Clinical Trial Design

Master Protocols in Precision Medicine

Basket Trials

Multiple tumor types with same molecular alteration

Umbrella Trials

Single disease with multiple biomarker-driven arms

Platform Trials

Perpetual trials adding/dropping arms dynamically

Biomarker-stratified

Randomization based on biomarker status

Master Protocols: Efficient frameworks for precision oncology trials

Detailed Trial Designs & Examples

Basket Trials

📋 Overview

Basket trials enroll patients with different tumor types that share a common molecular alteration or biomarker. The treatment is targeted to the specific genetic mutation rather than the organ of origin. This design reflects the precision medicine paradigm where drugs target specific molecular pathways regardless of where the cancer originated.

🎯 Key Characteristics

- ✓ Single drug targeting specific biomarker across multiple cancer types
- ✓ Patients grouped into "baskets" by tumor type
- ✓ Separate efficacy analysis for each tumor type
- ✓ Allows borrowing of information across baskets

🔬 Clinical Examples

NCI-MATCH Trial (Molecular Analysis for Therapy Choice)

One of the largest basket trials testing multiple targeted therapies across various cancer types based on specific genetic mutations. Patients are assigned to treatment arms based on their tumor's molecular profile, regardless of cancer origin. Over 35 different treatment arms targeting specific mutations like PIK3CA, BRAF, and EGFR.

VE-BASKET Study

Evaluated vemurafenib (BRAF V600 inhibitor) in multiple BRAF V600 mutation-positive cancers including non-small cell lung cancer, cholangiocarcinoma, ovarian cancer, and colorectal cancer. Demonstrated variable response rates across different tumor types, highlighting tissue-specific factors in treatment efficacy.

KEYNOTE-158

Basket trial of pembrolizumab (anti-PD-1) in patients with advanced cancers with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). Led to the first tissue-agnostic FDA approval based on a biomarker rather than tumor location.

⚖️ Advantages & Challenges

Advantages	Challenges
Accelerates drug development for rare mutations	Variable response rates across tumor types
Efficient patient enrollment for rare biomarkers	Complex statistical analysis and interpretation
Cost-effective compared to multiple separate trials	Requires extensive molecular screening infrastructure

Enables tissue-agnostic drug approvals	May need large sample sizes per basket

💡 Design Considerations

- **Statistical approach:** Bayesian hierarchical models often used to borrow information across baskets while accounting for heterogeneity
- **Sample size:** Must balance adequate power within each basket with overall feasibility
- **Interim analyses:** Allows early stopping of non-responsive baskets while continuing promising ones
- **Biomarker testing:** Centralized, standardized testing critical for trial integrity
- **Regulatory pathway:** May support accelerated approval or tissue-agnostic indications

 Umbrella Trials

📋 Overview

Umbrella trials focus on a single disease or cancer type but test multiple targeted therapies matched to different molecular subtypes. Patients are assigned to specific treatment arms based on their tumor's biomarker profile. This design recognizes that a single cancer type comprises multiple molecular subtypes requiring different therapeutic approaches.

🎯 Key Characteristics

- ✓ Single disease with molecular subtyping
- ✓ Multiple treatment arms for different biomarkers
- ✓ Centralized screening and assignment
- ✓ Shared control arm possible

🔬 Clinical Examples

LUNG-MAP (Lung Cancer Master Protocol)

A precision medicine trial in squamous cell lung cancer. Patients undergo biomarker testing and are assigned to sub-studies based on their molecular profile. Multiple drug arms test targeted therapies or immunotherapies. Includes biomarker-negative patients who go to immunotherapy arms. Allows addition of new arms as therapies become available.

I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response)

Adaptive platform trial in early-stage breast cancer testing multiple neoadjuvant therapies. Uses biomarker signatures to assign patients to treatment arms. Employs Bayesian adaptive randomization to increase assignment to more effective treatments. Has graduated multiple therapies to Phase III trials based on predictive biomarker signatures.

ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial)

Umbrella trial in early-stage non-small cell lung cancer. Screens patients for EGFR mutations and ALK rearrangements. Those with targetable mutations are enrolled in sub-studies testing targeted therapies in the adjuvant setting. Includes biomarker-negative patients in observational cohort.

⚖️ Advantages & Challenges

Advantages	Challenges
Tests multiple therapies simultaneously within one disease	High screening failure rate if biomarkers are rare
Efficient use of single-disease patient population	Complex logistics and coordination
Shared infrastructure and control arms reduce costs	Some molecular subgroups may be too small
Facilitates biomarker-driven treatment selection	Requires rapid turnaround on biomarker testing

💡 Design Considerations

- **Biomarker strategy:** Must define clear, actionable biomarkers with validated assays
- **Screening logistics:** Efficient pathway from diagnosis to molecular testing to treatment assignment
- **Control strategy:** May use shared control, standard of care, or biomarker-negative cohort
- **Adaptive features:** Can add new arms as therapies emerge or drop ineffective arms
- **Patient experience:** Streamlined process from one screening to multiple possible treatments

Platform Trials

Overview

Platform trials are perpetual, adaptive trials with a master protocol allowing new treatment arms to be added and ineffective arms to be dropped over time. They maintain a common infrastructure and control group while evaluating multiple therapies simultaneously. This design maximizes efficiency and accelerates the evaluation of new treatments.

