Adaptive Trials in Stroke

Current Use and Future Directions

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Abstract

Inclusion of adaptive design features in a clinical trial provides preplanned flexibility to dynamically modify a trial during its conduct while preserving validity and integrity. Adaptive trials are needed to accelerate the conduct of more efficient, informative, and ethical clinical research in the field of neurology. Stroke is a natural candidate for adoption of these innovative approaches to trial design. This Research Methods in Neurology article is informed by a scoping review that identified 45 completed or ongoing adaptive clinical trials in stroke that were appraised: 15 trials had published results with or without a published protocol and 30 ongoing trials (14 trials had a published protocol, and 16 trials were registered only). Interventions spanned acute (n = 28), rehabilitation (n = 8), prevention (n = 8), and rehabilitation and prevention (n = 1). A subsample of these trials was selected to illustrate the utility of adaptive design features and discuss why each adaptive feature was incorporated in the design to best achieve the aim; whether each individual feature was used and whether it resulted in expected efficiencies; and any learnings during preparation, conduct, or reporting. We then discuss the operational, ethical, and regulatory considerations that warrant careful consideration during adaptive trial planning and reflect on the workforce readiness to deliver adaptive trials in practice. We conclude that adaptive trials can be designed, funded, conducted, and published for a wide range of research questions and offer future directions to support adoption of adaptive trial designs in stroke and neurologic research more broadly.

Introduction

Methodologists have long signaled that inclusion of adaptive design features in clinical trials can drive more efficient and ethical research across clinical trial phases compared with traditional fixed designs. An adaptive clinical trial offers preplanned opportunities to use accumulating data to modify design aspects during trial conduct while preserving validity and integrity.[1] Adaptations are implemented for the purpose of both maximizing statistical (and at times operational) efficiency and making better clinical decisions for participants and future patients.[2] Such goals can be achieved through a variety of adaptive features used individually or in combination (Table 1), with the most complex option being an adaptive platform trial. Common features include adapting sample size to gain sufficient power based on observed outcomes, removing interventions that are less effective, adapting randomization ratios in response to intervention outcomes, and enriching recruitment to specific subgroups that seem most likely to benefit. Enacting preplanned adaptive features due to futility may translate to fewer patients allocated to ineffective interventions, which presents a possible cost saving.

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Glossary

BOP = Bayesian Optimal Phase; **EVT** = endovascular thrombectomy; **ICH** = intracerebral haemorrhage; **STEP** = StrokeNet Thrombectomy Endovascular Platform; **UPLIFT** = UPper limb and Language Impairment and Functional Training.

Inclusion of adaptive features in clinical trials has been growing since early 2000s.[3] Several regulatory agencies have published guidance statements.[4,5] In 2020, the Adaptive designs CONSORT Extension (CONSORT-ACE) statement was published.[1] Such works have motivated funding bodies, researchers, and networks to consider the value of clinical trials inclusive of adaptive feature(s) to deliver their research agenda.[6,7] While historically the leading area of adaptive trial application was oncology,[3] accelerated implementation was observed during the coronavirus disease 2019 pandemic.[8] Despite adaptive trials being proposed as a possible solution to improve clinical trial conduct,[9] adoption in many conditions[3] including stroke is not well documented.

Clinical trials of stroke interventions are well suited to adaptive designs.[10] The term intervention is used to refer to any pharmacologic or nonpharmacologic treatment provided. There are many interventions across acute, rehabilitation, and prevention domains of the heterogeneous disease of stroke[10-13] that need to be efficiently screened and tested for clinical efficacy. This highlights an urgency to consider the advanced use of adaptive trial designs to identify early futility and eliminate ineffective interventions during trial conduct. Such impacts can prevent delays in testing alternative interventions while improving resource efficiency and minimizing how many patients are exposed to ineffective (and potentially harmful) interventions.[10] Because accumulated data inform preplanned adaptations, the very nature of an adaptive trial depends on the outcome of interest being observed precisely over a period that is substantially shorter than the overall trial duration. Primary outcomes for stroke trials can be measured as early as the first 24 hours (e.g., early neurologic recovery or imaging outcomes[14,15]) and 90 days after stroke (e.g., modified Rankin Scale in acute ischemic stroke[16] and rehabilitation[17]) or may even extend to 1 year and beyond (e.g., intracerebral hemorrhage [ICH][18] or composite outcomes in long-term prevention[19-21] trials). Some early outcomes (e.g., reperfusion within 24 hours after ischemic stroke) are also highly prognostic of longer term functional outcomes (e.g., 90-day modified Rankin Scale).[22] Collectively, this positions stroke as a natural candidate for embracing adaptive clinical trial designs.

This article examines the current use and future directions of adaptive features in stroke trials. Consideration of the differences between an adaptive and traditional trial design is outlined elsewhere.[2,10] With a focus on adaptive features in stroke trial design, we used a scoping review methodology to identify completed or ongoing adaptive clinical stroke trials to inform real-world case examples that illustrate utility of adaptive design features in practice. We subsequently consider the strengths and limitations of adaptive designs and workforce readiness to deliver adaptive trials (including the role of stroke organizations and trial networks). We conclude with future directions, for stroke and neurology broadly, to support adoption of adaptive trial designs to address important clinical research questions.

