# Recommendations for planning and conducting clinical trials with master protocol designs: Umbrella, Basket and Platform Trials

**Deliverable 14.2**

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ECRIN, July 2025

*This leaflet has been developed as part of the ERA4Health project, co-funded by the European Union under the Horizon Europe Framework Programme. Grant Agreement N° 101095426.*

Co-funded by the European Union

# Recommendations for planning and conducting clinical trials with master protocol designs: Umbrella, Basket and Platform Trials

The aim of this booklet is to offer a comprehensive overview of the key aspects of new trial methodologies and to provide solutions to the main challenges in developing, implementing and conducting trials with new designs namely master protocol with umbrella, basket, and adaptive platform design.

*This booklet has been adapted from ERA4Health's original document D14.2 "Recommendation booklet for investigators and sponsors in multi-country investigator initiated clinical studies". References cited in this document can be found at the original source (1).*

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Co-funded by the European Union

# Master protocol: umbrella, basket and platform trials

A **master protocol framework** allows for the simultaneous evaluation of multiple drugs or drug combinations across various patient populations, targeting a particular biomarker-defined population or disease subtypes, all within a single clinical trial infrastructure.

A master protocol may entail direct comparisons of competing therapies or be structured to evaluate, in parallel, various therapies relative to their respective controls (2).

Master protocols are characterised by two key innovations: the utilisation of a trial network equipped with established infrastructure to streamline trial logistics, enhance data quality, and facilitate data sharing; and the implementation of a common protocol integrating innovative statistical methodologies for study design and data analysis (3). This approach offers several advantages, including enhanced efficiency, flexibility, and the capacity to address a wider range of clinical questions within a shorter time frame.

Master protocols entail a single comprehensive protocol crafted to assess multiple hypotheses and can be delineated into various types, including umbrella, basket, and platform trials (Table 1 and Figure 1).

Furthermore, master protocols can naturally extend to adaptive trial designs, the use of adaptive trial designs is not a defining feature of master protocols nor of platform, basket, and umbrella trials.

| Type of master protocol designs | Objective |
|---|---|
| Umbrella trials | To study multi targeted therapies in context of a single disease |
| Basket trials | To study one single targeted therapy in context of multiple diseases or diseases subtypes |
| Platform trials | To study multiple targeted therapies in context of a single disease in a perpetual manner, with therapies allowed to enter and leave the platform on the basis of a decision algorithm |

