Adaptive versus Fixed Designs in Confirmatory Clinical Trials: Centering the Choice on Ethics

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[1] The MHRA welcomes and supports safe innovative approaches to clinical trials. Adaptations can be acceptable if they are safe and scientifically justified. There is no one-size-fits-all approach to these trials, and each trial is assessed at an individual level.

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Abstract

Importance: Because confirmatory clinical trials are costly, large-scale endeavors, the choice of their design carries significant weight. While the current methodological landscape offers tools to address residual pre-trial uncertainty through pre-specified adaptations to design elements, design choices remain frequently constrained by prevailing orthodoxies. We posit that trial design must transition from a habit-based process to one where pre-trial uncertainties are openly discussed and addressed. Strict adherence to default templates prevents stakeholders from matching the design strategy to the specific complexities of the research question.

Observations: We observe that the "gold standard" status of fixed designs often obscures their limitations in handling design uncertainties. A rigid adherence to these conventions can ethically hinder a trial's ability to deliver conclusive results. Conversely, while adaptive designs can offer tools to efficiently reduce uncertainty, we acknowledge that adaptive elements are not without cost; their implementation requires rigorous safeguards to manage specific risks to trial integrity and potential operational biases.

Conclusions and Relevance: To better align clinical research with its ethical and scientific mandates, we issue two calls to action. First, trial designers, including statisticians, must clearly articulate how target and design uncertainties impact ethical obligations, promoting an open-minded evaluation of both fixed and adaptive methods. Second, stakeholders must foreground ethical considerations during design selection, requiring explicit justification for the use—or non-use—of adaptive elements. The ethical path forward is not to default to the old or blindly adopt the new, but to explicitly justify the chosen design based on its responsiveness to the specific uncertainties of the trial.

Main text

Clinical trials are tools for generating the evidence that guides critical decision-making across the entire healthcare landscape. This evidence is relied upon by everyone from patients and clinicians to policy makers and researchers, influencing individual health, the safety, equity, and efficiency of health systems, the use of scarce resources, and the direction and pace of innovation. Clinical trials are also social undertakings that must advance and respect inherently ethical purposes. As a result, their design must be responsive to a complex mix of scientific, statistical, and ethical requirements. In April 2025 a workshop in Cambridge, UK, convened stakeholders to consider how adaptive trial designs relate to these requirements. The workshop, with 113 participants, included methodological statisticians, research ethicists, clinical trialists (from both industry and academia), as well as representatives of regulators, health technology assessment bodies, patients, and the public. This paper is a result of that workshop and subsequent discussions.

The interaction among these diverse stakeholders quickly surfaced two ethically relevant tensions. First, the task of ensuring that individual trials employ rigorous scientific, statistical, and ethical standards to advance clinical research objectives is hindered by persistent divergences in perspectives about what constitutes an adaptive design and by prevailing orthodoxies and heuristics regarding the merits of particular design elements. Second, many stakeholders do not appreciate the way that design uncertainty–understood as uncertainty about assumptions necessary to design a trial–can impact the statistical and ethical merits of a design. Specifically, trials are designed based on numerous assumptions—such as expected effect sizes or event rates—that are frequently uncertain or outright incorrect. These tensions also interact. As an example, the common heuristic of labeling certain design features as "gold standard" (such as a fixed total sample size, a fixed 1:1 randomization ratio, and a fixed set of interventions decided *a priori*) sets a default assumption in favor of fixed designs while obscuring the impact that incorrect design assumptions have on the scientific and ethical merits of those designs.

This paper's central claim is that stakeholders can better assess the merits of specific trial given the demands of the context by: (i) foregrounding the fundamentally ethical considerations that shape both the objectives and the constraints of the trial, (ii) requiring that the trial design be justified in terms of their responsiveness to these objectives and, (iii) including consideration of the impact of design uncertainty on proposed designs. This claim is supported by four arguments. Together, this claim and its supporting arguments ground a call to action for all stakeholders in this enterprise to shift away from simple generalizations about the merits of design elements and to better connect design choices to the ethical objectives that determine their merits in particular contexts and that justify the conduct of a particular trial.