Table 1 Glossary of Common Adaptive Design Features Synthesized From Guidance Documents[1,2,4]

Adaptations to the timing for stopping a trial (also referred to as group sequential): allows for 1 or more prospectively planned interim analyses of data with prespecified criteria for stopping the trial. Criteria for stopping may be for early efficacy, safety, or insufficient evidence of efficacy, which is often called stopping for futility
Adaptations to sample size: allows adaptive modification to the sample size based on interim estimates that uses intervention assignment information or comparative interim results
Adaptations to patient population: allows adaptive modifications to the patient population and often involves both (1) modification of design features, such as the enrolled population and the population evaluated in the primary analysis, based on comparative interim results, and (2) hypothesis tests in multiple populations, such as a targeted subpopulation and the overall population
Adaptations to patient allocation based on comparative baseline characteristic data: covariate-adaptive randomization is adaptive modification to intervention assignment depending on the patient's baseline characteristics and the intervention assignments of previously enrolled patients to reduce the covariate imbalance in intervention arms
Adaptations to patient allocation based on comparative outcome data: response-adaptive randomization is adaptive modification to intervention assignment based on accumulating outcome data of patients previously enrolled
Adaptations to intervention arm selection: allows adaptive modification to the intervention arms based on comparative interim result, which may see arms added or terminated
Adaptations to end point selection: allows adaptive modification of the primary end point based on comparative interim results
Adaptive platform trial: allows for the study of multiple interventions in a single disease (or condition) in a perpetual manner, with interventions allowed to enter or leave the platform based on a decision algorithm. This design is based on multiple arms studied over multiple stages with a common control group(s). Such designs are often driven by within-trial adaptations (e.g., adaptations to patient allocation based on comparative outcome data)

Table 2 Methods for Selection of Included Trials

Search period: 1 January 2018 to 2 May 2023
Search sources: Trial registries (Australian and New Zealand Clinical Trial Registry and ClinicalTrials.gov) and publications (protocols and completed trials) through PubMed Central. Reference lists of included studies were hand searched, and authorship knowledge of the field was used to identify additional stroke trials (published or registered trials). Late breaking trials sessions at major stroke conferences were also hand searched, for example, European Stroke Organisation Conference
Search terms: Stroke and trial* and (adapt* or Bayesian or platform) and adaptive feature specific words from the CONSORT-ACE statement[1] were used
Eligibility: Clinical trials (ongoing [registered trial or published protocol] or completed) that enrolled people with stroke to receive an acute, rehabilitation, or secondary preventative stroke intervention and their design included at least 1 adaptive feature (Table 1) to answer an efficacy or effectiveness research question (i.e., phase II, phase III, seamless phase I-II, or IIb-III)
Selection: All results were independently reviewed by 2 authors (K.H./E.D.) using Excel (registry results) or Covidence (PubMed results), and conflicts were resolved through discussion with a third reviewer (L.C.)
Extraction: Data were independently extracted by 1 author (E.D.) and verified by another author (K.H./B.C.V.C.). Conflicts were resolved through discussion with an additional independent author (K.H./B.C.V.C./L.C.)

Identification of Adaptive Clinical Trials in Stroke

45 trials were identified from a scoping review of clinical trial registries and PubMed (overview of trial methods in Table 2; detailed information in eAppendices 1 and 2). 15 adaptive trials had published results with or without a published protocol, 14 had a published protocol only, and 16 had registration only. Details of included trial characteristics, designs, and adaptive features used and enacted are provided in eTables 1 and 2 and references in eAppendix 3. Interventions spanned acute (n = 28), rehabilitation (n = 8), prevention (n = 8), and rehabilitation and prevention (n = 1). Most common adaptive features were group sequential (n = 29) and sample size reestimation (n = 17). High use of group sequential is consistent with other observations[23] and may relate to its broad definition (Table 1). Twenty-seven trials included 1 adaptive feature, 12 included 2, and 6 included 3 or more. Most trials were investigator-initiated (n = 26 investigator-initiated only, n = 12 investigator-initiated, industry-supported) with a high-income country–specific national agency being the primary funding source, for example, NIH. 3 trials included sites in upper middle–income, and 4 included sites in lower middle–income countries.

Utility of Adaptive Features in Stroke Trials

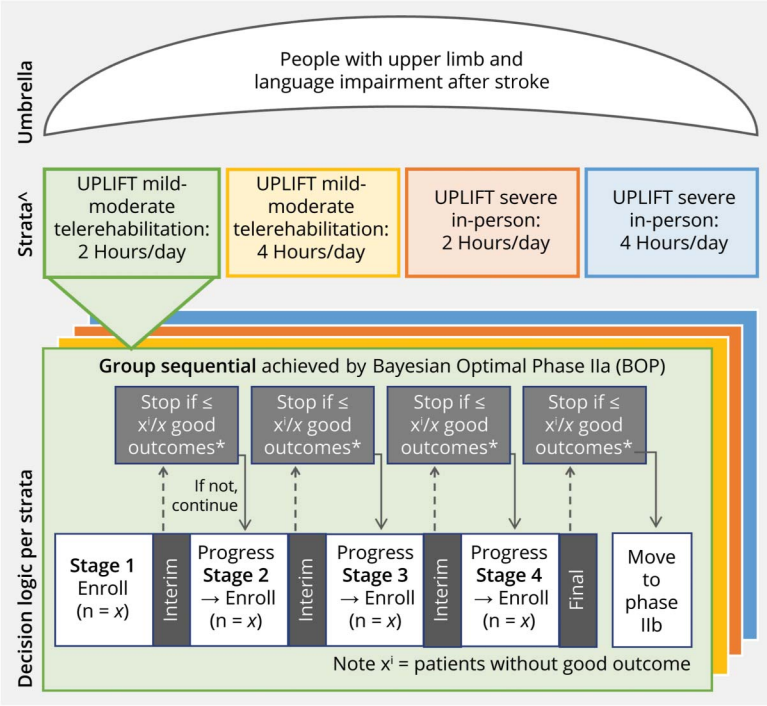
Each adaptive feature (Table 1) was linked to a real-world stroke trial (selected from eTables 1 and 2) to illustrate utility in written and visual format (Figures 1–3). Trials presented span acute/rehabilitation/prevention, trial phases, and stroke etiologies. 1 adaptive platform trial in the planning stage is also presented. To guide selection and facilitate a rich discussion of design and learnings, we focused on trials led by the authorship group. Each trial discussion focuses on why the adaptive features were incorporated in the design to best achieve the aim; reflection on whether each individual feature was used and whether it resulted in expected efficiencies; and any learnings during preparation, conduct, or reporting.

