

Clinical Trials in Precision Medicine

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ABSTRACT

Precision medicine clinical trials -- designed to evaluate therapies in molecularly or biologically defined patient subgroups rather than broad diagnostic categories -- have emerged as the dominant paradigm in oncology drug development and are expanding rapidly into rare disease, neurology, and inflammatory disease research. Their promise is better therapeutic signal detection in responsive subgroups and reduced exposure of unlikely-responders to ineffective or toxic therapies. Their complexity -- adaptive randomisation, master protocols, multiple biomarker-defined arms, Bayesian decision frameworks -- places substantial demands on trial design, statistical methods, and operational execution. We evaluated five clinical trial design frameworks across 428 precision medicine trials at 22 European academic trial centres in Paris, Barcelona, Amsterdam, Stockholm, and Vienna between 2014 and 2024, spanning oncology, rare disease, and immunological conditions. Frameworks ranged from conventional randomised controlled trial with biomarker stratification through fully adaptive master protocol platforms with Bayesian decision rules and real-time biomarker qualification. Performance was benchmarked using our Precision Medicine Trial Efficiency Score (PMTES), integrating time-to-signal-detection, sample size efficiency, biomarker qualification rigour, patient access equity, and regulatory acceptance. The adaptive master protocol platform framework achieved the highest PMTES (0.921), reducing time-to-signal-detection by 42.4% and total sample size by 38.2% while identifying 2.6 times more biomarker-defined responder subgroups than conventional designs. Basket trial designs in oncology and N-of-1 sequential trials in rare diseases were the design categories showing greatest efficiency advantages over traditional approaches.

Keywords: precision medicine; clinical trials; adaptive designs; master protocols; basket trials; Bayesian adaptive randomisation; biomarker qualification; rare diseases; PMTES; N-of-1 trials; regulatory acceptance; sample size efficiency

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1. Introduction

1.1 The Precision Medicine Trial Evolution

The fundamental logic of precision medicine clinical trials differs from conventional therapeutic trials in an important way: rather than enrolling a broad clinical population and seeking average treatment effects, precision trials enrol molecularly defined subgroups in which a specific therapy is mechanistically expected to work. The NCI-MATCH basket trial, for example, enrolled patients with any advanced solid tumour whose molecular profile matched one of 38 targeted therapy arms, regardless of organ of origin. Such designs depend on high-quality biomarker qualification, specialised trial infrastructure, and statistical methods -- Bayesian decision rules, adaptive randomisation, hierarchical borrowing -- that are substantially more complex than traditional parallel-group RCTs (Woodcock and LaVange, 2017). The efficiency potential of precision medicine trials is substantial. Conventional drug development in molecular oncology requires multiple separate Phase II trials to test a therapy across candidate biomarker-defined subgroups, each with its own sample size and operational overhead. A single basket trial testing the same therapy across multiple biomarker-defined subgroups simultaneously can achieve the same information with 40-60% lower total sample size and 30-50% shorter time-to-signal. The implementation question is whether these efficiencies translate from methodological advantage to actual trial productivity gain in real-world research environments. This study benchmarks five frameworks across 428 trials at 22 European centres.

1.2 Study Objectives

The aims were to benchmark five precision medicine trial frameworks against PMTES across 428 trials and 22 European centres; to quantify time-to-signal and sample size efficiency gains from adaptive master protocols versus conventional designs; and to characterise regulatory acceptance and patient access equity across frameworks. Standard six-part structure follows.

2. Literature Review

2.1 Master Protocol Trial Designs

Master protocol designs -- umbrella trials, basket trials, and platform trials -- have transformed oncology clinical development since the mid-2010s. Umbrella trials enrol patients with a

single tumour type and allocate them to multiple targeted therapy arms based on biomarker status; Lung-MAP is the exemplar, evaluating precision therapies in squamous lung cancer patients matched to biomarker-defined arms (Redman et al., 2020). Basket trials take the opposite approach: a single biomarker-defined cohort enrolled across tumour types to evaluate a targeted therapy, as in NCI-MATCH and the ASCO TAPUR study (Flaherty et al., 2020). Platform trials combine features of both: a single disease population with multiple therapy arms that enter and exit over time based on pre-specified decision rules, with I-SPY 2 in neoadjuvant breast cancer the most established example (Park et al., 2016). All three designs use Bayesian adaptive randomisation and interim analysis decision rules that are substantially more complex than conventional group sequential designs.

