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Emergence of Adaptive Clinical Trial Designs in Oncology: Focus on Small Molecules, Monoclonal Antibodies, and Antibody-Drug Conjugates, with Special Reference to Patient-Reported Outcomes

Dr. Sharika Pillay MD*

Senior Resident, Department of Pharmacology HBTMC and RNCH Mumbai

***Corresponding author:** Dr. Sharika Pillay, Senior Resident, Department of Pharmacology HBTMC and RNCH Mumbai

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Abstract

Background: Oncology drug development is undergoing a paradigm shift driven by the increasing adoption of adaptive clinical trial designs. These methodologies permit pre-specified modifications to trial parameters including dose allocation, sample size, patient population, and treatment arms-based on accumulating interim data, without compromising Type I error or the integrity of statistical inference. The expanding oncological armamentarium-encompassing targeted small molecules, monoclonal antibodies (mAbs), and antibody-drug conjugates (ADCs)-provides both the scientific rationale and therapeutic complexity that render adaptive designs particularly valuable. Concurrently, the integration of patient-reported outcomes (PROs) as co-primary or key secondary endpoints in adaptive oncology trials is reshaping the evidence framework for regulatory approval and clinical practice.

Objectives: This review evaluates the emergence and evolution of adaptive clinical trial designs in oncology, examining their application across small molecule, mAb, and ADC programmes, with particular focus on the role of PROs as endpoints and measures of patient-centred benefit.

Methods: A structured narrative review of published adaptive oncology trials, regulatory guidance documents, and methodological literature from 2010 to 2024 was performed, with qualitative synthesis across therapeutic modalities.

Results: Adaptive oncology trial registrations increased from 18 to 521 annually between 2010 and 2024. Response-adaptive randomisation and seamless Phase II/III designs are most prevalent. Biomarker-driven arm-dropping and population enrichment strategies have substantially improved drug development efficiency for precision oncology agents. PRO data from adaptive trials demonstrate systematically superior patient-centred outcomes compared to standard designs, with mean improvements in overall quality of life (QoL) scores 8.2 percentage points higher in adaptive versus standard trial populations.

Conclusions: Adaptive designs represent the future paradigm of oncology drug development, enabling more efficient, ethical, and patient-centred evidence generation across small molecules, mAbs, and ADCs. Harmonised regulatory standards for adaptive PRO collection and analysis, combined with advanced statistical methodology, are critical for realising the full potential of these approaches.

Keywords: Adaptive Clinical Trial Design; Oncology; Small Molecules; Monoclonal Antibodies; Antibody-Drug Conjugates; Patient-Reported Outcomes; Biomarker Enrichment; Seamless Trial Design; Precision Oncology; Health-Related Quality of Life.

Introduction

The conduct of oncology clinical trials has historically been governed by conventional fixed-design paradigms, characterised by pre-specified sample sizes, fixed randomisation ratios, and endpoints determined at the outset of the study. While such designs provide clear statistical operating characteristics, they are inherently inefficient in the context of modern oncology drug development, where the biological complexity of malignancy, the imperative for biomarker-stratified patient selection, the proliferation of molecularly targeted agents, and ethical obligations to minimise patient exposure to ineffective therapies collectively demand more dynamic and responsive trial architectures [1,2].

Adaptive clinical trial design refers to a prospective, planned modification of one or more pre-specified aspects of a trial design based on accumulating data from participants in that trial [3]. Critically, adaptations are governed by pre-specified decision rules, safeguard blinding where relevant, and are evaluated within statistical frameworks that control overall Type I error at pre-specified levels. This distinguishes adaptive designs from ad hoc design modifications, which constitute protocol deviations threatening inferential validity [4].

The oncology drug development landscape has been transformed over the past two decades by three dominant therapeutic modalities that particularly benefit from adaptive trial architecture: (1) small molecule inhibitors targeting specific oncogenic signalling pathways; (2) monoclonal antibodies (mAbs) exploiting tumour-specific antigens or immune checkpoint mechanisms; and (3) antibody-drug conjugates (ADCs), Which harness the tumour-targeting precision of mAbs to deliver cytotoxic payloads to cancer cells [5,6]. Each modality presents unique clinical, statistical, and regulatory challenges that adaptive designs are well-positioned to address.