Adaptations to the Timing for Stopping a Trial

The SELECT-2[24] and TENSION[25] acute trials tested the efficacy of endovascular thrombectomy (EVT) in patients with extensive ischemic injury. Because there were potential safety and futility concerns in the most severely affected patients, their chosen designs included group sequential testing with strict z-score boundaries to reduce the risk of stopping early for false-positive results. Owing to early evidence of efficacy, the SELECT-2 trial stopped after the second interim analysis results and the TENSION trial stopped after the first interim analysis results were available. Owing to ongoing recruitment while the interim analysis outcomes were accrued, the final sample size was larger, and this was tested at the conventional significance level in the final analysis. On completion, both trials demonstrated that among patients with large ischemic strokes, EVT resulted in better functional outcomes than medical care. These early and positive findings resulted in cost, resource, and time savings for the trial and future participants and led to rapid inclusion into clinical practice guidelines, for example, SELECT-2 included in the living Australian Stroke Clinical Guidelines[26] within 5 months of publication. It must be noted though that in SELECT-2 only, EVT was associated with early neurologic worsening and procedural complications.

The UPLIFT trial (UPper limb and Language Impairment and Functional Training, ACTRN12622000373774) is an ongoing rehabilitation trial that includes group sequential testing. This trial aims to efficiently develop evidence for a new model of stroke rehabilitation, during community living. An umbrella design with 4 simultaneous Bayesian Optimal Phase IIa (BOP)[27] strata was adopted. In this design, the outcomes from the 4 BOP strata are not compared with each other but rather with a prespecified objective performance criterion.[28] The overall goal is to select the dose(s) of the UPLIFT intervention with sufficient promise, probed through group sequential testing (3 interim analyses, 1 final decision analysis per stratum). This offers a flexible approach to identify promising individual interventions by screening multiple doses under a single trial infrastructure. The adopted compositive binary

Figure 1 Visual Representation of the Adaptive Feature of Group Sequential Testing Achieved Using a Bayesian Optimal Phase II Design in the UPLIFT Trial



^Mild-moderate: Neither upper limb or language impairment is severe, but is at least mild; Severe: One of upper limb or language impairment is severe; All strata balanced on time poststroke. *Good outcome: Prespecified combination of preliminary efficacy + feasibility + safety.

primary good outcome (inclusive of signal of efficacy, safety, and feasibility) is used to determine whether a specific individual UPLIFT intervention is stopped or continued at each interim analysis point. The field of stroke recovery is yet to deliver practice-changing interventions such as thrombolysis or thrombectomy. There is a time imperative to identify futility early for novel interventions, which was afforded by a group sequential testing within an umbrella trial design. Naturally, this design has limitations when applied beyond situations where there is a reasonable belief that at least 1 individual intervention is likely to be of sufficient promise. If none of the interventions have sufficient grounds to be assumed promising, such an approach is not likely to generate actionable evidence. During trial setup, ethical approval was efficient (<30 days from submission to approval), which was afforded by clear reporting of the adaptive design due to statistical input and oversight and use of a design overview figure (Figure 1). However, there were challenges associated with trial registration because the process

Figure 2 Visual Representation of the Adaptive Feature of Sample Size Reestimation Achieved Using the Mehta and Pocock Promising Zone Method in the EXTEND-IA TNK Trial

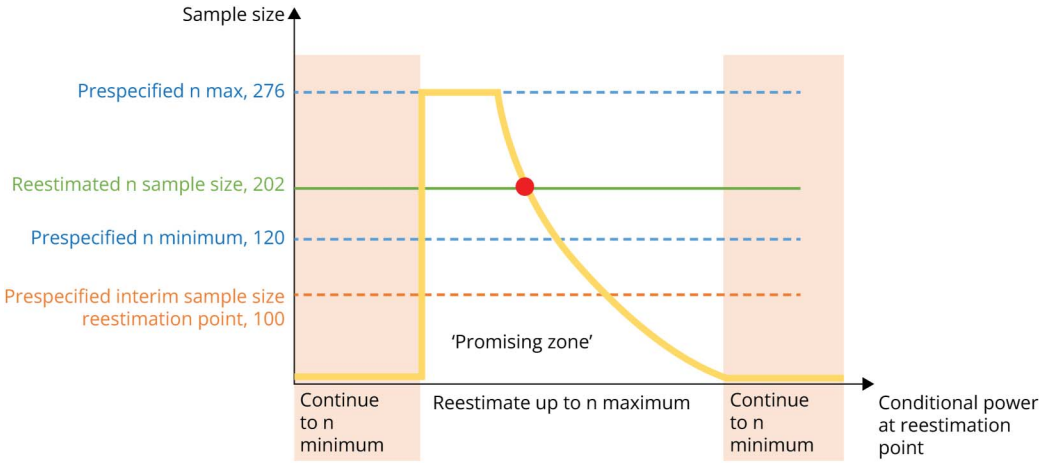
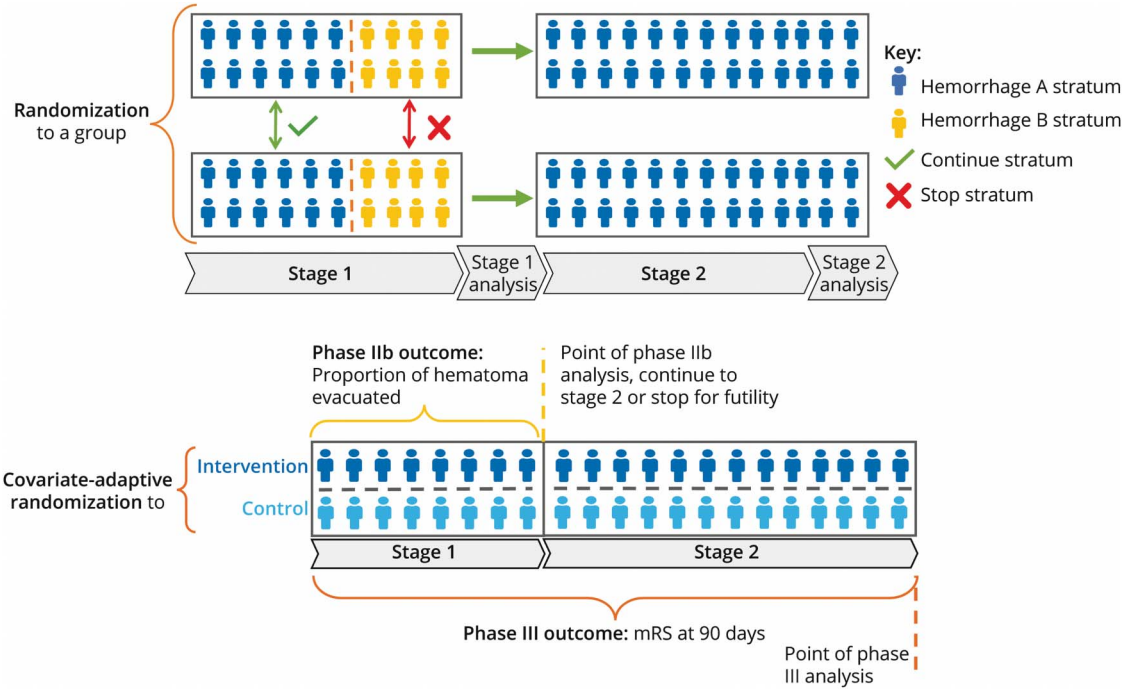


