Stroke

TOPICAL REVIEW

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Adaptive Clinical Trials in Stroke

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ABSTRACT: Designing a clinical trial to evaluate the efficacy of an intervention is often complicated by uncertainty over aspects of the study population, potential treatment effects, most relevant outcomes, dropouts, and other factors. However, once participants begin to be enrolled and partial trial data become available, this level of uncertainty is reduced. Adaptive clinical trials are designed to take advantage of the accumulating data during the conduct of a trial to make changes according to prespecified decision rules to increase the likelihood of success or statistical efficiency. Common adaptive rules address early stopping for benefit or futility, sample size reestimation, adding or dropping treatment arms or altering randomization ratios, and changing the eligibility criteria to focus on responder patient subgroups. Adaptive clinical trials are gaining popularity for clinical stroke research. We provide an overview of the methods, practical considerations, challenges and limitations, and potential future role of adaptive clinical trials in advancing knowledge and practice in stroke.

Key Words: adaptive clinical trials ■ early termination of clinical trials ■ randomized controlled trials ■ stroke ■ uncertainty

Randomized clinical trials are the most trusted approach to determining the efficacy and safety of new therapies, but they are often logistically complex, inefficient, costly, and require extended periods of time to complete. These challenges are critical barriers to the rapid generation of information on the efficacy and safety of interventions, including acute therapy and approaches to nursing care and rehabilitation, for patients experiencing ischemic or hemorrhagic stroke.

See related articles, p 2726, p 2742

Even after early-phase studies have been completed, uncertainty surrounding key trial parameters, such as the optimal dose, magnitude of treatment benefit, characteristics of responding patients, and variability in the primary outcome, can introduce challenges for planning an optimal clinical trial design. However, these pretrial uncertainties can be mitigated as enrollment progresses and data are collected during the trial.

Adaptive clinical trials are designed to improve trial performance by allowing for mid-trial changes in response to accumulating data (ie, at interim analyses) according to carefully selected and prespecified rules (Figure 1).[1–4] Adaptive rules are chosen to address the primary threats to trial success (eg, lack of information needed to select an optimum dose or the responding patient population), to generally improve statistical efficiency so that conclusions can be drawn more quickly, or to improve the expected outcomes of participants treated within the trial.

By prespecifying specific rules governing the adaptations that may occur within the trial, an adaptive clinical trial may be completely rigorous with well-defined operating characteristics, including protection from false-positive conclusions (ie, type I errors), power, and required sample size. A well-designed adaptive trial generally utilizes a parsimonious set of adaptive rules or features carefully matched to the specific uncertainties facing the clinical investigation.

Adaptive trials are most efficient when end points are observed quickly relative to the enrollment rate (eg, 30- or 90-day outcomes). They become less effective with long delays in end point observation, as in secondary prevention trials, because there is little opportunity to make impactful mid-trial changes by the time actionable information is gathered.

This article is Part 2 in a 5-part series. Parts 1–3 appear in the November 2024 issue of *Stroke*. Parts 4 and 5 will appear in subsequent issues.

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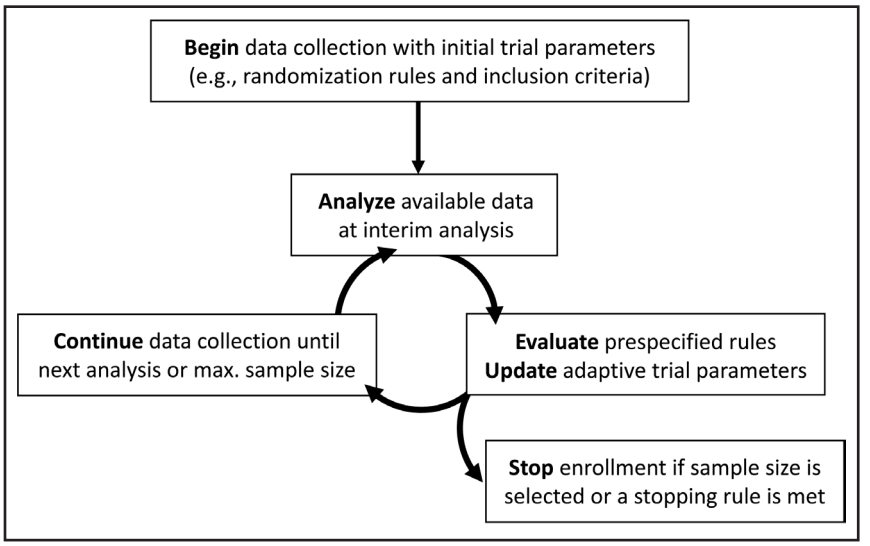

Figure 1. Adaptive clinical trial schema.
max. indicates maximum.

Adaptive clinical trials are increasing in number and degree of sophistication. They are now well accepted in all phases of therapeutic development, supported by guidance documents from the US Food and Drug Administration and the European Medicines Agency,[5–8] and funding by industry and government. Despite their growing use in many other therapeutic areas, many stroke neurologists and investigators focused on stroke may not be aware of the key motivations, design considerations, examples, and potential for the use of adaptive clinical trials in the investigation of treatments for stroke. We provide a summary of the common adaptations used in clinical trials and provide 4 detailed case studies from stroke research (a larger selection of adaptive trials in stroke is available in the Supplemental Material). We discuss practical considerations, limitations, barriers to increased use, and the potential for adaptive trials to accelerate knowledge generation in stroke.