The Ethical Pitfall of Persistent Divergence in Perspectives

Clinical trials require the cooperation of diverse stakeholders who often differ in their disciplinary background, their familiarity with the state of the art in these various fields, their practices for using particular terms, or the lessons they draw from salient cases. Despite a growing literature in statistics[1,2,3,4,5,6], ethics[7,8,9,10,11,12,13], and regulatory guidance[14,15,16,17] on adaptive trial designs, participants reflected lingering divergences in perspective also seen in the literature (Table 1).

These variations and divergent perspectives complicate communication and the process of evaluating particular designs based on common ground.

First, stakeholders often take the term “adaptive trial” to refer to different things. Some stakeholders lump together both pre-specified and ad hoc adaptations under the same heading. Others take the term to refer to specific types of adaptation, such as response-adaptive randomised designs, and to exclude group sequential designs. Some stakeholders associate adaptive designs with Bayesian methods while others recognize that this is not the case.

Second, these diverging associations are often connected to differing normative attitudes. Some regard the term “adaptive” as purely descriptive. Some associate adaptive designs with the stigma from early controversies over the use of response-adaptive elements in the ECMO trial[,18]. Others embrace adaptive designs for virtues prominently displayed during the COVID-19 pandemic[19] and the interest this spurred[20,21]. Adaptive designs are frequently referred to as novel, reinforcing the status of fixed designs as “traditional” and the “gold standard". In other cases, adaptive designs are associated with a particular type of ethical benefit, such as “individual ethics” understood as concern for promoting beneficial outcomes for trial participants, while fixed designs are associated with “collective ethics” understood as concern for the wellbeing of future patients[22,23,24].

Preferred Definitions

To avoid confusion, the stakeholders in clinical research require definitions that are analytically sound and both statistically and ethically relevant. We use the term “adaptive design element” to refer to any pre-specified, data-driven (meaning the data arising from the clinical trial itself) alteration to some aspect of a trial, paired with a prespecified design-based analysis. Adaptations can involve design elements such as the number of interventions, the procedure for participant allocation, sample size, trial population, or some aspect of the trial hypothesis (see Figure 1a). In contrast, a “fixed design element” refers to a feature of a trial that is determined at the design stage and it remains unchanged throughout the trial. We define an “adaptive trial” as any trial that includes *at least one* adaptive design element and a corresponding prespecified design-based analysis. In contrast, a “fixed design” is a trial in which *all* design elements are determined at the design stage and whose analysis assumes they remain unchanged throughout the trial[25].

These definitions have several virtues. First, they group aspects of trials together by shared features, such as whether they are altered in light of accumulating data, and the assumptions behind their analysis, rather than by social convention. Second, these shared features are not arbitrary, but relate directly to the statistical and ethical merits of a trial. Third, these definitions exclude ad hoc alterations to trials because they differ from both fixed and adaptive design elements in that they are not pre-specified and paired with a plan for analysis at the design phase. Finally, these definitions make it easier to highlight the way in which design uncertainty can impact the performance of trials that employ adaptive versus fixed design elements.

Prioritizing Ethical and Statistical Merit Over Convention in Design Choice

Our claim is that stakeholders can better coordinate to identify the best design in particular cases by foregrounding the ethical values at stake and then considering whether fixed or adaptive design elements best promote these values under the circumstances that are likely to obtain in actual practice.

For clarity, we divide the relevant ethical values into three categories. The first involves the core mission of clinical research, namely, generating the evidence needed to improve the safety, effectiveness and equity of the care received by patients and the efficiency of the health systems that deliver it[26]. These considerations together constitute the "social value" of the information generated in research[27]. The second involves eliminating or reducing avoidable harms and burdens to participants including harms from allocating more participants than needed to establish interventions are more (or less) beneficial than a feasible alternative. The third involves responsible stewardship of scarce resources where this includes clinical personnel as well as the financial costs associated with running a trial.