*Table 1: Types of Master protocols adapted from Woodcock J. et al (3).*

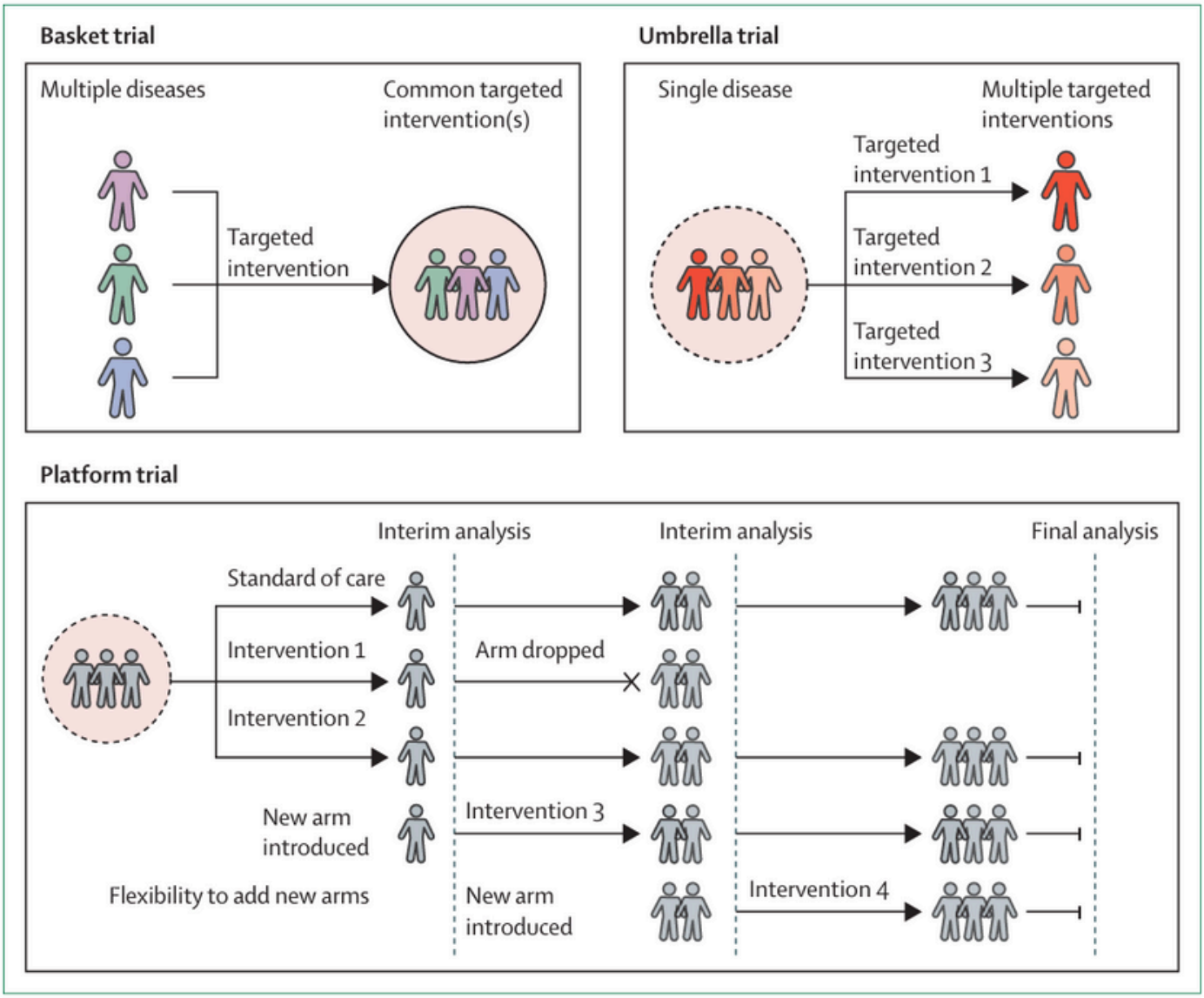


*Figure 1: Master protocols designs: basket trials, umbrella trials, and platform trial adapted from Park JJH et al. Licensed by CC-BY (4).*

Although these innovative trial designs offer unprecedented opportunities to truly accelerate drug development, they also create new challenges due to their heightened complexity (2,5-8).

These challenges impact a wide range of stakeholders, including patients, investigators, regulatory agencies, and industry. Several factors contribute to this growing trial complexity, including the reliance on biomarkers, innovative biostatistical methodologies, advocacy groups' pressures, regulatory requirements, recognition of diverse unmet clinical needs, and enhanced comprehension of clinical research methodologies. In addition, prior to trial initiation, rigorous pre-trial discussions among sponsoring entities providing therapies for evaluation and stakeholders involved in trial oversight and governance are indispensable.

Some challenges are shared among all master protocol trial designs, umbrella, basket, and platform trials, while others are more specific to trial designs due to their distinctive features. Significantly, multiple stakeholders have engaged in collaborative efforts and initiatives, leading to the issuance of numerous recommendations and guidance documents concerning innovative or complex clinical trials, as detailed in Table 2.

Effective communication among pharmaceutical industry, academia, regulatory agencies, and patients plays a major role in addressing many of these challenges.

| Initiatives | Guidance/recommendation |
|---|---|
| US Department of Health and Human Services, Food and Drug Administration (FDA) | FDA Guidance Document. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry. Guidance for Industry. FDA; 2022 (67).<br>FDA guidance on COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention. May 2021 (68).<br>FDA Master protocol toolkit (9). |
| European Commission/Heads of Medicines Agencies/ European Medicines Agency (EC/HMA/EMA) | Guidance under the ACT EU initiative- Complex clinical trials – Questions and answers Version 2022-05-23 (10). |
| European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) | EMA-CHMP Concept paper on platform trials. 31 October 2022 (11). |
| European Commission and Heads of Medicine Agencies Clinical Trials Facilitation and Co-ordination Group (CTFG) | CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials 12 February 2019 (12). |
| National Institute for Health and Care Research (NIHR) along with health departments in Scotland, Wales and Northern Ireland | Recommendations to support further development and adoption of Complex Innovative Designed (CID) trials including master protocol trials (13). |
| Clinical Trials Transformation Initiative (CTTI) | Developed a robust set of resources including:<br>CTTI Master Protocol Design & Implementation Guide (14).<br>CTTI Value Proposition Guide (15).<br>CTTI-FDA Engagement Tool - that guide the appropriate use of master protocols (16). |
| European Federation of Pharmaceutical Industries and Associations (EFPIA) | EPFIA Clinical Research Expert Group published a white paper on Innovation in Clinical Trial Design: A review of The Clinical Trial Design Landscape in March 2020 (17). |
| EU-Patient Centric Clinical Trial Platforms (EU-PEARL)(18) | Public-private partnership funded through the Innovative Medicines Initiative, Grant no. 853966-2, developed several tools resources, publication and deliverables to facilitate the design, set-up and implementation of patient-centric collaborative platform trials in Europe. |
| European Clinical Research Infrastructure Network (ECRIN) | ECRIN Adaptive Platform Trial Toolbox (19). |

*Table 2: Initiatives, recommendations, and guidance published on master protocols and innovative or complex clinical trials.*

# Recommendations for master protocols

**Regulatory and ethical considerations**

Favouring the use of standardised nomenclature:

- Standardising master protocol nomenclature is crucial for effective communication, regulatory compliance, and ensuring patient safety in clinical trials.
- A common understanding of master protocol design terms is essential for regulatory boards and potential trial participants to ask pertinent questions regarding patient safety and trial efficacy (3,20,21).
- Standardised definitions can enhance collaboration and streamline research efforts by promoting uniform data collection and trial.

**Funding & funding mechanisms**

Developing funding opportunities is essential to support the creation and maintenance of existing master protocol trials. Existing master protocol studies have adopted various funding models, with many employing innovative public-private funding strategies involving multiple stakeholders (4,7,8,20,22,23,24):

- Common infrastructure or screening platform is typically funded by public funds or grants from non-profit organisations, while biopharmaceutical companies fund their respective arms or sub-trials.
- Funding models include paying per patient or covering participation costs through "pay-to-play" or "user fees" models.
- Funding arrangements typically require complex costings, contract negotiation, determining payment responsibilities, data access rights, and intellectual property ownership.

The future use of public or public-private partnerships to drive the development of master protocol studies should be considered (4,8,22,25,26,28,29):

- There is a need to shift towards new funding models prioritising long-term investments in stable research infrastructure to support master protocol trials from setup to maintenance.
- Co-funding from both public and private sectors in different models, for example, considering separating the funding in the set-up phase and the implementation phase, with dedicated funding for each sub-trial / arm independently.