COMMON ADAPTATIONS

While each research setting is unique, there are common areas of pretrial uncertainty for which adaptive strategies have been developed to improve trial performance. We describe 4 common trial adaptations related to sample size, randomization of treatments, definition of patient populations (ie, inclusion criteria), and the stage of clinical development (eg, phase 2 versus phase 3). We provide a summary of each adaptation and the pretrial uncertainty it addresses (Table). In practice, the strategies can be, and often are, combined.

Throughout the following sections, we refer to Bayesian analyses and quantities. This statistical paradigm provides a framework for making decisions by updating prior knowledge with new data to answer a scientific question. This approach can be well-suited for making adaptive trial decisions because it allows for updates as new data emerge over the course of the trial. For more information on the topic, the next article in this journal series will review Bayesian methods in stroke research. Adaptive platform trials will be covered in a separate article in the series.

Adaptive Sample Size

Determining the appropriate sample size for a trial is often challenging due to pretrial uncertainties about event rates, variability in the primary outcome, or the expected magnitude of the treatment effect. Adaptive sample size designs are particularly valuable when there is uncertainty surrounding these quantities, making it difficult to select an appropriate sample size based on the knowledge available when planning the trial. Adaptive sample size designs are characterized by their prespecified set of possible sample sizes and their ability to determine the final trial size based on emerging evidence of efficacy or futility as the trial is ongoing. Herein, the goal is to avoid a trial that is too large and unnecessarily exposes participants to risk or delays the detection of an effective treatment or alternatively is too small (ie, underpowered) to reliably answer the research question under investigation.

There are 2 general approaches to adaptation of sample size. The first consists of defining a maximum sample size, often based on adequate power to detect the minimum treatment effect of clinical interest, and includes the possibility of selecting a smaller sample size if evidence of success or futility emerges. Sample size selection occurs at interim analyses, which are scheduled evaluations of data gathered during the trial and conducted before the trial is completed. These are among the most common adaptive designs. The second approach consists of defining an initial maximum sample size and recalculating a larger maximum at some point during the trial if there is evidence that a larger trial will substantially increase the chance of finding a positive result. These approaches can be combined, and both address the same pretrial uncertainties.

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Table. Common Parameters in an Adaptive Trial Design, by Primary Goals, Advantages, and Considerations

Adaptive parameter	Primary goals and advantages of adapting the trial parameter	Primary design considerations for adapting the trial parameter
Sample size	Goal: optimize trial size using predefined rules that allow stopping enrollment at an interim analysis if evidence of efficacy or futility emerges, or by recalculating sample size before trial completion Advantage: alleviate pretrial uncertainties about the magnitude of the treatment effect or the variability of the trial end point, which are used to determine sample size	Select stopping and/or sample size recalculation criteria including statistical methodology and strategy for control of type I error risk Determine interim analysis schedule including number, timing, and implied minimum and maximum possible sample sizes
Randomization rules	Goal: the best-performing arm(s) in a multiarm trial using predefined rules to stop or reduce randomization to the worst performing arm(s) based on accruing trial data Advantage: alleviate pretrial uncertainties about the optimal dose or duration of an intervention	Select adaptive randomization strategy including the allowable range of randomization probabilities, maintenance of control allocation, and strategy for control of type I error risk Determine frequency of interim analyses for randomization rule updates Balance adaptive randomization to maximize statistical efficiency while achieving minimum acceptable sample sizes for all arms
Patient population (enrichment designs)	Goal: to identify the optimal inclusion/exclusion criteria for trial enrollment using predefined rules for enriching the population based on accruing trial data Advantage: alleviate pretrial uncertainties about who to enroll in a trial; balancing the breadth of inclusion criteria with the magnitude of observed benefit	Identify inclusion/exclusion criteria that will be candidates for adaptive enrichment (ie, patient baseline characteristics that may lead to differential treatment effects or safety profiles) Define criteria to trigger enrichment to a narrower population Define final analysis population and strategy for control of type I error risk Clarification interpretation after enrichment (eg, application of trial result to entire population vs enriched population)
Development phase (seamless designs)	Goal: to allow a trial to trigger the seamless progression from one developmental phase to the next within one trial infrastructure using predefined rules Advantage: alleviate uncertainty around the trial parameter settings for a late-phase design without requiring a hiatus between development phases to make the decision	Clarification of primary goal for each phase of development Operationally or inferentially seamless design Strategy for control of type I error risk if inferentially seamless

Stopping for Efficacy

To avoid conducting a trial that is larger than necessary, an interim analysis sample size can be selected if there is evidence that the intervention does, or will likely, demonstrate significant benefit. Figure 2A depicts the general setup for an adaptive trial with 3 planned interim analyses. Figure 2B is an example of an adaptive sample size trial that stopped enrollment at the second interim analysis. The decision to stop enrollment at an interim analysis is based on prospective statistical criteria.