Articulating the likely circumstances under which a design will be implemented requires explicit consideration of uncertainty around assumptions required for such a trial to advance these ethical goals. This includes elaborating the conditions under which fixed or adaptive design elements are feasible and the ease or difficulty of implementing them adequately in practice. For example, feasibility requires the primary outcome of adaptation to be observable in enough time to allow for the design modification[28], while maintaining integrity during correct implementation often requires stringent firewalls and procedures when data is analyzed more often, such as in frequent interim analyses. The absence or lowered quality of these firewalls inherently poses a heightened risk to trial integrity—a risk less likely to occur in a non-adaptive, fixed design.

Four arguments support our claim.

First, there are circumstances in which fixed designs fail to advance any of the ethical values outlined here and this outcome could be avoided with the careful use of adaptive design elements. These circumstances arise when trials fail to produce information that answers their motivating question due to faulty assumptions about an important design element[29]. Such trials lack social value, subject trial participants to unnecessary risk and burden, and waste the time and resources of stakeholders. A recent review of Cochrane meta-analyses[30] indicates that "underpowered studies made up the entirety of the evidence in most Cochrane reviews." While the specific causes of this underpowering vary and we cannot precisely quantify the proportion of these trials that were intended as confirmatory, this serves as a proxy for the magnitude of the problem. When this problem is driven by uncertainty in pre-trial assumptions, an adaptive design becomes a valuable choice.

For a fixed design to advance these three ethical objectives, it requires that no circumstances–and in particular no circumstances relating to data emerging from the trial itself–arise that necessitate major changes to the trial. However, such circumstances are common and a weakness of fixed designs is that they do not specify in advance how to respond to potentially foreseeable eventualities in ways that address each of these ethical concerns in a principled way (Figure 1a and 1b).

For example, to determine the necessary sample size of a trial, researchers must estimate the variance of the treatment effect estimator of interest to ensure sufficient power to detect a true

meaningful difference of interest (see Figure 1b). In a fixed design, researchers typically use an estimate of this variance, determine the total size of the trial and run it to completion. However, despite a well justified choice of an estimate, if this is lower than the true variance (as suggested by the trial data), maintaining the plan can result in an underpowered trial, reducing social value and potentially requiring additional studies to answer the trial question[30]. An adaptive strategy like sample size re-estimation (SSR) can better respond to this uncertainty: by adding pre-specified interim look at the accumulating trial data, for example, chosen to coincide with the initially planned total sample size of a fixed design, at which point the trial data is analyzed so that researchers can obtain a more accurate estimate of the variance and adjust the final sample size accordingly to ensure the desired statistical power is maintained. However, this flexibility is not without risk. A crucial part of this consideration is determining the necessary level of unblinding required to execute the SSR with minimal risks to the trial integrity.

An advantage of adaptive designs is that they use predetermined strategies to respond to uncertainty around crucial assumptions by updating estimates as data accumulate and, if necessary, alter the original design's elements. When studies (fixed or adaptive) lack adequate power, error rate control, bias mitigation, or suffer from other methodological shortcomings, they can expose participants to the cost, inconvenience, risk, and harms associated with trial participation without producing the social value that was regarded as necessary to justify those burdens at the time the trial was designed. This was illustrated during the COVID-19 pandemic where the proliferation of small, uncoordinated studies produced redundant efforts, wasted resources, and imposed unredeemed burdens on participants[31,32].

Our contention is that stakeholders will be better able to advance the social and scientific purposes of confirmatory trials if they routinely consider the merits of adaptive designs as a strategy to address design uncertainty.