Figure 3 Visual Representation of Adaptations to Patient Population and End Point Outcome



Panel A: Visual representation of adaptations to the patient population, in this example, based on a stratum of hemorrhage location, which was applied in the ENRICH Trial. Panel B: Visual representation of adaptations to the end point outcome selected at phase IIb (hematoma evacuation) and phase III (modified Rankin scale [mRS] at 90 days) in the context of the EVACUATE trial.

at the time was not customized to cover for umbrella designs with adaptive features.

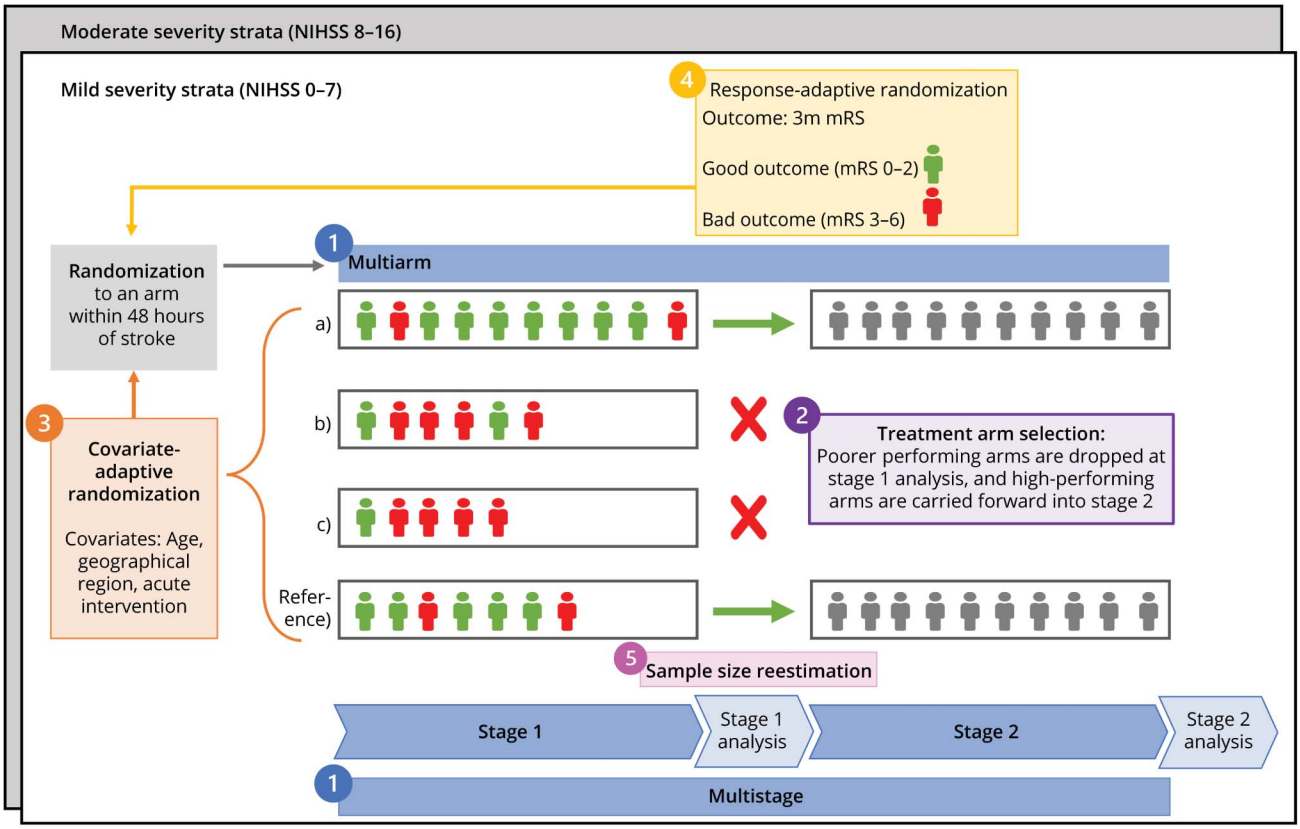
Adaptations to Sample Size

The EXTEND-IA TNK trial[29] compared 2 different clot-dissolving medicines (alteplase and tenecteplase) before EVT in a phase II noninferiority design using reperfusion at the initial angiogram as the primary outcome. Given the uncertainty around the expected effect size, an adaptive sample size reestimation was applied using the Mehta and Pocock[30] promising zone method (Figure 2). This has the advantage of being fully prespecified and reestimates the sample size within a specified range, based on the conditional power observed at the time of sample size reestimation. The choice of when to perform the adaptive sample size reestimation is a balance between greater precision with larger participant numbers and sufficient time to accumulate evidence regarding the primary outcome, accounting for recruitment rate, before reaching the minimum sample size. In EXTEND-IA TNK, the primary outcome was collected within hours of enrollment. This short period over which to observe the outcome allowed the reestimation to occur closer to the originally planned full sample size than it would have been had an outcome been collected at 3 months. The prespecified mechanism of the Mehta and Pocock method does not impose alpha-spending penalties for multiplicity of testing and uses the threshold of $p = 0.05$ for the final analysis. It is important to note that the intent of adaptive sample size reestimation is quite different to that used by group sequential testing, which imposes a stringent (e.g., $p < 0.001$) early stopping boundary to demonstrate early efficacy. In this trial, the estimated sample size was set at a minimum of 120 with a potential increase up to the maximum of 276 patients. The prespecified sample size reestimation occurred at 100 patients and established a final sample size of 202 patients. On completion, it was demonstrated that tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset.