There are a variety of sample size selection algorithms that can be used for efficacy stopping. A common approach is the group sequential design,[9] which combines the primary analysis hypothesis test with the sample size selection. In the group sequential approach, the primary analysis is conducted at each interim analysis with the available data. The resulting *P* value is compared with a predefined threshold. If the *P* value is below the threshold, trial enrollment is halted and the primary analysis is considered successful.

To control the rate of drawing a false-positive conclusion or type I error, denoted alpha (α), the thresholds used to define statistical significance at each interim analysis must be stricter than required with a single analysis at the end of the trial. The trial's overall type I error rate is effectively spread out, or spent, over the scheduled interim analyses. Spending functions are adopted to emulate common group sequential designs such as the O'Brien-Fleming design. These functions tend to allocate a larger portion of alpha to later interim analyses as a way of being conservative at earlier interim analyses.[10–14] These designs are often desirable because they have analytical (ie, mathematically provable) control of the type I error rate.

Interim analyses occur while the trial is ongoing, and it is expected that participants enrolled just before the interim analysis will not have complete follow-up available at the time of the primary analysis. One drawback of the classic group sequential design is that outstanding outcomes from these participants are not explicitly considered in the primary hypothesis test that occurs at the interim analysis.

Another approach to efficacy stopping is the Goldilocks design,[15] which separates the decision to select a sample size from the primary analysis test. This design ensures that all enrolled participants can be fully followed before the primary analysis is performed. At an interim analysis, the predictive probability that the trial will meet the primary analysis success criteria (whether those criteria are Bayesian or frequentist) is calculated based on complete follow-up of all enrolled patients. If the probability is high, the trial selects the current sample size, and the primary analysis is conducted after the completion of follow-up on all enrolled participants. One drawback of these designs is that they typically require computer simulations to demonstrate control of type I error.[5]

Stopping for Futility

Adaptive trials may stop for futility at an interim analysis, limiting the trial size if it appears unlikely that the trial will reach its objective even with continued enrollment. The

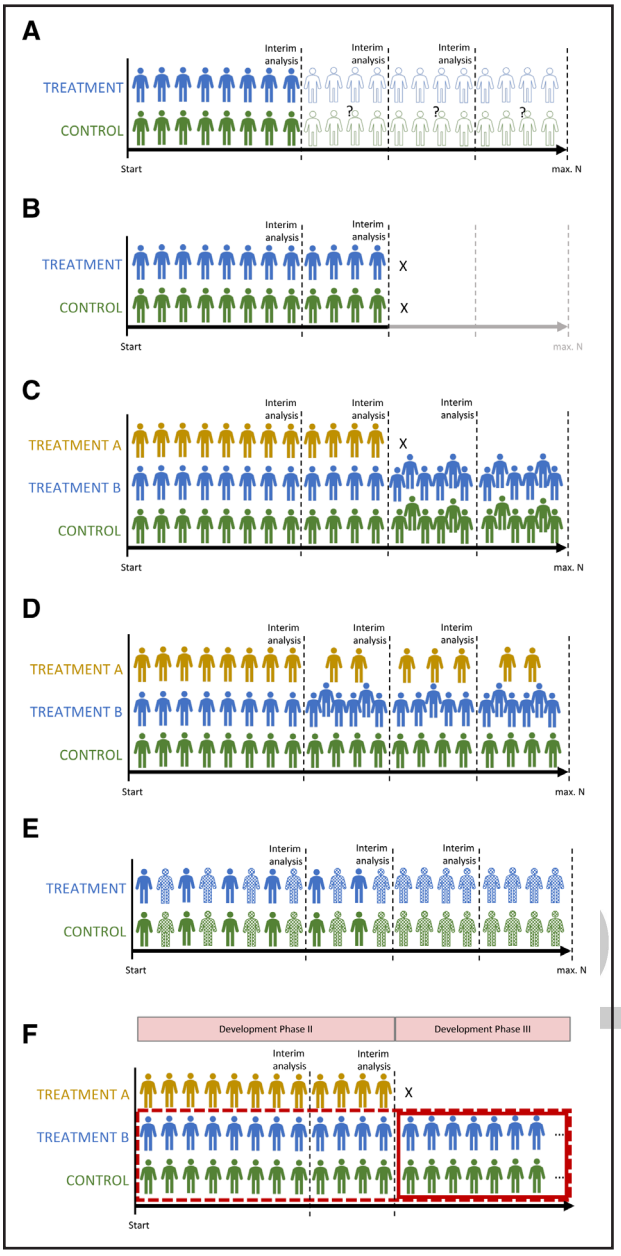

Figure 2. Collection of trial schematics that demonstrate common adaptive trial designs.
Each portion shows a trial that adapts a key design parameter and one way that the adaptive trial could progress. **A**, Adaptive trial design (general). A generic adaptive trial setup with 3 planned interim analyses at which adaptations to trial parameters could occur. **B**, Adaptive sample size. Participant enrollment until the second interim analysis when a prospective sample size selection rule is triggered and the trial is stopped. **C**, Adaptive randomization rule: arm dropping. Participants are randomized to treatment A, treatment B, or control until the second interim analysis, when an arm dropping trigger is met for treatment A. The randomization probability for treatment A is set to zero, and the trial proceeds to randomize to treatment B and control. **D**, Adaptive randomization rule: response-adaptive randomization (RAR). Participants are randomized to treatment A, treatment B, or control. At each interim analysis, randomization probabilities for each treatment arm are updated to favor the better-performing arm in the trial. **E**, Adaptive patient population. The trial begins with a wide set of inclusion criteria, enrolling 2 subgroups of participants (solid and hatched). The trial continues this way until the (*Continued*)

goal of futility stopping is to limit participant exposure to a treatment that is unlikely to benefit them and to avoid subjecting them to unnecessary experimentation in trials that are unlikely to demonstrate efficacy.[16] It is important to note that a triggered futility rule indicates that the trial is unlikely to reach a conclusion within the available resources but not necessarily that the treatment is futile.