Second, at the design stage, every trial requires that the ethical values articulated here be integrated or balanced appropriately. Adaptive designs can make it easier to remain faithful to that balancing once a design is implemented. For example, ethical research begins in a state of uncertainty about the relative clinical merits of a set of interventions and each trial must specify the features of the evidence (e.g., power to detect an effect of a certain size) that will count as a sufficient reduction in uncertainty *ex post*[33]. Pre-specified stopping rules enable stakeholders to articulate precise conditions under which evidence of futility or benefit that arises during the conduct of the trial is sufficiently strong that continuing with the initial randomization scheme would intentionally subject some trial participants to harms that are now avoidable, given the weight of accumulating evidence in the trial. Stopping early can avert unnecessary harms and the expenditure of resources that are unlikely to be redeemed by the social value of the information generated. Though early stopping can reduce the precision of effect estimates or introduce bias[34,35], preplanning enables stakeholders to anticipate and manage these issues within defined criteria, potentially making the primary trial result more credible and action-guiding[36,37]. Stopping studies in the absence of pre-specified stopping rules can delay the stopping time, introduce bias, and lead to type I error rate inflation. Some avoidable harms related to safety can be averted through the use of independent data monitoring committees (IDMCs). But if the underlying trial design is fixed, IDMCs must make ad hoc judgements about efficacy or the tradeoffs between participant burden and benefit (see middle part of Figure 1a).

Third, our claim can encourage stakeholders to consider whether these ethical values can be better advanced by increased coordination and planning not just within individual studies, but

across “trajectories” of inquiry. During the COVID-19 pandemic, global platform trials like RECOVERY[38] and SOLIDARITY[39] examined numerous interventions, delivering rapid, reliable answers. Master protocols require stakeholders to consider not just the design of individual trials, but the design of sets or “trajectories” of trials and can fruitfully employ adaptive elements, for example, to prospectively determine when to add or drop arms or to dynamically adjust sample size. These strategies can reduce the time between trial phases and the time and effort expended on independent review of individual trials. Enforcing a common statistical framework on “trajectories” of trials can also increase the bandwidth of information produced and promote interoperability[40]. In the context of rare diseases, employing such a common statistical framework can permit the testing of more interventions with fewer participants than uncoordinated pair-wise trials.

Finally, by asking stakeholders to evaluate the relative merits of alternative designs in relationship to these core ethical values, our claim centers on reasoned assessments and the ethical grounds of designs. This focus provides a counterweight to fads, stigma, uncritical adherence to convention, and advocacy for particular designs or statistical traditions (such as Bayesian or frequentist schools). We have tried to illustrate how adaptive designs can better advance these goals in some cases. However, adaptive designs do not advance these goals in other cases. Some adaptations can introduce internal validity threats that must be stringently addressed and managed. Other adaptations can tax the ability of downstream evidence users to formulate independent interpretations of trial results. Adaptations motivated by a sponsor’s goals may cut short data collection that other stakeholders may need. Their increasing design complexity can challenge the ability of stakeholders to comprehend the cumulative effects of the design choices on the dimensions outlined here[13,41]. More complex designs can also make higher demands on infrastructure, from computing capacity, to the availability of experienced statisticians and the capacity of various review committees to oversee their conduct. Whether these hurdles are surmountable depends on the types of adaptations contemplated, and the level of resources and infrastructure available. The proliferation of more complex designs has the potential to worsen health research disparities. Stakeholders from low and middle-income countries (LMICs) and other under-resourced settings should consider these practicalities and balance the added complexities and validity threats for adaptive designs against their capacity to respond to design uncertainty using fixed designs. The potential benefits of adaptive design elements may not always justify their added costs and complexity, particularly when there are statistical reasons to avoid them, such as the difficulty of handling substantial temporal trends within a pre-specified analysis plan[42,43].