Adaptations to Patient Population

ENRICH was a randomized trial[31,32] of minimally invasive surgery for ICH. The trial used a Bayesian design with adaptive enrichment. Scheduled interim analyses, beginning after 150 patients (and then at 175, 200, 225, 250, and 275, with the trial maximum sample of 300 patients) had been enrolled, were used to guide study enrichment based on hemorrhage location. A visual representation of how adaptive enrichment works is illustrated in Figure 3A. At interim analysis (adaptive feature of group sequential testing), the anterior basal ganglia stratum was closed early due to futility according to prespecified thresholds for enrichment while the lobar stratum continued. The final trial results were positive, driven by the benefit in enriched lobar ICH, with

Figure 4 Visual Representation of the 5 Adaptive Features (Numerically Numbered) of (1) Multiarm, Multistage; (2) Treatment Arm Selection; (3) Covariate-Adaptive Randomization; (4) Response-Adaptive Randomization; and (5) Sample Size Reestimation Included in the AVERT-DOSE Trial



neutral effect in the anterior basal ganglia group. ENRICH is the first trial to enact adaptive enrichment. Previously completed SELECT-2,[24] DEFUSE 3,[33] and DAWN[34] trials all prespecified the potential for adaptive enrichment to allow for sequential exclusion of subpopulations that were likely to have the worst prognosis and enrich the remaining trial population, should the overall interim result cross a safety or futility boundary. However, none of these 3 trials needed to enact adaptive enrichment.

Adaptations to Patient Allocation Based on Comparative Baseline Characteristic Data

The TELEREHAB-2 trial[35] was designed to determine whether intervention targeting arm movement delivered with a home-based telerehabilitation system had comparable efficacy with dose-matched, intensity-matched therapy delivered in a traditional in-clinic setting and to examine whether this system had comparable efficacy for providing stroke education. Baseline characteristics were selected as covariates, based on established evidence on potential confounding, in an attempt to prevent serious imbalances across the 2 intervention groups. The covariates used in this trial (time after stroke, severity of impairment, age, enrollment site, and stroke subtype) were balanced across the 2 intervention groups. Figure 4 illustrates a visual representation of this adaptive feature.

Adaptations to Patient Allocation Based on Comparative Outcome Data

MOST[31] is a multiarm trial of stroke thrombolysis to determine the safety and efficacy of intravenous therapy with argatroban or eptifibatide compared with placebo in patients with acute ischemic stroke treated with intravenous recombinant tissue plasminogen activator within 3 hours of symptom onset. Interim analyses were planned to occur after 500, 700, and 900 patients were randomized. Using a Bayesian approach, the predictive probability of a successful final analysis was calculated based on different assumptions about the remaining patients to be enrolled. When n = 500, 1 (or both) experimental arm(s) may be stopped for futility if there is less than 20% probability of demonstrating benefit compared with the control arm in either experimental intervention. Next, 1 (or both) experimental arm(s) may be stopped for futility when n = 700 or n = 900 if there is less than 5% probability of demonstrating benefit in either experimental arm if the trial were to continue. 1 (or both) arm(s) may be stopped early for efficacy after 700 or 900 patients if an arm has an expected successful predictive probability of demonstrating superiority to control of at least 99%. This trial, reported at International Stroke Conference 2024,[36] was stopped for early futility (n = 514 patients) after recommendation from the Data Safety and Monitoring Board. Figure 4 visually illustrates adaptation to patient allocation.

Adaptations to Intervention Arm Selection

The AVERT-DOSE trial (ACTRN12619000557134)[37] is an ongoing rehabilitation trial that includes 5 adaptive features, including adaptation to intervention arm selection. This trial aims to define optimal early (commenced within 48 hours) mobility intervention regimens for patients with ischemic stroke of mild and moderate severity across 7 countries (Australia, Malaysia, United Kingdom, Ireland, India, Brazil, Singapore). Ongoing uncertainty around the world about the safest and most effective early training approaches after stroke prompted this clinical trial.[38] The developed adaptive design is one of the most complex designs ongoing in stroke because it includes multiarm, multistage with intervention selection, covariate-adjusted and response-adaptive randomization, and sample size reestimation (Figure 4). Unlike the MOST trial, AVERT-DOSE is performing response-adaptive randomization within the frequentist rather than Bayesian framework. Focusing on the adaptive feature of intervention selection, in stage 1 (mild or moderate severity strata), 25% of patients will be randomized into the reference arm while randomization into 3 intervention arms is guided by the adaptive algorithm. At stage 2, randomization into the reference arm and the single selected intervention arm will be guided by the adaptive algorithm. Implementing this adaptive trial design enabled a wider variety of mobility regimes (3 regimens per stratum) to be tested than a traditional 2-arm design, enabling more efficient testing than otherwise possible.