Futility analyses do not spend alpha because there is no opportunity to declare efficacy erroneously. There is, however, the risk of stopping a trial for futility at an early, random low estimate of the treatment effect when the treatment would have gone on to demonstrate benefit; this risk can be mitigated with appropriately chosen futility boundaries. Futility rules can be based on *P* values using an analogous methodology to group sequential methods.[7,17] However, the Goldilocks framework is a natural choice for futility stopping because it directly addresses the likelihood of declaring significance at the maximum allotment of resources for the trial using Bayesian predictive probabilities. These predictive probabilities incorporate uncertainty in the observed treatment effect estimate and the uncertainty in future data.[18] If it is unlikely that the trial will be able to demonstrate efficacy on the primary end point with maximum time, resources, and information, then it is generally appropriate to stop enrollment.

Sample Size Recalculation

The promising zone is another sample size selection approach that can adjust the maximum sample size of the trial based on accumulating evidence at prespecified interim analyses.[19] At an interim analysis, conditional power is calculated based on the treatment effect estimated using the observed data.[20] Conditional power is the probability the trial will ultimately yield a positive result, assuming the currently observed treatment effect point estimate is the true value of the treatment effect in the population. The conditional power is categorized into 3 zones: unfavorable, promising, and favorable. If the value falls into the favorable or unfavorable zone, the trial will continue to the planned maximum sample size. If the value falls into the promising zone, the treatment effect is not as favorable as expected, and a larger sample size is needed to achieve sufficient statistical power. Hence, trials in the promising zone will adjust by increasing the sample size to achieve a prespecified value for

Figure 2 Continued. second interim analysis when an enrichment trigger is met and the solid subgroup of participants are excluded from inclusion criteria for the remainder of the trial. **F**, Adaptive development phase. This trial seamlessly graduates from phase 2 to phase 3 of development at the second interim analysis. Treatment A is dropped from the study, and treatment B is carried forward for phase 3 development. The primary analysis of treatment B vs control can include participants from both phases (inferentially seamless; dotted red box) or restrict to only the late-phase participants (operationally seamless; solid red box). max indicates maximum.

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conditional power (eg, 80%), or to a secondary maximum sample size, whichever is smaller.

One appealing feature of this methodology is that no formal adjustment is needed to control the type I error (ie, no alpha spending). However, in practice, the promising zone is often narrow with respect to the range of effect sizes that meet its criteria, thereby limiting the opportunity to increase trial power through a sample size recalculation. Moreover, conditional power calculations assume that the observed point estimate for the treatment effect is the true underlying treatment effect in the population, which ignores uncertainty surrounding the estimated treatment effect.

Further Considerations

Careful planning for these designs involves determining both the minimum and maximum possible sample sizes for a trial, balancing statistical considerations, the potential risks and benefits of the treatment strategy, and practical constraints such as funding, timelines, and regulatory requirements. A minimum sample size may be selected to ensure the availability of a sufficient safety database and to provide sufficient evidence to impact knowledge and practice. The primary benefit of a sample size selection algorithm is the ability to ensure the right-sized trial is conducted. A disadvantage, however, is that compared with a trial enrolling to a fixed maximum sample size, an adaptive trial with interim analyses may lead to slightly lower overall power for the same maximum sample size due to the need to distribute alpha over multiple analyses that could result in trial success. In addition, there is potential bias in the estimated treatment effect obtained from clinical trials that stop early, although the magnitude of that bias is almost always clinically negligible.[21,22] In addition to meeting prospective efficacy or futility criteria, there are other reasons to stop a clinical trial before its planned maximum sample size, such as safety or because new external evidence has become available. Strong et al[23] discuss the implications of these trial stops and highlight the need for careful planning and adherence to prospective adaptive designs in randomized trials for acute stroke.

Adaptive Randomization Rules

During the early phases of development, there is often uncertainty regarding the optimal dose or exposure of an intervention. Traditional strategies for dose selection include choosing a single dose to study based on pharmacokinetic-pharmacodynamic modeling or studying a small number (eg, 2–4) of doses and then comparing the results at the end of the trial to determine which doses to investigate further. An adaptive strategy is to explore multiple doses (potentially many over a wide range) and use the observed data to adaptively randomize participants to the various doses as the trial is ongoing.[24] For example, the ASTIN trial (Acute Stroke Therapy by Inhibition of Neutrophils),[25,26] to be discussed later, used adaptive randomization rules to explore 15 experimental doses and control.

Adaptive randomization can lead to efficient and early identification of 1 or more doses that are most likely to be promising in later phases of development. These strategies can increase the probability of identifying the best arm, accurately estimate the treatment effect for the best arm, and optimize patient care in the trial.[27] Adaptive randomization designs can generally be classified as arm dropping, response-adaptive randomization (RAR), or rule-based dose finding.