Ensuring that stakeholders, across the full range of global settings, understand the benefits and limits of designs, adaptive and non-adaptive, and the conditions under which they best realize these ethical advantages is necessary to ensure that every trial design is justified by the requirements of the clinical trial and the ethical and methodological merits of the approach taken. There is (ethical) work for stakeholders in this enterprise to do to remove systemic barriers to ensure equitable consideration of design options, to foster awareness of design uncertainty, and the relative merits and challenges associated with fixed and adaptive elements for delivering high quality evidence that advances the ethical objectives elaborated here. Some of this work has begun and is in development (see Table 2). For example, the FDA Complex Innovative Trial Design (CID) program[44] and recent regulatory guidance on adaptive designs such as ICH E20[16] represent a movement in the right direction. However, given the diversity of stakeholders and the challenges of communicating across disciplinary boundaries, we need

imaginative strategies for fostering reasoned evaluations. This is not just about the dissemination of information but requires active involvement with stakeholders including patients and publics. One of the key learnings from our work with patient and public contributors was about the need for engagement strategies which go beyond lectures and training courses, and include bespoke approaches which give those stakeholders direct exposure to ethical considerations around the use of these techniques and how to think through their application in real cases.

Conclusion

Stakeholders in clinical research require a framework for evaluating clinical trial designs that fosters an open-minded evaluation of the relative merits of fixed versus adaptive design elements. We have argued that this might be achieved by foregrounding fundamentally ethical considerations. That is, through proactive consideration of design uncertainty and whether fixed or prespecified, data-driven adaptations best promote social value, reduce harms to participants, and make effective use of scarce resources. This shift in perspective would enable a more explicit evaluation of the potential benefits of adaptive methodologies (where feasible) and facilitate their adoption where they serve these ethical objectives through a rigorous system of operational safeguards. These arguments have important practical consequences for stakeholders, particularly methodologists and regulators, by encouraging a pathway for this change across the clinical trials landscape.

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Table 1: Examples of persistent differences in perspective on adaptive design elements and adaptive trials.

The gold standard	"Fixed randomized clinical trials (RCTs) are widely considered the gold standard for determining the relative efficacy of medical treatments." (1) "Fixed randomized clinical trials are considered the current gold standard for evaluating the efficacy of novel treatments, where the anticipated effect size and the estimated event rate in the control group are used to determine a fixed sample size." (2) "Fixed randomized controlled trials remain the gold standard in clinical drug development; however, there is growing interest in innovative trial designs with the potential to increase the efficiency of the development process." (3) "EFPIA acknowledges that the traditional RCT is the current gold standard for providing robust evidence to support an evaluation of efficacy and safety leading to the registration of a medicinal product." (4)
Adaptive designs and novelty	"Although adaptive designs have been the focus of continuing research and debate in recent years, they have never become part of mainstream clinical research methodology" (5) Authors searched for adaptive designs in all trials on ClinicalTrials.gov from Jan 2006 to July 2021 and only found <300 examples (6)
Ad hoc adaptations included as an "adaptive" element or adaptive trial.	"an adaptive design that falls into a gray area with respect to whether or not it meets the FDA definition of being pre-specified" (7) Unplanned arm adding (8) Unplanned sample size increase (9) "The DSMB is in a tempting position to be able to implement adaptive trial methods after the examination of interim data. This currently runs specifically against the regulatory concepts of adaptive trial designs, in which adaptive designs must be prespecified before an interim analysis, as the FDA draft guidance for adaptive trial designs describes, but might be permissible under the independent oversight of a DSMB. The FDA does recognize that during the course of a trial,