- Funding not only new master protocols but also already established infrastructures with experience in implementing and conducting master protocols with different designs. This approach ensures continuity and sustainability.
- In the EU, there is a crucial need for funding mechanisms capable of promptly leveraging EU funding and integrating it with national public funding programs, acting as incentives for active participation in multinational clinical trials by academic institutions, hospitals, and patient organisations.

**Sponsorship & Governance**

Designating the right sponsor

Non-profit organisations naturally emerge as ideal candidates to sponsor master protocol trials due to (4,22,24,28,30,32,33):

- Their disease-specific focus and commitment to scientific rigour.
- Their neutrality and independence foster trust among industry stakeholders and regulators, potentially facilitating collaboration even before commercial partners are identified.
- They help to mitigate potential conflicts of interest that may arise from companies developing competing compounds. Ensuring that the trial remains unbiased and focused on scientific advancement rather than commercial interests.

Establishing an appropriate Governance model

Establishing an effective governance model with a robust leadership to guarantee multidisciplinary engagement upfront is imperative for the success of master protocol trials. This model should clearly define roles and responsibilities, establish decision-making mechanisms, conflict resolution strategies, intellectual property rights arrangements, transparency measures, and mechanisms for fostering accountability throughout the trial process (4,8,24,34,35):

- Appropriate leadership is crucial in master protocol trials, guiding the strategic direction, decision-making, and overall management of the trial.
- Usually, clinical leadership has been shared between a few co-investigators, each named as a specific treatment cohort clinical lead within the protocol, allowing the increased clinical burden associated with a master protocol design to be shared.
- During the COVID-19 pandemic, projects financed by the European Commission, such as EU-RESPONSE, RECOVER, ECRAID-Prime, and VACCELERATE, established a joint coordination module known as the Joint Access Advisory Mechanism (JAAM) (36). This mechanism prioritises intervention arms for EU-funded COVID-19 platform trials and has expanded to include other respiratory syndromes.

**Trial management**

Establishing/using sustainable infrastructure

- With the anticipated rapid increase in master protocols, it's crucial to establish appropriate infrastructure supporting clinical operations while preventing duplication and resource wastage. Leveraging existing infrastructures with expertise in master protocols for trials in various fields is essential for efficiency and effectiveness (3,4,8,26,32,34,35,37).
- Developing an investigator research network is paramount for the success of master protocol trials. Leveraging existing networks in relevant disease areas can expedite trial setup and ensure broader participation (38).

**Statistical analysis**

Choosing the appropriate statistical approach

- Existing sophisticated analysis models, which incorporate the sharing of information between subgroups (preferably among those with comparable treatment effects only) have been used, such as Bayesian hierarchical models, allowing information borrowing across subgroups to increase power (39-41,43,45-47).
- Further statistical methods aim to increase master protocols' flexibility with mid-trial adaptations, such as seamlessly adding new treatments as they emerge and dropping poorly performing treatments with frequent interim looks, while maintaining strong type I error control (39).
- The solution to statistical challenges will typically vary depending on the variant of trial design chosen and study-specific requirements (25,26,40,41)
- The analysis plan for these trials demands thoughtful consideration in the preparation phase and during the trial, accompanied by meticulous documentation of parameter specifications, operating characteristics, and the utilisation of suitable statistical tools, including user-friendly software. Implementing these measures will contribute to bolstering the credibility and trustworthiness of these models.

# Recommendations for umbrella trials

Umbrella trials represent one class of master protocol design that evaluates multiple targeted therapies within a single disease setting in different sub-trials (48). These sub-trials are defined by a disease subtype or individual patient characteristics thought to be associated with treatment response.

**Regulatory and ethical considerations**

Ensuring social and scientific validity

- Fostering collaboration among researchers, regulators, and other stakeholders to optimise trial design.
- Guaranteeing the accrual to treatment arms by implementing proactive recruitment strategies, such as collaboration with multiple research centres, patient advocacy groups, and international consortia.
- Providing detailed documentation of trial protocols, justifying all protocol modifications, end points, and analytical methodologies to ensure transparency and to maintain the integrity of the research process, providing assurance to both participants and stakeholders that the trial is conducted with rigour and adherence to ethical standards.

Ensuring appropriate benefit/risk assessment

- All clinical trials should uphold the principle of equipoise, with benefits expected to accrue for future patients rather than participants themselves. Trials should not be viewed as a shortcut to access unproven treatment without rigorous clinical testing.
- Approaches like genome-driven stratification may not be sufficient for delivering appropriate therapies tailored to the heterogeneous nature of tumours (49-51).

Tailoring informed consent process for personalised medicine trials (umbrella and basket trials):

- Participants need to understand the evolving nature of the study and how it may affect their involvement. It is important to manage patient expectations (better responses and fewer adverse events) accordingly, as only a few patients benefit from personalised medicine trials (e.g. a favourable risk-benefit ratio may not always be guaranteed) (48,52).
- Investigators can employ various strategies to enhance understanding during the consent process, such as iterative explanations, multimedia platforms, simplified consent documents, extended discussion times, and quizzes to assess participants' comprehension and provide feedback.

- Investigators must communicate about participant privacy and confidentiality, but also clearly explain the privacy risks and limitations of privacy protections, particularly when related to genetic information.

**Protocol design or methodological considerations**

Considering scheme allocation for patients testing positive for multiple biomarkers under investigation

- Define clear guidelines for managing cases where patients test positive for multiple biomarkers (32).
- Among the allocation schemes, various strategies can be adopted, such as weighted allocation based on subgroup prevalence, a hierarchy of biomarkers approach, a ranking algorithm, pre-specified prioritisation, and assignment to non-matched arms.
- The most common approaches are randomly assigning patients to one of the two sub-trials with equal probability, and pragmatic allocation. For the latter, patients are allocated to the sub-trial with fewer enrolled patients at the time (53).