Arm Dropping

Arm dropping designs use accumulating trial information to halt accrual to arms that do not have promising safety/efficacy profiles, effectively dropping them from the study.[28–30] Arm dropping actions are based on predetermined criteria and occur at interim analyses. This allows the recruitment of future participants to focus on gathering information on the better-performing arm. Figure 2C depicts a trial with treatment strategy arms A and B and a control arm. At the second interim analysis, treatment strategy A is dropped from the study and the remaining planned resources are allocated to strategy B and control.

Arm-dropping designs can be simple (drop underperforming arms based on efficacy signal)[31] or more complex (drop arms in order based on dosing strength or frequency; drop arms based on a combination of safety and efficacy signals). One class of arm-dropping designs that has been gaining popularity is multiarm multistage designs.[28,30]

Response-Adaptive Randomization

RAR is a less extreme version of arm dropping, where instead of setting the randomization for underperforming arms to 0 irreversibly (ie, dropping them), the allocation proportions are updated to decrease randomization to poor arms and favor the better-performing arms.[32–34] These updates occur frequently at scheduled interim analyses after an initial burn-in period with fixed randomization. These designs often use guardrails to ensure that each arm is assigned to a reasonable number of participants in the trial while accumulating as much information on the most promising arms as is feasible. Figure 2D depicts a trial where treatment strategy A is worse than strategy B, which is similar to the arm-dropping example. RAR allows for strategy A to continue to accrue information, albeit slowly as more participants receive strategy B.

RAR is most valuable in multiarm settings, for example, when ≥2 interventions are compared with a control or when the comparative effectiveness of ≥3 interventions is studied. RAR is generally not recommended for simple 2-arm settings.[35] In trials with a control arm, it is recommended that a fixed randomization rate for the control

arm and RAR to allocate the remaining probability across multiple experimental arms is used.[36] It is not advisable to adjust randomization to the control arm based on the outcomes of the control participants.

Adaptive Randomization for Rule-Based Dose Finding

RAR or arm-dropping approaches can be used for dose finding, but there is a specific set of adaptive randomization designs that have the goal of identifying the most clinically appropriate dose, usually for further testing. The continual reassessment method (CRM) is a common adaptive design for dose finding.[37] The trial begins by enrolling a cohort of participants to an initial dose that is typically chosen conservatively for safety. Dose-limiting toxicities and efficacy are evaluated, and if the observed toxicity is acceptable and the efficacy criteria are not yet met, the dose is increased for the next cohort. Conversely, if dose-limiting toxicities are excessive, the dose may be deescalated. Typically, the CRM uses a Bayesian framework to allow the model to incorporate information from neighboring doses and to provide a natural framework to update the dose-limiting toxicity estimates and make escalation/deescalation decisions after each cohort. Stopping rules may be used to stop the trial when a certain level of toxicity or efficacy is reached. Adaptations in CRM minimize the number of participants exposed to suboptimal or toxic doses. An example of a CRM in stroke is the NeuroNEXT trial NN104 RHAPSODY, a multicenter, phase 2 trial that used a CRM to determine the safety and tolerability of 3K3A-APC, a recombinant variant of human activated protein C, in combination with intravenous thrombolysis with tissue-type plasminogen activator, endovascular thrombectomy (EVT), or both in participants with moderate-to-severe acute ischemic stroke (AIS).[38]

Further Considerations

Adaptive sample size determination is a natural companion and often a consequence of adaptive randomization rules. For example, if all treatment arms meet arm-dropping criteria, then the entire study is stopped early for futility. In the examples provided in Figure 2C and 2D, where treatment B outperforms treatment A, the trial could prespecify a rule that allows for early stopping for success if treatment B demonstrates significant benefit when compared with control at the third interim analysis.

Adaptive Patient Population

One key challenge in any randomized controlled trial is identifying the ideal responder patient population, as defined by a particular set of inclusion and exclusion criteria for enrollment. If these criteria are too broad and inclusive, the trial may enroll participants who experience little or no benefit from the experimental intervention and hence fail to demonstrate benefit. Alternatively, if the criteria are too restrictive, investigators may miss important subsets of the population that could receive benefit. The latter would also mean that the evidence generated from the trial would only justify the use of the treatment in the more restrictive population, reducing its value to society. In settings with substantial uncertainty regarding the populations most likely to benefit, investigators can leverage adaptive enrichment strategies to learn about the maximally responding patient population from the accumulating trial data.[39] The adaptive enrichment approach aligns with the principles of stratified and personalized medicine, which aim to tailor treatments to specific patient subgroups.

Suppose there are 2 subpopulations of interest for a given disease, A and B. Before conducting the study, investigators suspect that the treatment may have a differential benefit in the 2 subpopulations; however, they do not want to miss the opportunity to demonstrate benefit in both A and B if, in fact, the treatment benefits both groups. In this situation, trial investigators could begin by enrolling both populations (all-comers) and then use a prespecified adaptive enrichment criterion that allows the trial to adaptively modify the inclusion/exclusion criteria based on the observed data if evidence emerges that only one of the 2 populations appears to benefit from the treatment.