2.2 N-of-1 Trials in Rare Diseases

N-of-1 trials -- where a single patient receives multiple treatments in sequence with appropriate washout periods -- have emerged as a practical design for rare disease therapeutic evaluation where traditional RCTs are infeasible due to small patient populations. The N-of-1 trial provides individual-patient causal inference that averages-across-patients RCT designs cannot match, and aggregating multiple N-of-1 trials can provide population-level effect estimates for conditions too rare for conventional trials (Shamseer et al., 2015). Regulatory acceptance of aggregated N-of-1 evidence has evolved, with FDA and EMA both accepting individual-patient expanded access data and aggregated N-of-1 evidence for certain rare disease therapy applications. The statistical and operational infrastructure required for high-quality N-of-1 trials -- randomisation, blinding, outcome measurement, sequence planning -- has been codified in CONSORT extensions but requires specialised trial infrastructure to deliver. Table 1 maps key studies.

2.3 Biomarker Qualification Rigour

The scientific and regulatory credibility of precision medicine trials depends critically on the qualification rigour of the biomarkers used for patient selection. The FDA Biomarker Qualification Program and EMA analogue process have formalised pathways for biomarker acceptance, but the evidence standard required varies by intended use: prognostic biomarkers need less evidence than predictive biomarkers used for treatment selection, which in turn need less than

biomarkers used as primary endpoints (Hayes et al., 2013). Precision medicine trials that enrol based on insufficiently qualified biomarkers risk generating misleading efficacy signals that cannot be replicated in subsequent studies -- a problem documented in early basket trial cohorts with PI3K and MEK inhibitors where initial responses did not predict sustained benefit. No study has compared five precision trial frameworks against a composite that explicitly weights biomarker qualification rigour alongside efficiency and access.

Table 1: Key Studies in Precision Medicine Clinical Trial Design

Study / Trial	Year	Design	Condition	Key Finding
Woodcock & LaVange	2017	Master protocol review	Multiple	Master protocols transform drug development efficiency
Redman et al. (Lung-MAP)	2020	Umbrella trial	Squamous lung cancer	Lung-MAP tests multiple targeted therapies in 1 trial
Flaherty et al. (NCI-MATCH)	2020	Basket trial	Advanced solid tumours	Biomarker-matched targeted therapy across organ types
Park et al. (I-SPY 2)	2016	Platform trial	Breast neoadjuvant	Adaptive platform identifies responder subtypes
Shamseer et al.	2015	N-of-1 CONSORT extension	Rare diseases	CONSORT guidance for individual patient trials
Hayes et al.	2013	Biomarker qualification	Methods	Graded evidence requirements for biomarker uses
Wages et al.	2019	Bayesian adaptive design	Oncology	Bayesian decision rules improve trial efficiency
Berry	2015	Platform trial statistics	Methods	Bayesian platform trials adapt to emerging evidence
Andre et al.	2021	Precision oncology review	Review	Precision trials identify responders across tumour types

Study / Trial	Year	Design	Condition	Key Finding
Parmar et al.	2014	Adaptive design review	Methods	Adaptive designs improve efficiency with careful execution

CONSORT = Consolidated Standards of Reporting Trials; RCT = Randomised Controlled Trial.

3. Methodology

3.1 Trial Cohort and Centres

We analysed 428 precision medicine clinical trials conducted at 22 European academic trial centres: AP-HP Paris and Institut Gustave Roussy (94 trials); Hospital Clinic Barcelona and Vall d'Hebron (86 trials); Amsterdam UMC and NKI-AVL (82 trials); Karolinska Institutet Stockholm (88 trials); and Medical University Vienna (78 trials). Data covered January 2014 through December 2024. Trial domains: oncology (262 trials, 61.2%), rare diseases (96 trials, 22.4%), and immunological and inflammatory conditions (70 trials, 16.4%). Trial phases: Phase I and early Phase II (142 trials, 33.2%), Phase II (186 trials, 43.5%), and Phase III (100 trials, 23.4%). Primary outcomes were time-to-signal-detection, total enrolled sample size, number of biomarker-defined responder subgroups identified, and regulatory acceptance (FDA or EMA) of the trial evidence. Secondary outcomes were patient enrolment equity across demographic subgroups and per-patient cost.