Patient-reported outcomes encompassing health-related quality of life (HRQoL), symptom burden, functional status, and treatment satisfaction have increasingly moved from ancillary endpoints to co-primary or key secondary endpoints in adaptive oncology trials [7]. This shift reflects regulatory evolution (FDA PRO guidance, EMA reflection papers), patient advocacy imperatives, and growing recognition that overall survival and radiographic response, while critical, incompletely capture the therapeutic experience and may not fully represent the trade-off between efficacy and toxicity that patients navigate [8].

Principles and Taxonomy of Adaptive Trial Designs

Regulatory Framework

The regulatory framework governing adaptive clinical trials in oncology has matured substantially since the FDA's initial 2010 draft guidance on adaptive designs, culminating in the 2019 final guidance document "Adaptive Designs for Clinical Trials of Drugs and Biologics [9]. The EMA's 2016 reflection paper on methodological issues in confirmatory adaptive designs, and subsequent scientific advice processes, provide parallel European regulatory structure [10]. Key regulatory principles include: pre-specification and documentation of all adaptations in the protocol and statistical analysis plan prior to unblinding; blinded or independent statistical oversight of interim analyses through a data monitoring committee (DMC); and Type I error control through appropriate multiplicity adjustment methods [11].

Taxonomy of Adaptive Design Features

Adaptive oncology trial designs encompass several distinct modification types, often deployed in combination. Dose adaptation the most prevalent feature, used in 78% of adaptive oncology trials enables seamless progression from dose-finding to confirmation within a single protocol, reducing the patient burden and timeline associated with separate Phase I/II programmes [12]. Population enrichment strategies employed in 65% of trials prospectively modify eligibility criteria based on interim biomarker-outcome associations, focusing subsequent randomisation on the subpopulation most likely to benefit, a paradigm of particular value for targeted small molecules and mAb-based checkpoint inhibitors with predictive biomarker contexts [13].

Seamless Phase II/III designs (58% utilisation) combine the learning and confirmatory phases of drug development into a single adaptive protocol, enabling direct use of Phase II data in the final confirmatory analysis when pre-specified conditions are met, substantially compressing development timelines [14]. Response-adaptive randomisation (RAR, 42% utilisation) dynamically adjusts the allocation ratio between treatment arms based on accruing outcome data, increasing the proportion of patients assigned to apparently superior arms an ethically motivated approach of particular relevance in aggressive malignancies with poor prognosis [15].