Sample size determination

- The calculation of sample size is influenced by the phase of the trial, with exploratory trials typically requiring smaller sample sizes compared to confirmatory trials.
- Computation is the most common way to determine sample size, and the determination of the number of patients required for each sub-trial is done separately (per module) using the Bayesian approach (38,40,42,49,50).

Inclusion of a control group and randomisation

- Inclusion of control enhances prognostic homogeneity and helps mitigate the risk of false positives. Comparing safety outcomes without an appropriate control arm can complicate the attribution of adverse events.
- The control group may be a placebo in cases where there is no established standard of care, or it may involve using the current standard of care for the disease under study uniformly across all subgroups. Alternatively, different controls may be employed across sub-trials (26,48,54).

Ensuring accuracy in biomarker assays for basket and umbrella trial designs (26,54)

- Incorporating false-positive rates of biomarker tests during trial planning is essential.
- Centralised screening tests are preferred for multiple biomarkers due to their higher reproducibility compared to locally conducted genotyping.

- Benefits of centralising assays include pre-specification and control of key elements like assay reagents, equipment, protocols, and computational methods, predetermined results of assay analytical validation ensuring precision, minimising false positives and negatives, facilitating regulatory approval and expediting the translation of assays and drugs to clinical use upon trial success.
- Investigators may employ local screening for trial enrolment while using centralised screening to confirm.
- Optimising the biomarker–drug co-development
- Computational approaches can help identify novel biomarkers, predict treatment response, and optimise patient selection criteria (48, 55).
- Collaboration between academic institutions, pharmaceutical and technology companies, data analytics experts, and regulatory agencies is essential to translate biomarker discoveries into clinically useful assays (56,57).
- Implementing robust quality assurance measures across different laboratories, especially concerning new biomarkers and analysis methodologies, is imperative to guarantee consistency and reliability in biomarker assay results (54,58).
- Continuous monitoring and auditing of laboratory practices are necessary throughout the trial to maintain high-quality standards and ensure the validity of trial findings.

# Recommendations for basket trials

A master protocol designed to evaluate a single investigational drug or drug combination in different disease populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics is commonly referred to as a basket trial (5).

**Regulatory and ethical considerations**

Considering national recommendations on the acceptability of the trial results

- The French National Authority for Health recommends the emphasis of genuine comparative strategies and the inclusion of stratified randomisation based on tumor location or including clinically and genetically annotated retrospective cohorts as external controls when randomised controlled trials are not feasible, and the recording of all data in registries for future reuse as external controls, especially in rare diseases (60).
- The NIH (National Institute for Health), English Health Technology Assessment (HTA) agency, recommends being more pragmatic for patient access to treatment by providing conditional approval and coverage for drugs tested through basket trials. Full approval would be granted upon re-evaluation of additional evidence later (61).

**Protocol design or methodological considerations**

Carefully considering the use of molecular biomarkers

In oncology studies, the impact of the tumour's environment, location, on its mutational profile and treatment response must be considered:

- Existing clinical evidence might not sufficiently endorse replacing histological tumour typing with molecular descriptors.
- Future research endeavours should focus on integrating anatomical, mutational, and functional molecular profiling, using advanced proteomic technologies, and exploring multi-gene signatures and combination therapies (25,56,59,62).

Selecting the right biomarker

- The recommendations for optimising the biomarker-drug co-development process outlined in umbrella trials also apply to basket trials.

Inclusion of a control group and randomisation

- Randomisation in basket trials should be considered only when there is equipoise, indicating a lack of consensus or clear evidence favouring one treatment over another in terms of efficacy or safety.
- Factors influencing the decision to include a control arm in a basket trial include the trial's stage, disease prevalence, control availability, and ethical considerations (60).
- Basket trials often employ non-comparative study designs in early clinical development to identify relevant patient populations for targeted therapies.
- The complexity of using the standard of care as the control across different disease populations is heightened in certain diseases compared to others. For instance, various autoimmune diseases share a common standard of care, whereas in oncology, each tumour type typically has its own distinct standard of care protocol (25,54).

Selection of validated surrogate endpoints (63-65)

- The utilisation of surrogate outcomes should be restricted to scenarios where a surrogate has unequivocally demonstrated its capacity to reliably predict meaningful clinical benefits, or in cases of dire, rare, or limited treatment options. For instance, the FDA provides a list of validated and likely surrogates (66).
- The justification for employing surrogate endpoints in specific phases of research lies in their ability to provide information on the effect of a drug more swiftly compared to long-term clinical outcomes. However, recent evidence has increasingly demonstrated that surrogate endpoints may not reliably reflect patient-centred outcomes.

# Recommendations for adaptive platform trials

Adaptive platform trials are one type of master protocol that offers a dynamic approach to testing multiple interventions within a single disease context, offering the flexibility to add or drop treatment arms as needed (30). They often incorporate shared control arms and utilise pre-planned interim analyses with stopping guidelines to prioritise promising research comparisons.

**Regulatory and ethical considerations**

Considering the regulatory framework for adaptive platform trials

- Several regulatory guidance documents focusing on the conduct of clinical trials utilising master protocols and adaptive design have been developed (7-19,67,68).
- It is recommended to establish dialogue and collaboration with regulators from the protocol development and planning of the platform trial to enhance mutual understanding. Early engagement with regulators can address potential issues and align the expectations of both regulators and trialists from the beginning, particularly since adaptive platform trials are increasingly used in epidemic research (8,23).
- For clinical trials running in Europe, CTIS (Clinical Trials Information System) still raises technical hurdles and challenges that need to be solved, such as national requirements harmonisation, complexity, and costs and dealing with multiple amendments simultaneously.