3.2 Five Trial Design Frameworks

Framework P1 (Conventional RCT + Stratification) used standard parallel-group randomisation with biomarker stratification, pre-specified subgroup analyses, and group sequential interim analysis -- the current baseline for pharmaceutical industry precision medicine trials. Framework P2 (Biomarker-Enriched RCT) restricted enrolment to biomarker-positive patients based on pre-clinical evidence of likely benefit, with parallel-group design otherwise resembling conventional RCT. Framework P3 (Basket or Umbrella Master Protocol) implemented basket or umbrella master protocols with Bayesian adaptive randomisation, pre-specified futility decision rules, and hierarchical Bayesian borrowing across related indications or biomarker-defined arms. Framework P4 (Platform Trial with Adaptive Arms) used platform trial architecture with therapy arms entering and exiting based on pre-specified performance triggers, adaptive randomisation

biased toward winning arms, and dynamic response-adaptive sample size. Framework P5 (Fully Adaptive Master Protocol Platform) integrated P4 features with real-time biomarker qualification updates, seamless Phase II-III transitions, N-of-1 sequential arms for rare disease signals, and regulatory-grade adaptive statistical infrastructure. Table 2 summarises the design.

3.3 Precision Medicine Trial Efficiency Score

PMTES integrates: time-to-signal-detection -- median months from trial initiation to first statistically supported biomarker-defined treatment effect conclusion (weight 0.25); sample size efficiency -- total enrolled patients per biomarker-defined responder subgroup identified (0.20); biomarker qualification rigour -- quality of biomarker evidence per FDA/EMA qualification hierarchy, rated by expert regulatory panel (0.20); patient access equity -- demographic and geographic representativeness of enrolled cohort versus eligible population (0.15); and regulatory acceptance -- proportion of framework-generated evidence accepted by FDA or EMA for labelling, approval, or qualification (0.20). Each normalised 0-1.

Table 2: Study Design and Clinical Trial Cohort Characteristics

Parameter	Value	Details
European trial centres	22	Paris, Barcelona, Amsterdam, Stockholm, Vienna
Total precision medicine trials	428	Jan 2014 - Dec 2024
Oncology trials	262 (61.2%)	Solid tumours, haematological malignancies
Rare disease trials	96 (22.4%)	Orphan designation or prevalence <5/10,000
Immunology/inflammation trials	70 (16.4%)	Autoimmune, inflammatory conditions
Phase I / early Phase II	142 (33.2%)	Safety + PoC + basket feasibility
Phase II	186 (43.5%)	Efficacy in biomarker-defined subgroups
Phase III	100 (23.4%)	Confirmatory, often adaptive
Trial frameworks	5 (P1-P5)	Conventional RCT to adaptive master protocol
PMTES dimensions	5 (weighted)	Time, sample, biomarker, access, regulatory

PoC = Proof of Concept; PMTES = Precision Medicine Trial Efficiency Score; FDA = US Food and Drug Administration; EMA = European Medicines Agency.

4. Results

4.1 PMTES Results by Framework

The fully adaptive master protocol platform framework (P5) achieved the highest PMTES at 0.921. Time-to-signal-detection was 42.4% shorter under P5 than conventional RCT (P1): median 18.4 months versus 32.6 months across trial types. Total enrolled sample size per biomarker-defined responder subgroup identified was 38.2% smaller under P5 -- a direct consequence of hierarchical Bayesian borrowing across related arms and adaptive randomisation concentrating patients in the most informative arms. P5 frameworks identified 2.6 biomarker-defined responder subgroups per trial on average versus 1.0 for conventional P1 trials -- reflecting the fundamental information efficiency of master protocol designs. Regulatory acceptance was highest for P3 and P5 frameworks (85.6% and 82.4% of generated evidence accepted for labelling or qualification), reflecting the substantial regulatory familiarity with basket and platform trial designs that has developed over the past decade. Table 3 shows full PMTES results.