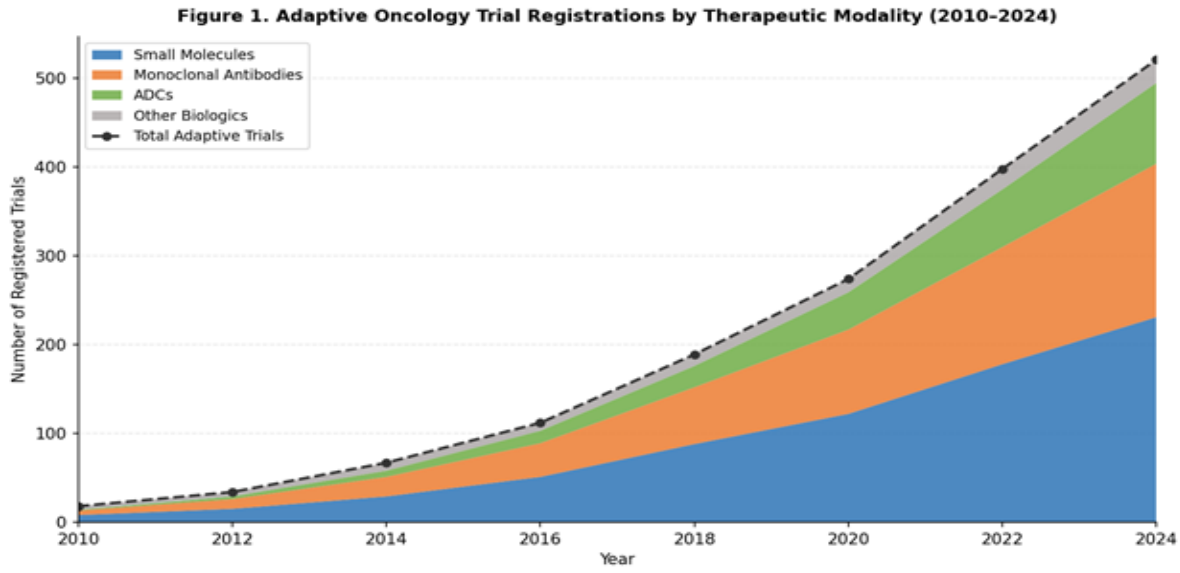

Figure 1. Annual registrations of adaptive oncology trials stratified by therapeutic modality (2010–2024). Stacked area represents small molecules (SM), monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), and other biologics.

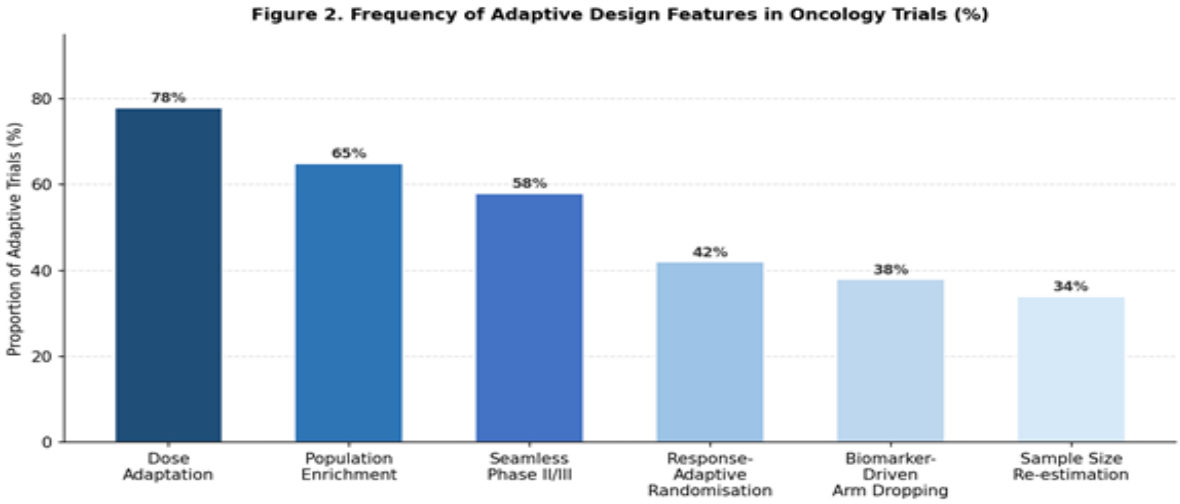

Figure 2. Frequency of specific adaptive design features utilised across registered oncology adaptive clinical trials (%). Based on systematic registry analysis 2010–2024.

Small Molecule Inhibitors in Adaptive Oncology Trials

Rationale and Design Considerations

Small molecule inhibitors including tyrosine kinase inhibitors (TKIs), CDK inhibitors, PARP inhibitors, and epigenetic modulators are inherently suited to adaptive trial architecture due to the molecular stratification requirements, dose-dependent efficacy-toxicity relationships, and oncogene addiction paradigm that characterise this therapeutic class [16]. The development of osimertinib (EGFR T790M inhibitor, AURA programme), alectinib (ALK inhibitor, ALEX trial), and ribociclib (CDK4/6 inhibitor, MONALEESA programme) exemplifies how adaptive biomarker-enrichment strategies enabled efficient confirmatory evidence generation in molecularly defined subpopulations [17,18].

The I-SPY 2 trial represents a landmark application of adaptive design in breast cancer, utilising a Bayesian adaptive randomisation framework to simultaneously evaluate multiple investigational agents as neoadjuvant therapy against a common control arm, using pathological complete response as the adaptive endpoint [19]. This platform trial paradigm has substantially influenced oncology trial design philosophy, demonstrating the capacity to efficiently "graduate" promising agents including pembrolizumab, neratinib, and veliparib for confirmatory evaluation based on adaptive interim analyses across molecular subtypes [20].