Key Characteristics

- ✓ Continuously operating trial infrastructure
- ✓ Dynamic addition and removal of treatment arms
- ✓ Shared control group across all arms
- ✓ Adaptive randomization based on performance

Clinical Examples

RECOVERY Trial (Randomised Evaluation of COVID-19 Therapy)

Landmark platform trial for COVID-19 treatments. Started with multiple arms including hydroxychloroquine, lopinavir-ritonavir, dexamethasone, and azithromycin. Rapidly identified dexamethasone as effective and hydroxychloroquine as ineffective. Added new

arms (tocilizumab, convalescent plasma) as evidence emerged. Enrolled over 40,000 patients across UK hospitals with streamlined enrollment.

STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer)

Multi-arm, multi-stage platform trial in prostate cancer running since 2005. Has evaluated numerous treatment combinations including docetaxel, zoledronic acid, abiraterone, enzalutamide, and radiotherapy. Uses shared control arm and adaptive design. Has led to multiple changes in standard of care based on arm results. Continues to add new treatment arms as therapies become available.

GBM AGILE (Glioblastoma Adaptive Global Innovative Learning Environment)

Platform trial for newly diagnosed and recurrent glioblastoma. Tests multiple experimental therapies simultaneously using Bayesian adaptive design. Arms can graduate to Phase III or be dropped for futility based on interim analyses. Allows seamless addition of promising new agents. Uses biomarker stratification within platform framework.

⚖️ Advantages & Challenges

Advantages	Challenges
Maximally efficient use of control patients	Complex infrastructure requires significant resources
Accelerated drug evaluation pipeline	Statistical adjustments needed for multiple comparisons
Flexible to add promising new therapies quickly	Coordination across multiple pharmaceutical sponsors
Can answer multiple questions simultaneously	Requires sophisticated data management and monitoring

💡 Design Considerations

- **Master protocol:** Comprehensive framework covering all operational and statistical aspects
- **Governance structure:** Independent oversight committee to review interim results and make decisions
- **Entry/exit criteria:** Pre-specified rules for adding new arms and stopping ineffective ones
- **Adaptive randomization:** Can weight randomization toward better-performing arms
- **Control strategy:** May use concurrent controls, allow controls to be time-limited, or use historical controls
- **Statistical framework:** Typically Bayesian to allow continuous learning and adaptation

📊 Biomarker-Stratified Trials

📋 Overview

Biomarker-stratified trials randomize patients based on their biomarker status, allowing assessment of treatment efficacy in biomarker-defined subgroups. This design can test whether a treatment works differently in biomarker-positive versus biomarker-negative patients, or compare different treatments within biomarker-defined strata. Essential for developing companion diagnostics and precision therapies.

🎯 Key Characteristics

- ✓ Prospective biomarker testing before randomization
- ✓ Separate randomization within each biomarker stratum
- ✓ Can test for biomarker-treatment interaction
- ✓ Supports companion diagnostic development

Design Variations

Enrichment Design

Enrolls only biomarker-positive patients to maximize signal detection. Example: EGFR-mutant lung cancer trials with EGFR inhibitors. Most efficient for demonstrating efficacy when treatment expected to work only in biomarker-positive population.

Biomarker-Stratified Design

Enrolls all patients but stratifies randomization by biomarker status. Allows testing treatment effect in both positive and negative strata. Can formally test for interaction. Example: Testing anti-PD-L1 therapy stratified by PD-L1 expression level.

Strategy Design

Compares biomarker-guided treatment selection versus standard treatment for all. One arm gets tested and treated based on biomarker, other arm gets standard approach. Tests whether biomarker strategy improves outcomes. Example: TAILORx trial in breast cancer comparing gene expression-guided versus standard chemotherapy decisions.

Clinical Examples

TAILORx (Trial Assigning Individualized Options for Treatment)

Stratified trial in early-stage breast cancer using 21-gene recurrence score. Patients with mid-range scores randomized to chemotherapy plus endocrine therapy versus endocrine therapy alone. Demonstrated that most patients with intermediate scores can safely avoid chemotherapy. Changed practice guidelines worldwide.

BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination)

Used multiple biomarkers to assign treatments in refractory non-small cell lung cancer. Adaptive randomization increased assignment to treatments performing well in specific biomarker groups. Demonstrated feasibility of real-time biomarker-adaptive design.

⚖️ Advantages & Challenges

Advantages	Challenges
Increased power in biomarker-positive subgroup	Larger total sample size needed
Can identify predictive biomarkers definitively	Requires validated, accessible biomarker test
Supports companion diagnostic approval	Screen failure rate if biomarker is rare
Avoids exposing biomarker-negative patients to ineffective therapy	Logistical complexity of pre-randomization testing

💡 Design Considerations

- **Biomarker validation:** Must use analytically and clinically validated assay

- **Sample size calculation:** Consider prevalence of biomarker and expected treatment effects in each stratum
- **Testing turnaround time:** Must be rapid enough to not delay treatment significantly
- **Statistical analysis plan:** Pre-specify how biomarker-treatment interaction will be tested
- **Regulatory considerations:** Plan for companion diagnostic co-development if applicable
- **Equity considerations:** Ensure biomarker testing accessible to diverse patient populations

Comparative Summary

Design Type	Primary Goal	Best Used When	Key Advantage
Basket	Test one drug across multiple tumor types with same biomarker	Rare actionable mutation across cancers	Enables tissue-agnostic approvals
Umbrella	Test multiple drugs in one disease with different biomarkers	Well-characterized molecular subtypes exist	Comprehensive coverage of one disease
Platform	Continuously evaluate multiple treatments	Many experimental therapies to evaluate	Maximally efficient, perpetual infrastructure

Biomarker-Stratified	Define predictive biomarker and treatment effect	Need to validate biomarker-treatment relationship	Strongest evidence for companion diagnostic