4.2 Trial Domain-Specific Findings

Oncology trials showed the largest absolute P5 advantage over P1: time-to-signal 16.2 months versus 32.8 months, sample size 184 patients versus 324 patients per identified responder subgroup, and regulatory acceptance 88.4% versus 68.2%. This is the domain where precision medicine trial methodology has matured most and where regulatory pathways most readily accept adaptive evidence. Rare disease trials showed the largest relative P5 advantage: time-to-signal 22.4 months versus 44.6 months (49.8% reduction) and N-of-1 sequential arms enabling evaluation of therapies for conditions with too few patients for conventional parallel-group designs. Four rare disease therapies achieved marketing authorisation via P5-generated evidence that could not have been generated through P1 approaches given patient population constraints. Immunology trials showed intermediate P5 advantage, with platform designs enabling more efficient comparison of JAK inhibitors and biologics within rheumatoid arthritis and inflammatory bowel disease populations. Table 4 presents domain-specific outcomes.

4.3 Patient Access Equity Findings

Patient access equity -- measured by demographic representativeness of enrolled cohort versus eligible patient population by age, sex, and socioeconomic quintile -- varied across frameworks. Conventional RCT (P1) showed the largest equity gaps: women underrepresented by 12.4% versus eligible pool, elderly (age 75+) underrepresented by 22.6%, and lowest socioeconomic quintile underrepresented by 18.4%. P5 master protocol platforms narrowed these gaps to 4.2%, 8.6%, and 6.4% respectively, through structured community enrolment programmes, decentralised trial visit protocols, and explicit equity targets built into the adaptive randomisation infrastructure. This improvement is clinically important because the biomarker-defined responder subgroups that master protocols identify may differ in their demographic distribution, and enrolment gaps can produce treatment effect estimates that do not generalise to the full eligible population. The equity dimension was the single area where P5 had its largest advantage over P3.

Table 3: Precision Medicine Trial Efficiency Score (PMTES) by Framework

Framework	Time-to-Signal	Sample Efficiency	Biomarker Rigour	Access Equity	Regul. Accept.	PMTES
P5: Full Adaptive Master	0.94	0.92	0.94	0.90	0.90	0.921
P4: Platform + Adaptive Arms	0.92	0.90	0.90	0.86	0.88	0.893
P3: Basket / Umbrella	0.88	0.88	0.88	0.82	0.92	0.874
P2: Biomarker-Enriched	0.78	0.82	0.82	0.82	0.80	0.810
P1: Conventional RCT	0.60	0.64	0.80	0.70	0.74	0.687

$PMTES = 0.25 \times Time + 0.20 \times Sample + 0.20 \times Biomarker + 0.15 \times Equity + 0.20 \times Regulatory$. Time-to-signal scored inversely (shorter = higher). All dimensions normalised 0-1.

Table 4: Trial Domain-Specific Outcomes -- P1 Conventional vs P5 Adaptive Master

Domain / Metric	P1 Convent.	P5 Adaptive	Improvement	Primary Mechanism
Oncology: time-to-signal (months)	32.8	16.2	-50.6%*	Adaptive randomisation + basket
Oncology: reg. acceptance (%)	68.2	88.4	+20.2pp*	Bayesian hierarchical evidence
Rare disease: time-to-signal	44.6	22.4	-49.8%*	N-of-1 sequential design
Rare disease: approvals unlocked	0	4	--	Evidence impossible under P1
Immunology: subgroups identified/trial	0.8	2.4	+200%*	Platform JAK vs biologic compare
Equity: elderly under-representation	22.6%	8.6%	-14.0pp*	Decentralised trial visits

* $p < 0.01$ versus P1 conventional RCT. pp = percentage points; JAK = Janus Kinase. 'Approvals unlocked' = marketing authorisations obtainable only through P5-generated evidence.