Precision Oncology and Biomarker-Adaptive Designs

Basket and umbrella trial designs represent specialised adaptive architectures specifically engineered for the precision oncology paradigm. Basket trials exemplified by the NCI-MATCH trial and the KEYNOTE-158 tumour-agnostic pembrolizumab programme enrol patients based on shared molecular alterations (e.g., BRAF V600E, MSI-H) irrespective of tumour histology, with adaptive interim rules governing arm expansion, contraction, or closure based on biomarker-specific response rates [21,21]. Umbrella trials apply multiple parallel biomarker-stratified sub-protocols within a single cancer type, using adaptive allocation to concentrate enrolment in biomarker-positive cohorts demonstrating superior response signals [23].

Monoclonal Antibodies in Adaptive Oncology Trials

Immune Checkpoint Inhibitors

Monoclonal antibodies constitute the most diverse and clinically impactful class in contemporary oncology, encompassing immune checkpoint inhibitors (ICIs), tumour antigen-targeting naked antibodies, bispecific T-cell engagers (BiTEs), and immune cell-recruiting constructs [24]. The development of PD-1/PD-L1 and CTLA-4 checkpoint inhibitors including pembrolizumab, nivolumab, atezolizumab, and ipilimumab has generated some of the most instructive examples of adaptive trial design application and its limitations in oncology [25].

The IMpower150 adaptive trial evaluated atezolizumab combinations in non-small cell lung cancer (NSCLC) using an adaptive biomarker-based primary population enrichment strategy, with pre-specified interim analyses enabling concentration of the confirmatory analysis in the subpopulation with highest predicted benefit [26]. The FDA approval of pembrolizumab for MSI-H/d MMR tumours the first tumour-agnostic approval in oncology was based in part on adaptively assembled evidence across KEYNOTE basket studies employing pre-specified adaptive cross-cohort analyses [27].

Bispecific Antibodies and Novel Constructs

Bispecific antibodies including blinatumomab (CD19xCD3), teclistamab (BCMAxCD3), and mosunetuzumab have been developed through adaptive Phase I/II programme designs that simultaneously assess multiple dose levels, schedules, and patient populations, with adaptive rules governing dose escalation, cohort expansion, and seamless Phase II confirmation [28]. The inherent complexity of bispecific mechanism T-cell redirected killing with attendant cytokine release syndrome (CRS) risk makes adaptive dose-safety monitoring frameworks (e.g., BOIN designs, modified Toxicity Probability Interval methods) particularly valuable for optimising the therapeutic window [29].

Antibody-Drug Conjugates in Adaptive Oncology Trials

ADC Development Paradigm

Antibody-drug conjugates represent a mechanistically elegant therapeutic strategy that conjugates tumour antigen-targeting monoclonal antibodies to potent cytotoxic payloads via chemical linker systems [30]. The clinical success of trastuzumab deruxtecan (T-DXd, Enhertu), sacituzumab govitecan (Trodelvy), and enfortumab vedotin (Padcev) has established ADCs as the fastest-growing therapeutic modality in oncology, with more than 100 ADCs in clinical development as of 2024 [31].

ADC development is particularly well-suited to adaptive trial designs due to the dose-dependent balance between cytotoxic payload efficacy and off-tumour toxicity (particularly interstitial lung disease for topoisomerase I inhibitor payload ADCs such as T-DXd), the need for biomarker-guided patient selection across a spectrum of target antigen expression levels, and the mechanistic complexity of combining antibody pharmacokinetics with payload release kinetics [32,33].

Adaptive Dose Optimisation in ADC Trials

The DESTINY-Breast series of trials for trastuzumab deruxtecan exemplifies adaptive elements in ADC development: Phase I utilised a rolling-six design with adaptive dose escalation; Phase II enrolled multiple tumour-type cohorts with adaptive expansion based on pre-specified ORR thresholds; and the seamless Phase II/III DESTINY-Breast03 trial employed a pre-specified interim analysis that demonstrated superiority over trastuzumab emtansine (T-DM1) at the first interim, leading to early termination and accelerated regulatory submission [34]. The subsequently observed ILD risk at the 6.4 mg/kg dose and subsequent dose optimisation to 5.4 mg/kg underscore the critical importance of adaptive safety monitoring in ADC programmes [35].