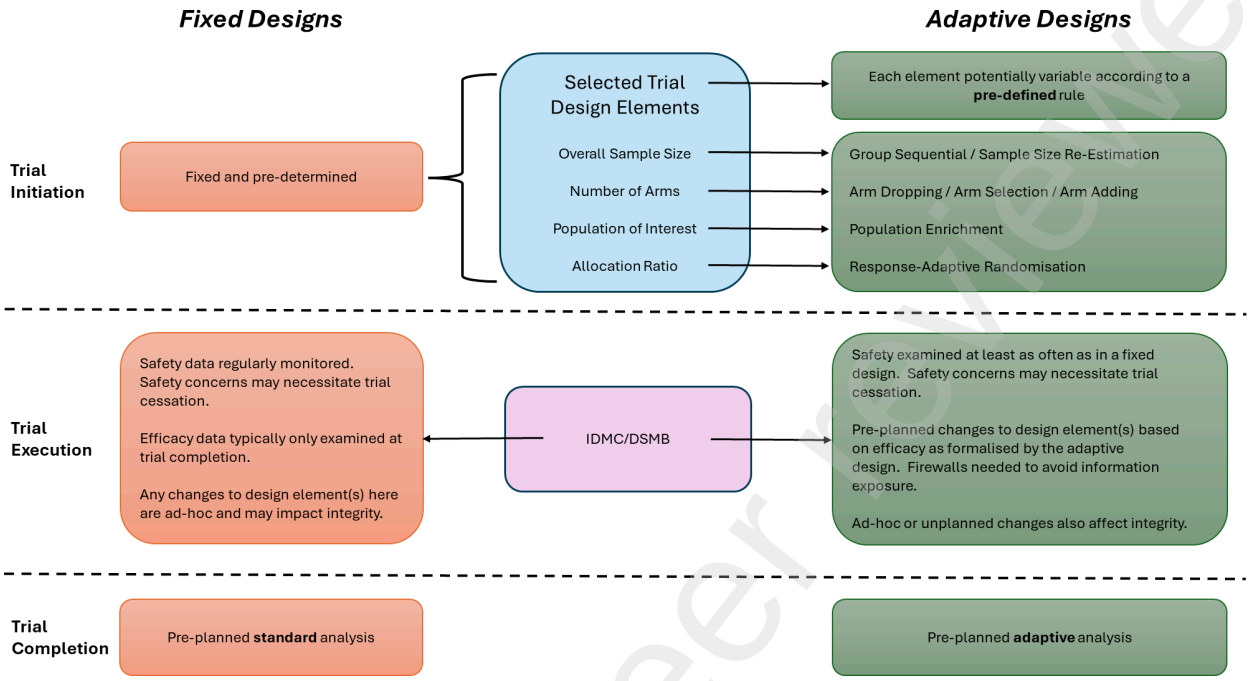
	outside information may become available that suggests that trial changes should be made to protect patient safety. FDA guidance comments that in such a case, an adaptive implementation may be warranted, and the sponsor should still remain blinded to the interim results. The DSMB may thus be the best positioned to help with a conversion to an adaptive design." (10)
Uncertainty about whether group sequential designs are adaptive designs	"In the beginning, the already well-established group sequential community was reluctant to accept connections between adaptive and group sequential designs. There was a sharp controversial discussion on the scientific value of applying adaptive designs in contrast to group sequential designs 14, 15, 16, 17, 18 mainly because of the violation of the sufficiency principle 19. Moreover, this critical view stated that classical group sequential designs are flexible and adaptive enough, in the sense that the sample size is changed in a data-driven way through the introduction of stopping rules. Interestingly, although the arguments have not changed, some of the authors having been very critical initially are nowadays accepting adaptive designs. Today, it is commonly accepted that group sequential trials can be considered as a special case of the more general adaptive designs" (11) "We do not regard [group sequential designs as] adaptive designs here because neither involves modifying a study element and continuing the trial with the revised methods." (12) "Trials with traditional (or classical) group sequential design are not allowed to modify the pre-specified study criteria, such as sample size, frequency of interim analyses, length of study and trial stopping rule [33]. Because of this, in this review this design is not considered to be an adaptive design." (13) "There are a multitude of adaptive designs, with the most common including group sequential designs, adaptive randomization, pick-the-winner/drop-the-loser, sample size reestimation, adaptive enrichment, and Bayesian adaptive designs" (14)

Table 2. Adaptive Trial Elements: Methodological Concepts and Illustrative Trial Examples

This table lists several adaptive elements (Column 1), gives references of trials where the design included said elements (Column 2), and provides methodological references (Column 3).