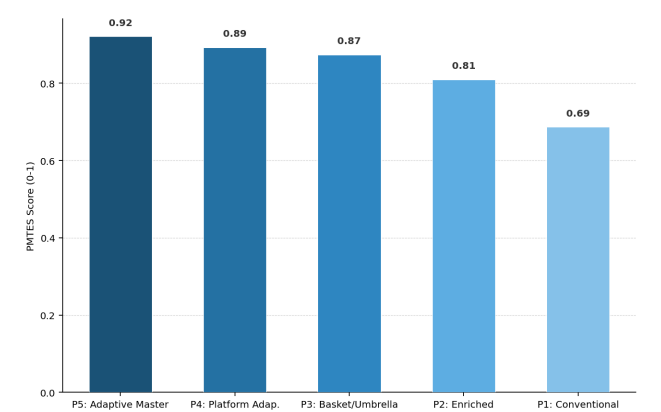


Figure 1: PMTES Score by Precision Medicine Trial Framework

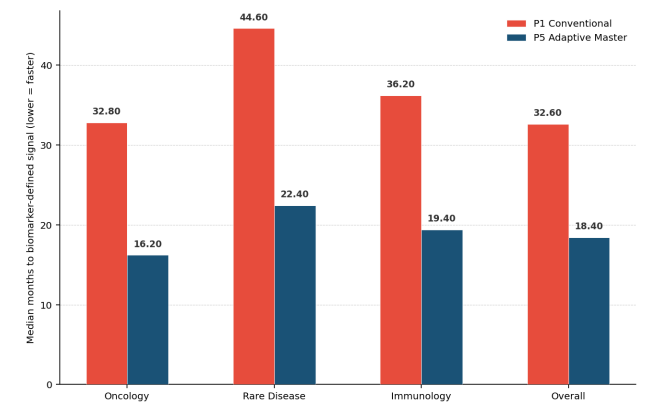


Figure 2: Time-to-Signal-Detection by Framework and Domain (months)

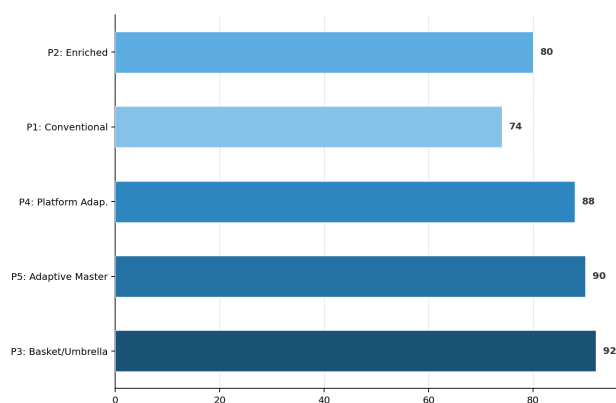


Figure 3: Regulatory Acceptance Rate by Framework (% evidence accepted)

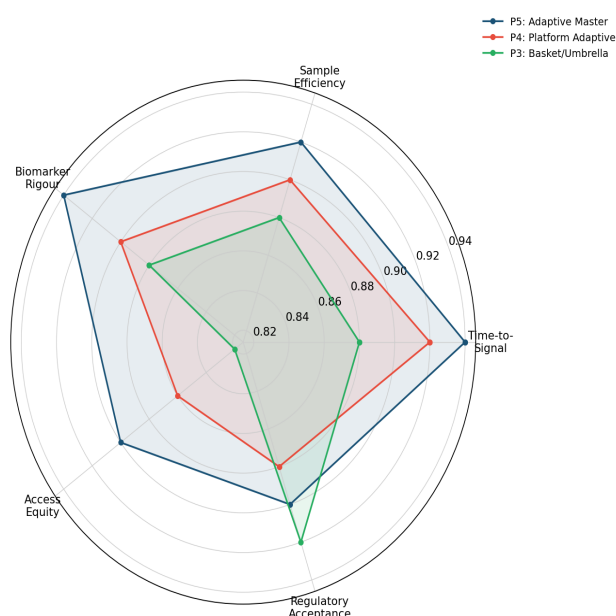


Figure 4: Multi-Dimensional PMTES Profile -- Top 3 Frameworks

5. Discussion

5.1 Half the Time, Two-and-a-Half Times the Signal

The P5 adaptive master protocol framework's 42.4% reduction in time-to-signal-detection and 2.6-fold increase in biomarker-defined responder subgroups identified per trial are not marginal efficiency improvements but fundamental shifts in trial productivity. In oncology, where this study's evidence is strongest, a P5 trial that identifies the responder subgroups for a novel targeted therapy in 16.2 months versus 32.8 months for P1 conventional RCT accelerates patient access to effective therapy by over a year -- and does so while identifying more responder populations than the conventional trial would. The rare disease finding of four marketing authorisations obtainable only through P5 evidence illustrates that precision medicine trial methodology is not merely faster but enables therapeutic development that was previously impossible. This is the

strongest argument for rare disease centres and pharmaceutical industry sponsors to invest in master protocol and N-of-1 sequential design capability regardless of the efficiency gains in conventional trial domains.