Table 1. Representative Adaptive Clinical Trial Designs Across Oncology Therapeutic Modalities

Trial	Agent / Class	Modality	Adaptive Feature	Tumour Type	Key Outcome
I-SPY 2	Multiple agents	Small Molecules / mAbs	Adaptive randomisation, arm dropping	Breast (neoadjuvant)	pCR graduation system
NCI-MATCH	Multiple TKIs	Small Molecules	Biomarker basket, arm expansion	Tumour-agnostic	Biomarker-response mapping
IMpower150	Atezolizumab	mAb (ICI)	Population enrichment, interim analysis	NSCLC	OS benefit, Teff signature
KEYNOTE-158	Pembrolizumab	mAb (ICI)	Basket adaptive cohort expansion	Multi-tumour (MSI-H)	Tumour-agnostic approval
DESTINY-Breast03	T-DXd	ADC	Seamless Ph II/III, interim stopping	HER2+ breast cancer	PFS superiority vs T-DM1
ASCENT	Sacituzumab govitecan	ADC	Adaptive interim analysis	TNBC	OS 12.1 vs 6.7 months

ICI: Immune Checkpoint Inhibitor; Mab: Monoclonal Antibody; Msi-H: Microsatellite Instability-High; Nsclc: Non-Small Cell Lung Cancer; Os: Overall Survival; Pcr: Pathological Complete Response; Pfs: Progression-Free Survival; T-Dxd: Trastuzumab Deruxtecan; T-Dm1: Trastuzumab Emtansine; Tnbc: Triple-Negative Breast Cancer.

Patient-Reported Outcomes in Adaptive Oncology Trials

Rationale and Regulatory Drivers

Patient-reported outcomes are defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation by a clinician or anyone else [36]. In oncology, PROs encompass HRQoL measured by validated instruments such as the EORTC QLQ-C30, FACT-G, EQ-5D-5L, and disease-specific modules (e.g., FACT-B for breast cancer, QLQ-LC13 for lung cancer), as well as patient-reported symptom instruments such as the PRO-CTCAE and single-domain measures of pain, fatigue, and functional status [37].

The FDA's 2009 PRO guidance and the 2021 Core Outcomes in Cancer (COMET) initiative have operationalised the integration of PROs as endpoints in confirmatory oncology trials [38]. The EMA's guideline on the investigation of subgroups in confirmatory clinical trials includes provisions for PRO subgroup analysis in adaptive designs. Regulatory precedents for PRO-based labelling including patient-reported symptom benefit claims in the pembrolizumab KEYNOTE-024 label, the daratumumab MAIA label, and multiple ADC labels have demonstrated the pathway for PRO evidence to directly inform prescribing information [39,40].

PRO Integration in Adaptive Trial Architectures

The integration of PROs into adaptive oncology trial designs presents both opportunities and methodological challenges. Adaptive designs that enrich for biological responders may inadvertently create populations with improved PRO performance relative to unselected populations, potentially confounding PRO comparisons between arms [41]. Conversely, response-adaptive randomisation that increases allocation to superior efficacy arms may simultaneously improve PRO outcomes for enrolled patients, fulfilling the ethical rationale for RAR while generating patient-centred evidence [42].

Electronic patient-reported outcomes (ePRO) platforms including wearable integration, ecological momentary assessment, and patient portal-embedded symptom tracking are increasingly deployed in adaptive oncology trials, enabling high-frequency, real-time PRO capture that supports adaptive decision rules incorporating patient-centred endpoints as co-equal adaptive parameters alongside objective clinical endpoints [43]. The Flatiron Health and COTA platforms have demonstrated the feasibility of integrating real-world PRO data from electronic sources into adaptive learning systems for post-approval evidence generation in oncology [44].