Adaptations to End Point Selection

The EVACUATE trial (NCT04434807) is an ongoing trial testing ultraearly minimally invasive evacuation of ICH. This has been proposed as a means to reduce ICH growth, secondary injury from mass effect, thrombin, and iron toxicity. The MISTIE-III trial[18] provided proof of principle that effective ICH evacuation may reduce disability with a strong association between the proportion of ICH evacuation and the residual volume with functional outcome. This study also justified the use of the proportion of hematoma evacuated as an intermediate outcome (end point) in the EVACUATE seamless phase IIb/III 2-arm, 2-stage randomized trial with the primary outcome (end point) of mRS score at 90 days (Figure 3B). A 2-arm, 2-stage design is a specific case of a multiarm, multistage adaptive design[11] that capitalizes on the principles of group sequential testing and complements it with additional useful adaptive features. A seamless IIb/III design is particularly advantageous in a relatively rare condition such as ICH, in that the phase IIb patients can also contribute to the phase III analysis of functional outcomes. There are also logistical efficiencies in being able to proceed directly from phase IIb to III without stopping to resubmit ethics, obtain governance, and reinitiate sites. However, the use of an intermediate outcome to determine progression of the trial to the second stage (phase III) is fully predicated on demonstrated prognostic properties of this outcome in relation to the primary outcome. In this trial, the 2-arm, 2-stage design was complemented by an adaptive sample size reestimation within the second stage using the Mehta and Pocock method described above.[30] The randomization for this trial uses the covariate-adaptive common scale minimum sufficient balance algorithm[39] that improves the balance of key prognostic variables while maximizing the randomness of allocation.

Planned Adaptive Platform Trial

Recent pivotal trials have shown EVT to have large intervention effects in highly selected subsets of patients with acute ischemic stroke due to large vessel occlusions.[24,25,40] These have raised questions about whether more broadly selected patients would benefit from endovascular therapy. Furthermore, despite large intervention effects, most endovascularly treated patients remain functionally disabled, raising many new intervention and management questions in urgent need of answers. Each of these questions would need large and expensive clinical trials if performed in a traditional manner, and major therapeutic advancements would be prohibitively expensive. Therefore, the StrokeNet Thrombectomy Endovascular Platform (STEP) has been designed within NIH StrokeNet to address these questions using statistical and operational efficiencies. STEP (NCT06289985) is designed to determine the optimal intervention strategies for patients with acute ischemic stroke due to large or medium vessel arterial occlusions potentially amenable to endovascular therapy. The planning grant is nearing completion (NIH/National Institute of Neurological Disorders and Stroke OT2NS129366) and initial enrollment in the platform trial is anticipated in 2024.

STEP is a randomized, multifactorial adaptive platform trial that aims to study which patients with ischemic stroke should be treated with endovascular therapy and how to optimize that care further, regarding newer devices or techniques, adjunctive therapies, newer diagnostic strategies, and systems of care delivery.[41] The primary outcome is global functional outcome measured using the utility-weighted modified Rankin Scale assessed at 90 days. The platform will include 50 comprehensive stroke centers across the United States and Canada. The sites will work under a master protocol that integrates domains that include 1 or more intervention strategies that share a common clinical mode of action or context of use. Domain-specific modeling is integrated into 1 inferential statistical model, and the model allows for frequent adaptive analyses to assess the effects of distinct interventions.

The first domain, STEP Endovascular Thrombectomy Indication Expansion (STEP-EVT Indication Expansion), will assess EVT vs medical management in subgroups of patients with acute ischemic stroke with low NIHSS scores and/or medium and distal vessel arterial occlusions. Patients will be concurrently randomized to other domains, as they become funded by the NIH and initiated within the platform, and the model will estimate the effects of other domains using that domain's specific modeling that explicitly accounts for

potential interactions with other domains. Adaptive conclusions for each domain will be triggered by the primary Bayesian model run at a prespecified frequency. Adaptive decisions for each domain may include response adaptive randomization.

An adaptive platform trial, such as STEP, demonstrates how access to initial planning funds is critical to support the development of the platform and supporting infrastructure. Appropriate planning is important, given adaptive platform trials can run for a long period. National funding agencies in the United States, Australia, and the United Kingdom have recently had targeted funding calls for adaptive platform trials. Although not a formal requirement of an adaptive platform trial,[2] a feature of this trial is a shared control group, which allows new interventions to be compared with a common control and direct comparison of effect sizes between interventions and reduces the likelihood that a patient will end up in the control group.[8,42] However, use of a shared control does rely on the assumption that it remains equally acceptable to patients with time.[8] There are other considerations related to chronological bias including trends in outcome measures that may be caused by changes in standard of care, adding or dropping of participating centers, shifts in the patient population, systematic variations in participant responses to the control, or changes in expectancy effects when a new intervention that is perceived as particularly promising enters or leaves the trial.[8,42]

Strengths and Limitations of Adaptive Trials

Adaptive trial designs are heralded as a suite of tools to deliver more efficient trials. There are many aspects to consider whether this goal is achievable. Depending on the specific clinical research question, adaptive features may or may not be appropriate. The very nature of an adaptive trial depends on the outcome of interest being observed over a period that is substantially shorter than the overall trial duration to inform preplanned adaptations. As such, adaptive trials may not be suitable when the outcome of interest is collected years later, for example, long follow-up in secondary prevention trials. Alternatively, there may be limited or no access to appropriate statistical design and analysis support. Adaptive trials may increase the practical complexity and, in doing so, eliminate the theoretical efficiency gains.[43] Table 3 provides a narrative synthesis of documented operational, ethical, scientific, and regulatory considerations; supporting references for the table can be found in eAppendix 4. Because this review is primarily for a clinical readership, in-depth discussion of statistical considerations[1,23] is beyond its scope.

Clinical, Research, and Technical Workforce Readiness

Adaptive trials require access to statistical, data, and trial management workforce who are fluent in their design[44] to manage the potential impact on trial costs. A mock-costing exercise completed with 7 UK Clinical Trial Units estimated that nonplatform adaptive trials with pharmacologic interventions were 2%–4% more expensive than a nonadaptive trial equivalent.[45] The highest increase was for statistical staff, with lower increases for data/trial management staff.[45] Costings for appropriate statistical staff are highly dependent on the nature of the adaptive feature(s) included.[44] During trial conduct, adaptations that occur at prespecified interim analyses (e.g., sample size reestimation, multiarm, and multistage) may require more intensive ongoing input than adaptations managed on a day-to-day basis (e.g., software to adaptively randomize individual participants such as covariate-adjusted, response-adaptive). However, such randomization methods often require bespoke software[37,46] to be developed before trial start for which the code is generally not publicly available.[47] It is important to note such skills are different to those required to perform trial design and analysis work reflecting a unique workforce requirement for some adaptive designs.