For example, as shown in Figure 2E, it may become evident through prespecified interim analyses that subgroup A is not benefiting from the experimental treatment, but there are signals of potential benefit in subgroup B. If the inclusion/exclusion criteria are modified to drop subgroup A and enroll only subgroup B participants subsequently, this would increase the chances of demonstrating benefit in subgroup B without increasing the trial size and avoiding being weighed down by the lack of benefit in subgroup A. A trade-off may be extending the time needed to complete the trial, depending on the sample size planned for the enriched population and the relative prevalence of subgroups. The key feature of this approach is that the decision to enrich to subgroup B is based on the observed data (per a prespecified adaptive algorithm) rather than relying on a pretrial assumption of benefit in one or both groups. In other words, an enrichment design allows the observed data to inform the inclusion/exclusion criteria, allowing investigators to demonstrate benefit in the entire population while maintaining a safety net in case benefit is only observed in a subpopulation. The ENRICH study (Early Minimally Invasive Removal of Intracerebral Hemorrhage), discussed later, used this adaptive enrichment strategy to demonstrate benefit of a minimally invasive surgical approach to removing supratentorial intracerebral hemorrhage (ICH) compared with best medical management.[40,41]

Designs with adaptive enrichment can be simple (eg, 2 predefined subgroups) or complex (eg, adaptively select

subpopulation by optimizing an enrichment cutoff for a key covariate such as infarct core volume or time since last known well) and are selected to address the uncertainty for the specific disease or trial objectives. Once again, all enrichment decision rules need to be prespecified. Moreover, the analysis plan should be clear as to which participant outcomes are included in the final analysis (all versus enriched population) and to which populations the conclusions are generalizable, as well as the impact of enrichment on the design operating characteristics.

Adaptive Development Phase (Seamless Designs)

The traditional development pipeline compartmentalizes the evaluation process into sequential steps, completing one trial before starting the planning activities for the next. Consider a therapy that has shown a promising safety and efficacy profile in an early-phase trial. Investigators want to choose 1 of 2 doses to move into late-stage, large-scale development. The investigators could run a stand-alone trial to gain information on 2 dosing strategies, pick 1, and then initiate another stand-alone trial for confirmation. Alternatively, investigators could use a seamless design, as shown in Figure 2F, which allows dose selection and seamless progression across developmental phases within the same trial framework.[42–44] These designs are particularly useful to address uncertainties about the exact trial parameters to move into late-stage research. The uncertainties do not necessarily need to pertain to the magnitude of the treatment benefit; for example, the uncertainties addressed in a seamless design could pertain to late-phase inclusion/exclusion criteria, duration of participant follow-up, or selection of an optimal dose. Graduation from one stage to the next happens at an interim analysis, driven by the accumulating trial data and prespecified decision criteria.

Generally, there are 2 classifications of seamless designs. First, the trial could be considered inferentially seamless, where conclusions are drawn using data from combined phases based on robust statistical analyses (see the dotted red box in Figure 2F). Second, the trial could be strictly operationally seamless and draw conclusions only using data acquired after the graduation trigger (see the solid red box in Figure 2F). These latter designs retain the administrative and logistical benefits, using the same infrastructure for 2 phases of development, but do not leverage the statistical efficiencies provided by an inferentially seamless design. To conduct an inferentially seamless design, the data from the first phase must remain blinded to trial investigators so that the final analysis of the later phase can benefit from the earlier phase data. If investigators are unblinded to the earlier phase data, then only data accrued in the second phase of the trial may be used for the final analysis; otherwise, concerns of bias may arise.

CASE STUDIES OF ADAPTIVE TRIALS IN STROKE

Adaptive trials have become a key feature in the landscape of clinical stroke research. In past randomized controlled trials, adaptive elements were adopted to address uncertainties existing at the time of planning the design in relation to the magnitude of the treatment effect, which characteristics the population would stand most to benefit, or in selecting an optimal dose to balance efficacy and safety. Here, we outline 4 case studies to illustrate the adaptive features used to address uncertainties and align with the goals of the therapeutic development program. Although there are overlapping design features in the 4 examples, the results of the trials differ from one another, exemplifying the idea that similar trial designs can result in different trials depending on the observed data.

The ASTIN Trial

Published in 2003, ASTIN was a phase 2 dose-finding, proof-of-concept study that aimed to establish whether UK-279276, a recombinant glycoprotein that inhibits neutrophils, improves outcome after AIS and, if so, to identify a dose for further study.[25] The primary end point was defined as the change in neurological impairment, as assessed on the Scandinavian Stroke Scale from baseline to day 90. The primary objective was to establish the minimum dose that delivered 95% of the maximum efficacy (ED_{95}) and to explore the dose-response relationship.

The study used a Bayesian adaptive design with a flexible sample size between 500 and 1300 participants that allowed for early termination due to futility or efficacy and adaptive allocation to placebo or 15 different doses of UK-279276. At interim analyses, the study was designed to stop for futility if the probability that ED_{95} had <1-point change on the Scandinavian Stroke Scale was >80%, or efficacy if the probability that ED_{95} had at least a 2-point change on the Scandinavian Stroke Scale was >80%. To address the uncertainty over the dose-response relationship, the adaptive allocation algorithm randomized new participants among the doses and placebo based on the latest available dose-response data. The algorithm's goal was to minimize the predicted variance of the response of ED_{95} as the trial was ongoing.