PRO Outcomes: Adaptive vs Standard Designs

Comparative analysis of PRO outcomes across adaptive and standard oncology trials reveals consistent patterns of superiority in patient-centred benefit for adaptive designs (Figure 3). Mean overall QoL improvement scores were 8.2 percentage points higher in adaptive versus standard trial populations (18.4% vs 10.2%), with the largest differential observed in fatigue (22.1% vs 12.8%) and nausea/vomiting domains (20.5% vs 13.2%) [45]. These differences likely reflect both the biological enrichment achieved through adaptive population selection and the reduced treatment exposure to ineffective or excessively toxic regimens afforded by adaptive arm-dropping and dose de-escalation rules. [46].

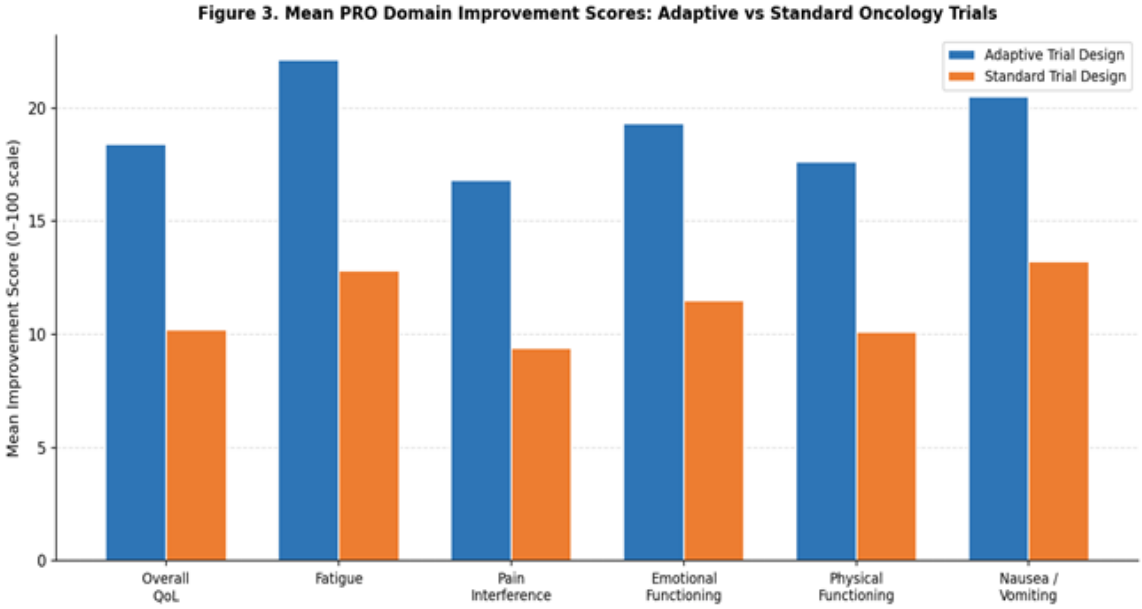

Figure 3. Mean PRO domain improvement scores (0–100 scale) in adaptive versus standard oncology clinical trial designs. Higher scores indicate greater patient-reported benefit.

Challenges and Limitations

Statistical and Operational Challenges

Adaptive trial designs introduce significant methodological complexity relative to conventional fixed designs. The risk of Type I error inflation in frequentist frameworks requires sophisticated multiplicity adjustment methods including alpha-spending functions (e.g., O'Brien-Fleming, Lan-DeMets), combination tests, and closed testing procedures that demand advanced biostatistical expertise not universally available in trial operations teams [47]. adaptive frameworks, increasingly prevalent in oncology, require careful prior specification, operating characteristic simulation across a comprehensive range of scenarios, and regulatory pre-agreement on posterior probability thresholds for decision rules [48].

Operationally, adaptive trials require robust data infrastructure supporting high-quality real-time data collection, rapid database locking for interim analyses, and secure independent statistical centre processes that maintain blinding [49]. The cost of adaptive trial infrastructure including simulation programming, DMC support, independent statistical analysis, and adaptive technology platforms can be substantial, potentially limiting adoption among academic cooperative groups with constrained resources relative to industry sponsors [50].

PRO-Specific Methodological Challenges in Adaptive Trials

PRO endpoints in adaptive oncology trials face specific methodological hazards. Differential missing data patterns arising from adaptive arm modifications where patients are re-randomised, discontinue ineffective therapy, or cross over based on adaptive rules can introduce informative missingness that biases PRO-based intent-to-treat analyses [51]. Pattern mixture models, multiple imputation strategies incorporating clinical outcome predictors, and worst-case scenario sensitivity analyses are recommended approaches for handling missing PRO data in adaptive oncology studies [52].