Adaptive designs can affect site clinical and trial management staff. There can be additional costs associated with supplementary training in adaptive trial processes and procedures, and time to gain consent may be longer due to the complexity of transparently discussing adaptive features with potential participants.[44] Countering potential increased costs, trials stopped for futility can create efficiencies that traditional trials cannot offer. For example, an adaptive platform trial allows the same participant to be enrolled in multiple distinct intervention domains, thereby answering many questions through participation in only 1 trial.[48] This may mitigate challenges for patients in choosing between trials and clinicians maintaining recruitment across competing trials. Some adaptive features (e.g., adaptive sample size reestimation and changes in intervention arms open to randomization[49]) can lead to uncertainty in the amount of staff required and result in short-term contracts to ensure adaptive features (whether enacted or not) can be accommodated. Other more enduring features (e.g., adaptive platform) may offer greater staff stability because of their perpetual nature.[48] As such, the impact on site workforce varies depending on the adaptive features used and the volume of trials operating at a site, whether the site is part of a network (e.g., NIH StrokeNet) or has an accessible Clinical Trial Unit (e.g., UK centers).[23,44] These issues have been largely acknowledged from high-income countries and may be more pronounced in low-middle income countries and rural/regional centers.

With growing uptake of adaptive features, it is important to consider the role of organizations (e.g., World Stroke Organization, European Stroke Organisation, World Federation of NeuroRehabilitation, and Society for Clinical Trials) and networks (e.g., CanStroke Recovery Trials, Canadian Stroke Consortium, Australasian Stroke Trials Network, NIH StrokeNet, Global Alliance of Independent Networks focused on Stroke trials, Indian Stroke Clinical Trial Network, and European Stroke Organisation Trial Alliance) to prepare clinical trialists to embrace, where appropriate, adaptive trial designs. Stakeholders have identified that broadening the acceptance and uptake of adaptive trials will depend on access to training,

Table 3 Narrative Synthesis of Operational, Ethical, Scientific, and Regulatory Considerations

	Possible strengths provided	Possible limitations introduced
Operational		
Timely delivery of trial	Design, statistical, and recruitment efficiencies can lead to shorter trial duration, which may be seen as increased feasibility to deliver on time[e1]	Preplanning adaptive design modifications can require more effort at the design stage, leading to longer lead time between planning and starting the trial[e1]
Funding agencies	Adaptive trials can be viewed as novel and innovative, which can see them embraced. Examples of this include recent funding agency statements and calls from the Medical Research Future Fund in Australia,[e2] NIH in the United States,[e3] and National Institute of Health and Care Research in the United Kingdom[e4]	Conservative decisions by funding agencies may limit development of an understanding of when adaptive trials are applicable, what they can (and cannot) accomplish, what their practice implications are, and potential results expected;[e5] can be challenging to secure funding for some adaptive features, for example, for a seamless phase IIb-III, some funding agencies may want to see phase IIb results before providing phase III funding
Infrastructure	(electronic)Case Record Forms built may be used for more than 1 study, for example, master protocol studies of adaptive platform, basket, or umbrella[e6,e7]	Shared trial infrastructure must be hosted and maintained by some entity, which may change or evolve with time.[e6] Infrastructure must be built to be flexible and scalable from the outset, which require considerable planning and cost investment[e8]
Costs	Median increase in cost compares favourably against the increase in efficiency that some adaptive designs can introduce, for example, group sequential[e9,e10]	Increased costs have been identified across all aspects of an adaptive trial, with the greatest increase in statistical and design-related costs[e11]
Logistics	Introducing adaptive designs from early conceptualization of the trial is more effective than fitting an adaptive design at later stages of design.[e12] Allowing sufficient time for the design process to evolve and garner input from clinicians, biostatisticians, and adaptive design and lived experience experts is necessary[e12]	Logistical challenges can include limited access to resources for planning and technical requirements before funding submissions,[e12] communicating protocol changes to all parties,[e13] costing and forecasting budgets,[e11] planning for product supply, access to high-quality interim data in a timely manner so that adaptive decision-making can be based on up-to-date and reliable results, and the potential need for real-time Data and Safety Monitoring Board decisions[e1]
Recruitment	Enhanced targeting of recruitment to the 'right' participants can arise during trial conduct because of inclusion of some adaptive features. Features of adaptive randomization or population enrichment have been viewed positively by enrolling participants[e14]	Cumbersome recruitment, identification, and consenting processes can be major barriers, especially at more novice trial centers.[e15] This can limit adaptive trials to primarily occur at large, academic medical centers with existing research infrastructure[e15]
Staffing	Staff working on adaptive trials have acknowledged that they were exposed to and gained experience in all stages of a trial in a much shorter window of time compared with more traditional trial designs.[e16] This has been viewed to create a challenging, yet fast-paced work environment with many career development opportunities[16]	Increased demands on staff do exist, especially master protocol adaptive trials where there is no end point.[e16] Uncertain staffing costs[e11] as adaptations from accumulating data may change recruitment needs or intervention arms that staff need to be trained to deliver, or trial amendments can lead to issues with ensuring adequate and timely access to intervention supplies.[e5] Technical staff considerations include the considerable skills needed to complete trial simulations for different scenarios before starting a trial[6] as was required for trials such as AVERT-DOSE[e17] and STEP.[e18] Additional statistical staff may also be required for interim analyses, protocol development, and statistical analysis planning and execution[11]
Ethical		
Ethical approval	Adaptive clinical trial designs have been viewed to pose few ethical disadvantages from a societal perspective[e12]	Communicating design aspects that may change down the track using study documents such as the Participant Information Sheet can pose challenges.[e5] Concerns have also been raised about whether ethical review boards are ready to accept adaptive designs,[e13] although the many completed and ongoing adaptive trials may counterbalance this concern. Manifold governance questions when dealing with multiple medicinal products or medical devices can discourage researchers working in small and moderate-sized universities[e19]
Changes mid trial, including stopping early based on reviewing data	Allows informative and more ethical decisions to be made in a timely manner during the trial, for example, increasing a participant's probability of being randomized into an arm that is higher performing.[e20] Reduces the number of patients exposed to unnecessary risk of an ineffective intervention and allows them the opportunity to explore more promising alternatives[e1,e20]	An adaptive change to a trial design may lead to results after the adaptation that are different from those before the adaptation.[e1] Knowledge of comparative interim results by trial management personnel in cases of unblinding may make it difficult for regulators to determine whether, for example, a protocol amendment seemingly well motivated by information external to the trial was influenced, in any way, by access to accumulating comparative data. In addition, changing rules in an ongoing trial can also create complications with regulators.[e21] Early stopping of a trial based on an intermediate outcome (e.g., a biomarker used to progress seamlessly from phase IIb to phase III) may add a risk of premature discontinuation of a potentially effective intervention due to insufficient predictive value of early biomarkers for definitive later outcomes