Ethical approval and oversight

- Enhanced collaboration between regulatory agencies, ethics committees, and trial sponsors is essential (2,8,24).
- Implementing a predetermined plan to make appropriate safety oversight of multiple IMPs, and to promptly disseminate new safety information to investigators, institutional review boards, regulators and update patients, as toxicities emerge.

**Protocol design or methodological considerations**

Being mindful about protocol structure, modular or integrated approach

- Careful evaluation is necessary, weighing the impact on trial set-up times, regulatory concerns, complexity versus performance, and the burden on participating sites.
- Adopting a modular approach can provide a more general platform, facilitating easier management of various treatment arms.
- In an integrated approach, protocol updates should be consolidated to minimise amendments.

**Sponsorship & Governance**

Oversight structures (24,30)

- Develop clear and robust oversight structures (see Master Protocol Recommendation for Sponsorship & Governance), including DSMB (Data Safety Monitoring Board) and TSC (Trial Steering Committee).
- Foster regular communication and collaboration among trial management, data management teams and oversight committees – DSMB and TSC. Ensure that all committee members are kept fully informed about trial protocols, ongoing data analysis, and any proposed adaptations.
- Prioritise scientific validity and integrity throughout the trial process.
- Promote transparency in decision-making processes regarding the addition of new research comparisons and recommendations for protocol adaptations.
- Be prepared to adapt trial protocols as needed based on emerging data and recommendations for oversight committees.

**Trial Management**

Fully understanding resource requirements is essential for those writing grant applications and critical, for those with the responsibility for deciding on funding to ensure adequate support and funding allocation (23,69,70,71).

Effective management of platform trials requires meticulous planning and strong collaboration among stakeholders (see Master Protocol Recommendation for Trial Management). Additional recommendations include (8,24,40,70):

- Establishing large central teams can alleviate the burden of individual trial units and ensure efficient trial management. Maintaining continuity of experienced staff within the trial's unit is beneficial for streamlining workflow and workload division, reducing the need for extensive training and mentoring.
- Provide comprehensive training for staff, both at trial sites and within the trial's unit, to handle the increased complexity of technical and logistical activities in platform protocols.
- Maintaining staff motivation and engagement is crucial for ensuring the success and sustainability.
- Acknowledging the complex, large-scale nature of platform trials and the heightened expectations they entail is crucial. These features can provide opportunities for professional development and foster high levels of loyalty and commitment among team members.

**Public/Patient Involvement**

Fostering patient engagement (23,72)

- EU PEARL initiative created a Patient Engagement Platform with a repository containing resources on engaging patients and communities in future platform trials (27).
- Patient and community involvement provides insights into motivations, barriers to trial participation, and expectations regarding reimbursement.
- Involving patients early in clinical trials enables direct feedback on the design from those affected by the condition, helping to identify potential pitfalls missed by researchers alone.
- Reinforcing the notion of a shared objective between patients, researchers, and clinicians to effectively address collaboration.
- Investigators and funders should maintain ongoing engagement with patient representatives throughout the trial's lifecycle.

**Data Management**

Data management activities and team (22,23,24, 30,31,40,69,73)

- Database design must be carefully considered to allow for efficient incorporation of future changes. Planning for flexibility and scalability during initial development is crucial to accommodate evolving trial requirements.
- Understanding the database structure is essential for optimising data storage and retrieval. This ensures efficient management of trial data throughout its lifecycle.
- The chosen Clinical Data Management System must be supported throughout the trial's life. This ensures continuity and reliability in data management processes.
- Implement a comprehensive data management plan, complemented by arm/cohort-specific project management plans, to effectively manage data cleaning and querying processes. This plan should outline strategies for handling competing demands and ensure adequate resources are allocated to manage accumulating data.
- Ensuring adequate training and documentation for data managers is crucial to effectively navigate the complexities of data management systems. Regularly review and update training materials to reflect changes in recruiting arms and trial procedures
- Given the concurrent nature of activities across various arms/cohorts and the significant volume of accumulating data, establish a data management team to adequately meet the demands of the platform trial.

# Bibliography

1. D14.2 Recommendation booklet for investigators and sponsors in multicountry IICS WP14. Available at: https://era4health.eu/results/deliverables.php.
2. Sudhop T, Brun NC, Riedel C, Rosso A, Broich K, Senderovitz T. Master protocols in clinical trials: a universal Swiss Army knife? Lancet Oncol. 2019 Jun;20(6):e336-e342. doi: 10.1016/S1470-2045(19)30271-2.
3. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017 Jul 6;377(1):62-70. doi: 10.1056/NEJMra1510062.
4. Park JJH, Ford N, Xavier D, Ashorn P, Grais RF, Bhutta ZA, Goossens H, Thorlund K, Socias ME, Mills EJ. Randomised trials at the level of the individual. Lancet Global Health, 2021. May;9(5):e691-e700. doi: 10.1016/S2214-109X(20)30540-4.
5. Park JJH, Dron L, Mills EJ. Moving forward in clinical research with master protocols. Contemp Clin Trials. 2021 Jul;106: 106438. doi: 10.1016/j.cct.2021.106438.
6. Cecchini M, Rubin EH, Blumenthal GM, Ayalew K, Burris HA, Russell-Einhorn M, Dillon H, Lyerly HK, Reaman GH, Boerner S, LoRusso PM. Challenges with Novel Clinical Trial Designs: Master Protocols. Clin Cancer Res. 2019 Apr 1;25(7):2049-2057. doi: 10.1158/1078-0432.CCR-18-3544.
7. Forrest JI, Rawat A, Duailibe F, Guo CM, Sprague S, McKay P, Reis G, Mills EJ. Resilient Clinical Trial Infrastructure in Response to the COVID-19 Pandemic: Lessons Learned from the TOGETHER Randomized Platform Clinical Trial. Am J Trop Med Hyg. 2022 Jan 7;106(2):389-393. doi: 10.4269/ajtmh.21-1202.
8. Snowdon C, Kernaghan S, Moretti L, Turner NC, Ring A, Wilkinson K, Martin S, Foster S, Kilburn LS, Bliss JM. Operational complexity versus design efficiency: challenges of implementing a phase IIa multiple parallel cohort targeted treatment platform trial in advanced breast cancer. Trials. 2022 May 7;23(1):372. doi: 10.1186/s13063-022-06312-x.
9. FDA Master protocol toolkit available in: https://toolkit.ncats.nih.gov/glossary/master-protocol/
10. Guidance under the ACT EU initiative- Complex clinical trials – Questions and answers Version 2022-05-23 Available online at https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf
11. EMA-CHMP Concept paper on platform trials. 31 October 2022 . Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-platform-trials_en.pdf
12. CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials 12 February 2019. Available online at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf

# Bibliography

13. NIHR / health departments in Scotland, Wales and Northern Ireland Recommendations to support further development and adoption of Complex Innovative Designed (CID) trials including master protocol trials. Available online at: https://www.nihr.ac.uk/partners-and-industry/industry/uk-research-delivery-spotlights/complex-innovative-trials.htm
14. CTTI Master Protocol Design & Implementation Guide. Available online at https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Master_Protocol_Roadmap.pdf
15. CTTI Value Proposition Guide. Available online at: https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Master_Protocol_Value_Prop_Guide.pdf
16. CTTI-FDA Engagement Tool - that guide the appropriate use of master protocols. Available online at: https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Master_Protocol_FDA_Engagement_Tool.pdf
17. EPFIA Clinical Research Expert Group published a white paper on Innovation in Clinical Trial Design: A review of The Clinical Trial Design Landscape in March 2020 .Available online at: https://www.efpia.eu/media/547507/efpia-position-paper-innovation-in-clinical-trial-design-white-paper.pdf
18. https://eu-pearl.eu/
19. ECRIN Adaptive Platform Trial Toolbox Available online at: https://ecrin.org/adaptive-platform-trial-tools.
20. Brown LC, Graham J, Fisher D, Adams R, Seligmann J, Seymour M, Kaplan R, Yates E, Parmar M, Richman SD, Quirke P, Butler R, Shiu K, Middleton G, Samuel L, Wilson RH, Maughan TS; FOCUS4 Trial Investigators. Experiences of running a stratified medicine adaptive platform trial: Challenges and lessons learned from 10 years of the FOCUS4 trial in metastatic colorectal cancer. Clin Trials. 2022 Apr;19(2):146-157. doi: 10.1177/17407745211069879.
21. Hirakawa A, Asano J, Sato H, Teramukai S. Master protocol trials in oncology: Review and new trial designs. Contemp Clin Trials Commun. 2018 Aug 24;12:1-8. doi: 10.1016/j.conctc.2018.08.009.
22. Bronson A, Chase MK, Fisher K, Millar D, Perlmutter J, Richardson N. Mobilizing the clinical trial ecosystem to drive adoption of master protocols. Clinical Trials. 2022;19(6):690-696. doi:10.1177/17407745221110199 .
23. Love, S.B., Cafferty, F., Snowdon, C. et al. Practical guidance for running late-phase platform protocols for clinical trials: lessons from experienced UK clinical trials units. Trials 23, 757 (2022). https://doi.org/10.1186/s13063-022-06680-4.
24 Schiavone, F., Bathia, R., Letchemanan, K. et al. This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols. Trials 20, 264 (2019). https://doi.org/10.1186/s13063-019-3216-8.
25. Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Ann Oncol. 2017 Jan 1;28(1):34-43. doi: 10.1093/annonc/mdw413.