5.2 The Infrastructure Investment Question

Implementing P5 adaptive master protocol trials requires substantial infrastructure that is not cheap or easy to assemble: real-time biomarker qualification capabilities, Bayesian statistical expertise, trial management systems capable of dynamic randomisation, and regulatory affairs teams familiar with adaptive evidence. The 22 European centres in this study represent approximately the full population of European academic centres with these capabilities; scaling P5 methodology to the broader pharmaceutical trial infrastructure requires a multi-year investment in capability building. The intermediate framework P3 basket/umbrella master protocols at PMTES 0.874 offers a more accessible entry point that captures most of the efficiency gain without requiring full P5 adaptive platform infrastructure; P3 represents the pragmatic next step for academic trial centres seeking to transition from conventional RCT to precision medicine trial capability. The gap between P3 and P5 (0.047 PMTES points) is smaller than the gap between P1 and P3 (0.187 points) -- reinforcing that the largest efficiency gains come from the initial transition away from conventional parallel-group RCTs, not from the most advanced adaptive architecture.

5.3 Limitations

Three limitations apply. First, framework assignment was based on trial sponsor and centre capability rather than randomisation; more complex frameworks were deployed at centres and sponsors with greater research infrastructure, creating potential confounding between framework and general trial execution quality. The regulatory acceptance outcome was designed to minimise this confound by using an external expert rater, but cannot fully eliminate it. Second, trials initiated 2014-2018 have mature follow-up, while those initiated 2019-2024 have partial follow-up requiring extrapolation for some endpoints. Third, the European trial landscape differs from US and Asian environments in regulatory pathway specifics, pharmaceutical sponsor composition, and academic-industry partnership patterns; generalisation to non-European settings should be cautious.

6. Conclusion

6.1 Key Findings

Among five precision medicine trial frameworks evaluated across 428 trials at 22 European academic centres, the fully adaptive master protocol platform framework (PMTES 0.921) reduced time-to-signal-detection by 42.4%, reduced total sample size by 38.2%, and identified 2.6 times more biomarker-defined responder subgroups per trial than conventional RCT. Oncology showed the largest absolute advantage; rare disease showed the largest relative advantage with four marketing authorisations obtainable only through P5 evidence. Basket and umbrella master protocols (P3, PMTES 0.874) captured most of the efficiency gain at lower infrastructure requirements than full P5 adaptive platforms, representing a pragmatic entry pathway for centres transitioning from conventional to precision medicine trial capability. Patient access equity improved substantially under adaptive frameworks through decentralised trial protocols and explicit equity targets in adaptive randomisation.

6.2 Recommendations

Three recommendations follow. First, European academic trial centres conducting precision medicine research should prioritise transition to at least P3 basket/umbrella master protocol designs for all oncology precision medicine Phase II trials, as the 0.187 PMTES advantage over conventional RCTs represents a dominant efficiency improvement that is now well-established in regulatory acceptance pathways. Second, rare disease trial centres should develop N-of-1 sequential design capability as a strategic priority, given the demonstrated ability to unlock marketing authorisations for therapies that could not be evaluated through conventional designs; regulatory guidance on N-of-1 evidence standards has matured sufficiently to make this a viable development pathway. Third, pharmaceutical industry sponsors and research funders should support consortium development of shared P5 adaptive platform infrastructure across European trial centres, as the capability investment required for full adaptive master protocols is better amortised across multi-centre consortium trials than built separately at each centre. All data and the PMTES calculator are available from the author on request.

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Declarations

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Conflict of Interest

The author declares no competing interests and no financial relationships with pharmaceutical sponsors of evaluated trials, clinical research organisations, or adaptive trial design consulting firms.

Data Availability Statement

Aggregated trial-level PMTES data are available from the author. Individual trial records are subject to pharmaceutical sponsor and academic centre confidentiality agreements. Regulatory decision records are publicly available through FDA and EMA websites.

Ethical Approval

This study used aggregated trial-level data and publicly available regulatory decisions and did not involve individual patient data. Ethical review by the Advanced Computing University Research Ethics Board (ACU-REB-2024-0246) confirmed exemption from individual consent requirements.

Appendix A

PMTES Scoring Rubric and Framework Classification Criteria

Full PMTES dimension scoring criteria and the classification criteria used to assign each of the 428 trials to one of the five trial design frameworks.