Continued

Table 3 Narrative Synthesis of Operational, Ethical, Scientific, and Regulatory Considerations *(continued)*

	Possible strengths provided	Possible limitations introduced
Scientific		
Statistical efficiency	May increase the chance to detect a true effect (greater statistical power) than nonadaptive trials, or may provide the same statistical power with a smaller expected sample size or shorter expected trial duration[e1]	The opportunity for efficiency gains may be limited by important scientific constraints or in certain clinical settings,[e1] for example, when a minimum sample size is expected for a reliable evaluation of other outcomes (safety or secondary end points) or when the primary outcome of interest is ascertained over a longer window than it takes to enroll most or all patients in the trial (prevention or delayed outcome).[e1] Greater efficiency may come at the cost of conducting multiple frequent interim analyses, which may lead to increase in type 1 error.[e22] Within the Bayesian statistical framework, this is not regarded as a major concern as continuing the study can be decided at any interim analysis based on the mixture of previous beliefs and available data.[e22] Within the frequentist framework, the issues of false-positive findings are addressed more rigorously by various techniques that ensure that the total amount of type 1 error rate alpha is constrained over the course of the adaptive trial through adjustment for multiplicity of interim analysis testing. Making trial decisions based on conditional power evaluated at interim analysis, while reflective of the data collected up to the moment before conducting an interim analysis, may introduce the risk of misestimation of the true effect or a sample size required for observing such an effect with sufficient power[e23]
Design complexity	Access to statistical support ensures that appropriate analytical methods are used to preserve trial validity and integrity[e24]	Widely recognized as more complex than traditional fixed designs,[e1,e5,e20,e24-e26] which can increase trial costs[e11]
Understanding of intervention effects	Can answer broader questions generally not feasible with nonadaptive designs, for example, adaptive enrichment enables efficacy/effectiveness in targeted subgroups of a population to be demonstrated where nonadaptive designs would require infeasibly large sample sizes[e1]	Inadequate access to statistical design support can increase the chance of erroneous conclusions and introduce bias in estimates[e1]
Regulatory		
Regulatory discussion	Not the intent of regulatory bodies, for example, US Food and Drug Administration[e1] or European Medicines Agency,[e27] to require or restrict the use of adaptive designs in general or specific settings	The increased complexity of some adaptive trials and uncertainties regarding their operating characteristics may warrant earlier and more extensive interactions with regulatory agencies than usual[e1]
Regulatory evaluations	Additional opportunities for review may help to maintain (or even enhance) trial integrity and validity[e1]	Review of complex adaptive designs often involves challenging evaluations of design operating characteristics, usually requiring extensive computer simulations and increased discussion across disciplines and regulatory offices about the evaluations.[e1] Regulatory agencies tend to review proposals for adaptive designs with greater scrutiny than they give to conventional designs.[e20] This arises from serious concern that poorly conceived designs may not control the type I error and may actually be less efficient than conventional designs[e20]

All references included in this table can be found in eAppendix 4.

guidelines, and toolkits to ensure proper use of adaptive trial designs in practice.[50] Currently, most educational opportunities (e.g., webinars and scientific meetings) do not provide the depth of training required.

Consumer Perspective on Adaptive Features

Few studies have examined the consumer perspective of enrollment into an adaptive trial. A qualitative study[51] within the MOST acute stroke trial (included adaptive randomization) identified some key learnings. While adaptive randomization was viewed as an increased chance of receiving a beneficial intervention, this equally highlighted areas of concern for misunderstanding. Explaining adaptive randomization was viewed as complex. Consumers required significant explanation to understand the way it would be performed in practice during consent. This raises concerns about the time it could take to clearly explain adaptive features and maintain trust, especially in the context of time-sensitive hyperacute stroke trials. The limited evidence base identified highlights considerable scope to investigate the consumer perspective of adaptive features and how the complexity of adaptive designs can be communicated to consumers.

Conclusions

There is considerable use of adaptive design features across efficacy and effectiveness trials of acute stroke interventions and emerging use for trials of rehabilitation or prevention. The trial examples highlight how meaningful adaptive trial design decisions can be applied in stroke to deliver more efficient and ethical trials, which may in turn deliver cost savings. From a public health perspective, adaptive trial designs can no longer be overlooked and warrant consideration by funding agencies. When adaptive features are incorporated, it is imperative they are used correctly to preserve trial validity and integrity. Inclusion of any adaptive feature(s) is no panacea. Researchers, funders, and sponsors will always need to carefully consider whether an adaptive design provides the most appropriate approach to answer the research question, just as with any suite of design tools. Time and resources must be allocated to the preparation work required to design an adaptive trial. Once doing an adaptive trial, comprehensive and transparent reporting across all trial sources (i.e., trial publications and registration) is essential. There is scope to improve reporting of adaptive features based on the number of trials identified through authorship knowledge of the field rather than explicit reporting in publications and registries. Adherence to guidelines (i.e., CONSORT-ACE[1]) can enhance quality of reporting and ability to find and learn from previous adaptive trials. Greater knowledge across the research workforce will support peer review of grants and publications that include adaptive design features. Overall, we have demonstrated that adaptive trials can be designed, funded, conducted, and published for a wide range of stroke research questions. We advocate for broader, responsible adoption of adaptive designs to address many amenable clinical research questions in a more efficient and flexible manner.

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