# Bibliography

26. Yee LM, McShane LM, Freidlin B, Mooney MM, Korn EL. Biostatistical and Logistical Considerations in the Development of Basket and Umbrella Clinical Trials. Cancer J. 2019 Jul/Aug;25(4):254-263. doi: 10.1097/PPO.0000000000000384.
27. https://eu-pearl.eu/patient-engagement-platform/
28. Tang M, Joensuu H, Simes RJ, Price TJ, Yip S, Hague W, Sjoquist KM, Zalcberg J. Challenges of international oncology trial collaboration-a call to action. Br J Cancer. 2019 Oct;121(7):515-521. doi: 10.1038/s41416-019-0532-4.
29. Goossens H, Derde L, Horby P, Bonten M. The European clinical research response to optimise treatment of patients with COVID-19: lessons learned, future perspective, and recommendations. Lancet Infect Dis. 2022 May;22(5):e153-e158. doi: 10.1016/S1473-3099(21)00705-2.
30. The Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. Nat Rev Drug Discov 18, 797–807 (2019). https://doi.org/10.1038/s41573-019-0034-3.
31. Sandercock PAG, Darbyshire J, DeMets D, Fowler R, Lalloo DG, Munavvar M, Staplin N, Warris A, Wittes J, Emberson JR. Experiences of the Data Monitoring Committee for the RECOVERY trial, a large-scale adaptive platform randomised trial of treatments for patients hospitalised with COVID-19. Trials. 2022 Oct 18;23(1):881. doi: 10.1186/s13063-022-06824-6.
32. Burd A, Schilsky RL, Byrd JC, Levine RL, Papadimitrakopoulou VA, Herbst RS, Redman MW, Druker BJ, Gandara DR. Challenges and approaches to implementing master/basket trials in oncology. Blood Adv. 2019 Jul 23;3(14):2237-2243. doi: 10.1182/bloodadvances.2019031229.
33. EU-PEARL. D1.7 Recommended Ethical, Information Governance and Security Policies for IRPs. Available in: https://eu-pearl.eu/deliverables-patient-centric-clinical-trial-platforms/
34. Siden EG, Park JJ, Zoratti MJ, Dron L, Harari O, Thorlund K, Mills EJ. Reporting of master protocols towards a standardized approach: A systematic review. Contemp Clin Trials Commun. 2019 Jul 4;15:100406. doi: 10.1016/j.conctc.2019.100406.
35. Bogin V. Master protocols: New directions in drug discovery. Contemp Clin Trials Commun. 2020 Apr 25;18:100568. doi: 10.1016/j.conctc.2020.100568.
36. https://covid19trials.eu/en/jaam
37. Park, J.J.H., Siden, E., Zoratti, M.J. et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials 20, 572 (2019). https://doi.org/10.1186/s13063-019-3664-1.
38. Wang H, Yee D. I-SPY 2: a Neoadjuvant Adaptive Clinical Trial Designed to Improve Outcomes in High-Risk Breast Cancer. Curr Breast Cancer Rep. 2019 Dec;11(4):303-310. doi: 10.1007/s12609-019-00334-2.
39. Yin J, Shen S, Shi Q. Challenges, opportunities, and innovative statistical designs for precision oncology trials. Ann Transl Med. 2022 Sep;10(18):1038. doi: 10.21037/atm-22-356.

# Bibliography

40. Lu CC, Li XN, Broglio K, Bycott P, Jiang Q, Li X, McGlothlin A, Tian H, Ye J. Practical Considerations and Recommendations for Master Protocol Framework: Basket, Umbrella and Platform Trials. Ther Innov Regul Sci. 2021 Nov;55(6):1145-1154. doi: 10.1007/s43441-021-00315-7.
41. Hobbs BP, Landin R. Bayesian basket trial design with exchangeability monitoring. Stat Med. 2018;37(25):3557–72.
42. Kesselmeier M, Benda N, Scherag A. Effect size estimates from umbrella designs: Handling patients with a positive test result for multiple biomarkers using random or pragmatic subtrial allocation. PLoS One. 2020 Aug 14;15(8):e0237441. doi: 10.1371/journal.pone.0237441.
43. Hu C, Dignam JJ. Biomarker-Driven Oncology Clinical Trials: Key Design Elements, Types, Features, and Practical Considerations. JCO Precis Oncol. 2019 Oct 24;3:PO.19.00086. doi: 10.1200/PO.19.00086.
44. Ryan, E.G., Brock, K., Gates, S. et al. Do we need to adjust for interim analyses in a Bayesian adaptive trial design?. BMC Med Res Methodol 20, 150 (2020).
45. Chen N, Lee JJ. Bayesian cluster hierarchical model for subgroup borrowing in the design and analysis of basket trials with binary endpoints. Stat Methods Med Res. 2020 Sep;29(9):2717-2732. doi: 10.1177/0962280220910186.
46. Zheng H, Wason JMS. Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy. Biostatistics. 2022 Jan 13;23(1):120-135. doi: 10.1093/biostatistics/kxaa019.
47. Kaizer AM, Hobbs BP, Koopmeiners JS. A multi-source adaptive platform design for testing sequential combinatorial therapeutic strategies. Biometrics. 2018 Sep;74(3):1082-1094. doi: 10.1111/biom.12841.
48. Ouma LO, Wason JMS, Zheng H, Wilson N, Grayling M. Design and analysis of umbrella trials: Where do we stand? Front Med (Lausanne). 2022 Oct 12;9:1037439. doi: 10.3389/fmed.2022.1037439.
49. Hey SP, Weijer C, Taljaard M, Kesselheim AS. Research ethics for emerging trial designs: does equipoise need to adapt? BMJ. 2018 Jan 25;360:k226. doi: 10.1136/bmj.k226.
50. Nicole Haloupek. Precision Medicine Stumbles in Umbrella Trial. Cancer Discov. 2020 Oct;10(10):1435. doi: 10.1158/2159-8290.CD-NB2020-076.
51. Gyawali B. Point: The Imprecise Pursuit of Precision Medicine: Are Biomarkers to Blame? J Natl Compr Canc Netw. 2017 Jul;15(7):859-862. doi: 10.6004/jnccn/2017.0126.
52. Strzebonska K, Waligora M. Umbrella and basket trials in oncology: ethical challenges. BMC Med Ethics. 2019 Aug 23;20(1):58. doi: 10.1186/s12910-019-0395-5.
53. Kesselmeier M, Benda N, Scherag A. Effect size estimates from umbrella designs: Handling patients with a positive test result for multiple biomarkers using random or pragmatic subtrial allocation. PLoS One. 2020 Aug 14;15(8):e0237441. doi: 10.1371/journal.pone.0237441.