The study stopped early for futility after 966 participants were enrolled. After searching a wide range of potential doses, the study concluded with a relatively flat and null dose-response curve. The study met futility with a posterior probability of futility of 0.89 (ie, the probability that ED_{95} had less than a 1-point change on Scandinavian Stroke Scale was 0.89). The adaptive design enabled a timely trial conclusion to be reached across multiple drug

doses and limited the exposure of participants to a therapy that did not show promise within ASTIN. Additional details of the ASTIN design, including motivation for the dose selection algorithm, are published.[26]

The SWIFT PRIME Trial

Published in 2015, SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) was among the first pivotal trials to demonstrate the safety and efficacy of EVT after intravenous thrombolysis versus intravenous thrombolysis alone in patients with AIS due to large vessel occlusion.[45] Like many EVT trials at that time, there was likely substantial pretrial uncertainty about the appropriate sample size required to properly assess the magnitude of treatment effect on the primary end point of functional outcome on the modified Rankin Scale (mRS). The trial used an adaptive sample size via group sequential methods so that the observed data would determine the appropriate final sample size. The trial could halt accrual at 200, 300, 400, 500, 600, or 750 randomized participants if evidence of efficacy, futility, or lack of safety emerged. As evidence for the efficacy of EVT emerged elsewhere, the first interim analysis was conducted after 196 participants were randomized upon the recommendation of the data and safety monitoring board (DSMB). The prespecified threshold for efficacy was crossed at the interim analysis, and the trial demonstrated superiority of EVT for improving functional outcomes after large vessel occlusion AIS. The adaptive design enabled a demonstration of superiority with a small sample size in the setting of a strong observed benefit. Additional details about the SWIFT PRIME protocol, including the group sequential thresholds for stopping criteria, are published.[46]

The DAWN Trial

Published in 2018, DAWN (Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) was designed to assess the efficacy of EVT in a late time window after the onset of large vessel occlusion AIS, between 6 and 24 hours from time last seen well, in participants with a favorable ischemia-infarction mismatch identified on diffusion-weighted magnetic resonance imaging.[47] The primary end point was the mRS analyzed using utility weights (defined in the range 0–10), often shortened as utility-weighted mRS.[48]

Although imaging mismatch is an important predictor of favorable clinical outcomes after reperfusion therapy, without clinical data to guide the inclusion/exclusion criteria for participants who present late, there was uncertainty about the treatment effect in relation to the size of the infarct core. One possibility was that the benefit of EVT would be limited to those with smaller core infarct volumes. To address this uncertainty and increase the likelihood of demonstrating benefit in the largest possible benefitting population, the trial was prospectively planned as a Bayesian adaptive enrichment design, allowing adaptation in the enrollment criteria based upon baseline core infarct size and the observed accruing outcomes. Sequential interim analyses were planned so that the trial could stop enrollment for participants with larger infarct sizes if the benefit of the intervention appeared to be restricted to participants with smaller baseline infarct sizes. As such, the appropriate upper bound for infarct size could be learned over the course of the trial.

The design also allowed for the stopping of new enrollment at interim analyses if EVT was highly likely to demonstrate a beneficial effect once the 90-day functional outcome was available for all enrolled participants. With these rules in place, the trial had a flexible sample size of 150 to 500 participants. The trial stopped after 200 participants were enrolled (the first opportunity to stop for success) because the predictive probability of superiority for EVT was sufficiently high (exceeding a prespecified threshold of 0.95). The primary analysis reported a mean benefit of 2.0 points in the 90-day utility-weighted mRS scores, with a posterior probability of superiority >0.999. The adaptive design enabled the trial to reach a positive conclusion with a small sample size due to the overwhelming observed benefit. The benefit was observed across the full range of baseline core infarct size, and the primary analysis included the full population because enrichment thresholds were not crossed. Additional details about the DAWN trial protocol and adaptive methods are published.[49]

The ENRICH Trial

Published in 2024, ENRICH is the first randomized controlled trial in acute ICH to demonstrate the benefit of surgical evacuation of the hematoma compared with the best medical management alone.[40] The surgical approach was a minimally invasive approach using a novel device.

The ENRICH investigators took an innovative approach that leveraged advantages of an adaptive trial design to evaluate the benefit of the surgery on utility-weighted mRS (defined in the range 0–1), 180 days, according to the different ICH locations, separating deep (anterior basal ganglia) and lobar. The study included prespecified interim analyses to select the appropriate sample size (between 150 and 300 participants) and to enrich or restrict the study population to those with only 1 of these 2 locations if prespecified efficacy, futility, and safety criteria were met.

The enrichment criteria were met at the time of the second interim analysis (175 participants enrolled), and the study stopped enrolling participants with a deep location

of the ICH and continued randomizing participants with lobar ICH. The primary analysis population included 208 lobar ICH and 92 deep ICH. The primary analysis of 180-day utility-weighted mRS in the population of pooled study participants with ICH in either location showed an estimated mean benefit of 0.084. However, the estimated subgroup-specific mean benefit of surgical evacuation was 0.127 in those with lobar ICH and −0.013 in those with deep ICH locations, indicating a lack of efficacy in those with deep ICH locations. The Bayesian probability of superiority of the surgical approach in the primary analysis was 0.9813, which exceeded the prespecified 0.975 threshold required for a positive trial.

