discuss adaptive design methodologies within the context of drug and cell-based therapeutics directed to the CNS. Although their applications to other therapeutic modalities are illustrated within the present discussion, a comprehensive review of adaptive trial designs for SCI clinical trials involving surgical, rehabilitation, and technology/device interventions is beyond the scope of this paper.

The SCI scientific community has decades of experience with traditional RCT. RCT and adaptive designs are not at odds. In fact, the majority of adaptive trial designs are randomized and controlled. Within this paper, we have outlined adaptive design methods that can be considered within an RCT framework for SCI trials. Pertinent questions are specifically, "what can be done now?" and "what has potential for the long term?"

What can be done now?

(1) Stakeholders of SCI clinical trials must become educated about the strengths and limitations of adaptive design methods. Increasing awareness is an essential first step, but education about implementation (when, how, why, benefits, risks) is essential. This paper is a first step toward a more formalized and inclusive endeavor of writing and disseminating more detailed analyses for the application of the adaptations described here into SCI clinical programs. A logical next step is to utilize existing SCI data sets to simulate use of accumulating study data to illustrate concepts discussed in this paper and to explore how they may improve efficiencies and endpoints of past SCI RCT trials. Use of clinical trial software such as nQuery and FACTS for these simulations will provide an opportunity for field-testing the software for SCI trials.

(2) Further guidance and education papers, tailored for SCI clinical trial programs and developed by key experts in RCT, adaptive trial designs, statistics, funders, sponsors, and consumers that outlines specific recommendations for integrating innovations in different types of SCI clinical trials, using data modeling to simulate these recommendations would serve the field well.

(3) Adaptive clinical trial protocols should include methods that address our most significant uncertainties and challenges. Specifically, such study protocols should include planned time points for interim analyses to identify optimal responders and optimal study endpoints, particularly in the early phases of the trial program. Prespecified rules for dropping non-responders and altering the randomization schedule, administrative route, and doses should be clearly defined and implemented. These adaptive methods can be implemented within an RCT framework, and are recommended for immediate consideration.

(4) During protocol development, methodologists and statisticians with expertise in adaptive trial designs and Bayesian statistics should be engaged. A robust discussion of the merits and risks of adaptive SCI studies should occur now.

(5) Sponsors of SCI research should consider a special call for proposals for intervention studies using adaptive designs. This may serve as the first step and necessary catalyst for SCI investigators to learn how to use adaptive methods within designs they are most familiar and comfortable with, and to develop new collaborations with experts in adaptive design and Bayesian statistics. Alternatively, or in addition, a special call for proposals for preparatory work (simulation and modeling, consultation with experts in adaptive designs, etc.) for a future study would be equally important. Financial support for "demonstration" studies and preparatory work is essential for our field to move forward.

(6) Whether a standard RCT or an adaptive trial design, simulation and modeling based on prior studies and registries should be expected as part of the development plan for a clinical trial—much like previous work or pilot work is required for preclinical research programs. Owing to the availability of SCI clinical and research registries, this should be the expected first step when designing a new SCI clinical trial. These simulations will likely lead to a greater understanding of what adaptations may have particular advantages for SCI trials. They would also contribute to the effort to educate the field about adaptive trial designs and more accurate outcome measures.

(7) Access to de-identified registry data should be streamlined while still ensuring the sustainability of continued registry enrollment and ongoing data collection.

(8) Encourage availability of clinical trial data that are not under the auspice of the NIH mandate to be publicly available.

What adaptive study designs have potential for SCI trials in the long term?

(1) Basket and umbrella protocol designs may be useful when genomic, proteomic, biochemical, and physiological biomarkers for SCI are identified and validated.
(2) The concept of platform trials is intriguing. Can we imagine shared governance and sponsorship across multiple studies, with a common statistical infrastructure and control group for SCI clinical trials? What would it take to begin a dialog about this idea? How can intellectual property and other financial considerations that are inherently important to clinical trial programs be balanced with the potential for shared infrastructure and successes?

Conclusion

This paper discussed limitations in SCI clinical trials that have become increasingly apparent in recent years, and identified adaptive approaches to overcome them. Specifically, the protracted time course and resource inputs that have been needed for RCTs that do not reach a conclusion for several years is no longer a sustainable research paradigm. The trial modifications possible with "adaptive" methodologies may resolve some limitations that have been encountered in conventional RCTs. This general review could not include a description or discussion of all adaptive clinical trial methodologies. We selected the concepts that are felt to be most feasible, and that potentially can have an immediate impact on overcoming challenges to conventional SCI RCTs of therapeutics targeting the CNS. In doing so, we have outlined suggestions for immediate consideration. We have also posed questions to facilitate forward thinking and dialog about important considerations for the future. We did not discuss adaptive designs as a function of the type of research. As an example, adaptive designs that may be most advantageous for clinical trials of rehabilitation interventions may not be the same as the adaptive methods that are most advantageous for clinical trials of surgical procedures or devices.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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