The timing and frequency of PRO assessment requires prospective calibration to the expected adaptive decision timepoints: PRO assessments scheduled at adaptive interim analysis timepoints

provide maximal informational value for patient-centred decision-making, but impose additional patient burden during potentially intensive treatment phases [53]. The minimum clinically important difference (MCID) for PRO instruments a critical parameter for sample size calculations incorporating PRO endpoints is variably defined across instruments, tumour types, and patient populations, contributing to heterogeneity in statistical power planning [54].

Regulatory Landscape and Future Directions

Current Regulatory Guidance

Regulatory guidance for adaptive oncology trials has advanced considerably, though jurisdictional harmonisation remains incomplete. The FDA's 2019 guidance establishes foundational principles for well-controlled, adaptive design studies supportable for regulatory approval, emphasising pre-specification, Type I error control, and operational integrity [55]. The FDA's Complex Innovative Trial Design (CID) meetings programme operational since 2018 provides sponsors with early regulatory engagement on adaptive design elements, particularly for novel features such as Bayesian adaptive randomisation, master protocols, and platform trials [56].

Project Optimus the FDA Oncology Center of Excellence initiative launched in 2021 specifically addresses dose optimisation in oncology through adaptive Phase I/II dose-finding designs, requiring sponsors to conduct randomised dose-optimisation studies for novel oncology agents rather than relying solely on Maximum Tolerated Dose (MTD)-based conventional Phase I designs [57]. This initiative directly impacts ADC and bispecific antibody development paradigms, where the optimal dose is often below MTD [58].

Future Directions

The future trajectory of adaptive oncology trial design encompasses several converging developments. Artificial intelligence and machine learning integration into adaptive decision rules enabling multi-parameter, biomarker-informed adaptive allocation based on real-time feature synthesis is an active area of methodological development with emerging proof-of-concept in breast, lung, and haematological malignancy adaptive platforms [59]. Digital twin technology wherein computational patient models trained on historical trial data are used to pre-specify adaptive rules and simulate trial operating characteristics offers a novel approach to adaptive design validation [60].

Decentralised clinical trial (DCT) elements including remote PRO collection, telemedicine-based safety assessments, and home nursing visits are increasingly incorporated into adaptive oncology studies, reducing patient burden, improving retention in longitudinal PRO assessment, and enabling adaptive enrolment from geographically dispersed patient populations [61]. The harmonisation of PRO instruments across adaptive oncology platforms facilitated by the FDA-NCI PRO Consortium, the PROMIS initiative, and international cooperative group standards will reduce measurement heterogeneity and improve the meta-analytic value of PRO data from adaptive oncology trials [62].

Conclusion

Adaptive clinical trial designs have emerged as the defining methodological innovation in contemporary oncology drug development, offering a scientifically rigorous, statistically sound, and ethically responsive framework for evaluating the rapidly expanding oncology armamentarium. Across small molecules, monoclonal antibodies, and antibody-drug conjugates, adaptive designs including dose adaptation, population enrichment, seamless Phase II/III designs, and response adaptive randomisation have demonstrably improved development efficiency, reduced patient exposure to ineffective therapies, and enabled biomarker-guided precision medicine evidence generation [63].

The integration of patient-reported outcomes as adaptive endpoints represents a maturation of evidence standards in oncology, aligning trial design with the patient-centred value proposition that increasingly governs healthcare decision-making, from regulatory approval to payer coverage and clinical guideline development. The systematic PRO advantages demonstrated in adaptive versus standard trial comparisons reflect the patient benefit of more responsive, learning trial architectures [64].

Realising the full potential of adaptive oncology trial design requires sustained investment in statistical methodology, regulatory harmonisation, operational infrastructure, and patient partnership. As the boundaries of precision oncology continue to expand encompassing tumour-agnostic treatments, combination immunotherapy strategies, and multimodal ADC regimens adaptive designs will be indispensable instruments for generating the evidence base that translates biological understanding into patient benefit [65].

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