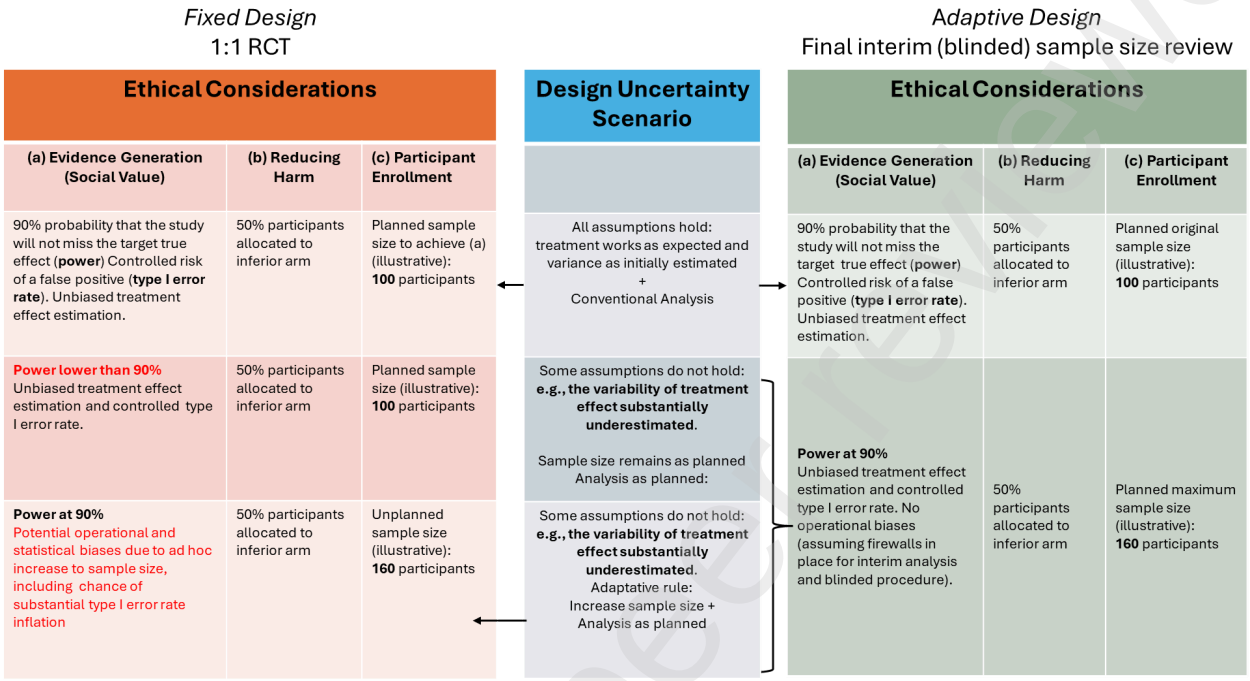
Adaptive element	**References to trial examples**	**References to methodological papers/books**
Group sequential / sample size reestimation	AIMM[45] , NOTACS[46]	Sources: 1,2
Adding/dropping/selecting treatment arms	RECOVERY[29]	Sources: 3
Population selection (adaptive enrichment designs)	TAPPAS[47]	Sources: 4, 5
Response-adaptive randomization	endTB[48]	Source: 6

Figure 1a: Key differences between *fixed* and adaptive designs



The top part of Figure 1a lists four selected design elements that are pre-determined and unchanged in a *fixed* randomized controlled trial design (left), and that can be altered according to pre-specified, data-driven rules in adaptive designs (right). The middle part of Figure 1a indicates differences in the ways in which an independent data monitoring committee (IDMC)/data and safety monitoring board (DSMB) work under a *fixed* design and an adaptive design. The bottom part of Figure 1a highlights the differences in preplanned analysis at the end in each case.

Figure 1b: Conceptual comparison of the ethical considerations of *fixed* versus adaptive designs for some scenarios



This schematic provides a conceptual overview of how a *fixed* design compares with sample size re-estimation (a type of adaptive design) under design uncertainty, in terms of the ethical dimensions of preserving social value, reducing harm to participants, and stewarding scarce resources. For clarity, we assume normally distributed data and a blinded sample size review procedure after a *fixed* sample size of participants data is collected. Operational bias refers to the unintentional influence on the outcome of a clinical trial by unblinded analysts having access to interim data.