Given the dramatic difference in the treatment effect seen between these 2 ICH locations, and assuming that future outcomes would have been similar to earlier outcomes in participants, the trial would have likely failed to demonstrate superiority if it had continued to enroll participants with both ICH locations (ie, without the use of enrichment). Hence, the Bayesian trial design identified a differential benefit between lobar and deep locations, and the enriched patient recruitment to the more promising subgroup was likely responsible for the overall successful primary analysis. Additional details about the study protocol and adaptive methods are published.[41]

Additional Adaptive Trials in Stroke Research

While the examples above include details for noteworthy adaptive trials conducted in stroke, the Supplemental Material provides a more extensive (though not exhaustive) collection of examples of adaptive trials in stroke, listing principle aims, primary outcome measures, and adaptive features. The examples in Table S1 were selected to represent a range of research questions with adaptive designs in stroke research.

PRACTICAL CONSIDERATIONS, CHALLENGES, AND LIMITATIONS

While adaptive clinical trials offer advantages over traditional fixed trial designs in many settings, there are practical considerations, challenges, and important limitations that need to be carefully considered. We highlight key topics here, but readers are encouraged to see the publications by Gaydos et al,[1] for more information about good practices for adaptive clinical trial designs, and Pallmann et al,[3] for guidance on how to run and report adaptive designs.

Because they are inherently more complex than traditional fixed design trials, designing an adaptive clinical trial requires specialized methodological and statistical expertise, often including the ability to conduct computer simulations of proposed trial designs or the use of Bayesian approaches. This expertise may not be available locally, even in many specialized and highly resourced academic or commercial settings.

As the time required to design an adaptive trial is front-loaded and generally more extensive than a traditional trial, the design work is best performed by an integrated and multidisciplinary team of scientific, clinical, statistical, and domain experts. Once the design is developed, additional work may be required to effectively communicate its properties and advantages to key stakeholders, including potential collaborators, grant reviewers, patient advocacy groups, members of ethics committees and institutional review boards, and regulatory authorities. Regulatory agencies may have varying levels of acceptance and familiarity with adaptive designs, potentially leading to additional scrutiny or delays in approval processes.

Implementing an adaptive trial may pose challenges relative to a traditional trial. The adaptive approach tends to require that partial clinical trial data be available in near real time to be used in frequent interim analyses rather than infrequently or only at the end of the trial. This may require modifications to data collection and management procedures, as well as a degree of flexibility that may be unfamiliar to contract research organizations. Meeting an adaptive trigger starts a chain of actions that need advanced consideration and planning. For example, if an arm-dropping trigger is met, the randomization system must be updated to reflect new randomization rates, and study forms may need to be amended to reflect the arms available in the trial.

To avoid operational bias—the potential for knowledge of interim efficacy results to alter participant recruitment, treatment, or collection of outcome data—firewalls must be enforced to ensure that those implementing the trial and interacting with participants are unaware of interim results. This generally requires maintaining both blinded and unblinded study personnel. In particular, an unblinded statistical team is formed to run the interim analyses and report the prespecified adaptive decisions to the DSMB in the closed session.

The DSMBs overseeing an adaptive trial must have the breadth and depth of expertise to understand the clinical, methodological, and ethical issues involved in the design, conduct, and interpretation of the trial. The adaptive design should run as specified in the protocol, and DSMB members must have a robust understanding of key issues (eg, safety or operational) that may motivate a recommendation to deviate from the prospective adaptive design. In general, the DSMB should avoid recommendations to modify an adaptive design based on unblinded efficacy results, as such actions may complicate the interpretation of trial results.

Adaptive trials rely on accumulating data to make adjustments that apply to participants enrolled later in the trial. Therefore, adaptive trials are most effective when information from participants is available quickly

relative to the enrollment rate. In cases where end points are observed long after enrollment, adaptive trials are less effective because their ability to respond to data is reduced. An example is a secondary prevention trial in which the low event rates occur in randomized participants who are treated long before meaningful outcome data accrue. By the time actionable information is gathered, there may be little opportunity left to make impactful changes to the trial.

Because adaptive trials use information acquired earlier in the trial to make changes to the trial that are applied to participants enrolled later, the statistical performance of the trial can be adversely affected by secular changes in patient populations, disease characteristics, or the effectiveness of background therapies. These are issues that must be carefully considered during the design of and the decision to implement an adaptive trial.

FUTURE ROLE OF ADAPTIVE CLINICAL TRIALS IN STROKE RESEARCH

Adaptive clinical trials have demonstrated tremendous value in supporting and accelerating the identification of new effective treatments for patients with stroke. Given the growing number and complexity of clinical questions needing to be answered, such as determining the limits of effective therapies across diverse populations and quantifying the effect of combination treatments, the role and value of adaptive clinical trials in stroke research is likely to increase. As expertise in adaptive approaches increases within the stroke community, as illustrated by the examples provided, research strategies are likely to expand and diversify across the field.

ARTICLE INFORMATION

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Supplemental Material

Table S1
References 1–20

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