# Bibliography

54. Park JJH, Hsu G, Siden EG, Thorlund K, Mills EJ. An overview of precision oncology basket and umbrella trials for clinicians. CA Cancer J Clin. 2020 Mar;70(2):125-137. doi: 10.3322/caac.21600.
55. Serelli-Lee V, Ito K, Koibuchi A, Tanigawa T, Ueno T, Matsushima N, Imai Y. A State-of-the-Art Roadmap for Biomarker-Driven Drug Development in the Era of Personalized Therapies. J Pers Med. 2022 Apr 21;12(5):669. doi: 10.3390/jpm12050669.
56. Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine. Nat Rev Clin Oncol. 2018 Jun;15(6):353-365. doi: 10.1038/s41571-018-0002-6.
57. Ko YK, Gim JA. New Drug Development and Clinical Trial Design by Applying Genomic Information Management. Pharmaceutics. 2022 Jul 24;14(8):1539. doi: 10.3390/pharmaceutics14081539
58. Richman SD, Hemmings G, Roberts H, Gallop N, Dodds R, Wilkinson L, Davis J, White R, Yates E, Jasani B, Brown L, Maughan TS, Butler R, Quirke P, Adams R. FOCUS4 biomarker laboratories: from the benefits to the practical and logistical issues faced during 6 years of centralised testing. J Clin Pathol. 2023 Aug;76(8):548-554. doi: 10.1136/jclinpath-2022-208233.
59. Selaru P, Tang Y, Huang B, Polli A, Wilner KD, Donnelly E, Cohen DP. Sufficiency of Single-Arm Studies to Support Registration of Targeted Agents in Molecularly Selected Patients with Cancer: Lessons from the Clinical Development of Crizotinib. Clin Transl Sci. 2016 Apr;9(2):63-73. doi: 10.1111/cts.12388.
60. Lengliné E, Peron J, Vanier A, Gueyffier F, Kouzan S, Dufour P, Guillot B, Blondon H, Clanet M, Cochat P, Degos F, Chevret S, Grande M, Putzolu J; Transparency Committee of the French National Authority for Health. Basket clinical trial design for targeted therapies for cancer: a French National Authority for Health statement for health technology assessment. Lancet Oncol. 2021 Oct;22(10):e430-e434. doi: 10.1016/S1470-2045(21)00337-5.
61. Popat S, Ramagopalan SV, Ray J, Roze S, Subbiah V. Assessment of tumour-agnostic therapies in basket trials. Lancet Oncol. 2022 Jan;23(1):e7. doi: 10.1016/S1470-2045(21)00714-2.
62. Klauschen F, Heim D, Stenzinger A. Histological tumor typing in the age of molecular profiling. Pathol Res Pract. 2015 Dec;211(12):897-900. doi: 10.1016/j.prp.2015.08.001.
63. Krendyukov A, Singhvi S, Zabransky M. Value of Adaptive Trials and Surrogate Endpoints for Clinical Decision-Making in Rare Cancers. Front Oncol. 2021 Mar 8;11:636561. doi: 10.3389/fonc.2021.636561.
64. McLeod C, Norman R, Litton E, Saville BR, Webb S, Snelling TL. Choosing primary endpoints for clinical trials of health care interventions. Contemp Clin Trials Commun. 2019 Nov 12;16:100486. doi: 10.1016/j.conctc.2019.100486.
65. Ciani O, Grigore B, Blommestein H, de Groot S, Möllenkamp M, Rabbe S, Daubner-Bendes R, Taylor RS. Validity of Surrogate Endpoints and Their Impact on Coverage Recommendations: A Retrospective Analysis across International Health Technology Assessment Agencies. Med Decis Making. 2021 May;41(4):439-452. doi: 10.1177/0272989X21994553.

# Bibliography

66. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.
67. US Department of Health and Human Services, Food and Drug Administration (FDA). Guidance Document. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry. Guidance for Industry. FDA; 2022. https://collections.awsprod.nlm.nih.gov/catalog/nlm:nlmuid-9918452088706676-pdf.
68. FDA guidance on COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention. May 2021. Available at https://www.fda.gov/news-events/press-announcements/fda-brief-fda-provides-guidance-master-protocols-evaluating-prevention-treatment-options-covid-19.
69. Li X, Lu C, Broglio K, Bycott P, Chen J, Jiang Q, Lin J, Ye J, Yin J. Current usage and challenges of master protocols-based on survey results by ASA BIOP oncology methodology working group master protocol sub-team. Ann Transl Med. 2022 Sep;10(18):1036. doi: 10.21037/atm-21-6139.
70. Morrell L, Hordern J, Brown L, Sydes MR, Amos CL, Kaplan RS, Parmar MKB, Maughan TS. Mind the gap? The platform trial as a working environment. Trials. 2019 May 29;20(1):297. doi: 10.1186/s13063-019-3377-5.
71. Wason JMS, Dimairo M, Biggs K, Bowden S, Brown J, Flight L, Hall J, Jaki T, Lowe R, Pallmann P, Pilling MA, Snowdon C, Sydes MR, Villar SS, Weir CJ, Wilson N, Yap C, Hancock H, Maier R. Practical guidance for planning resources required to support publicly-funded adaptive clinical trials. BMC Med. 2022 Aug 10;20(1):254. doi: 10.1186/s12916-022-02445-7.
72. Butler CC, Connor JT, Lewis RJ, Broglio K, Saville BR, Cook J, van der Velden A, Verheij T. Answering patient-centred questions efficiently: response-adaptive platform trials in primary care. Br J Gen Pract. 2018 Jun;68(671):294-295. doi: 10.3399/bjgp18X696569.
73. Hague D, Townsend S, Masters L, Rauchenberger M, Van Looy N, Diaz-Montana C, Gannon M, James N, Maughan T, Parmar MKB, Brown L, Sydes MR; STAMPEDE and FOCUS4 investigators. Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons. Trials. 2019 May 29;20(1):294. doi: 10.1186/s13063-019-3322-7.

This booklet has been developed by ECRIN within the context of the ERA4Health project.