ACCSCIENCE PUBLISHING

Tumor Discovery

REVIEW ARTICLE

Practice and consideration of master protocol in clinical trials

Jiali Song[1†], Zhiwei Rong[1†], Xinwen Zhong[1], Yuhong Lu[1], Jike Huang[1], Yipei Yu[1], Zhilin Liu[1], Xuyuan Quan[1], Nana Chen[1], Kang Li[2], Fengyu Sun[3*], and Yan Hou[1,4,5*]

[1]Department of Biostatistics, School of Public Health, Peking University, Beijing 100191, China

[2]Department of Epidemiology and Biostatistics, School of Public Health, Harbin Medical University, Harbin, 150086, China

[3]National Medical Products Administration, Beijing 100022, China

[4]Peking University Cancer Hospital and Institute, Beijing 100142, China

[5]Clinical Research Center, Peking University, Beijing 100191, China

Abstract

There is considerable interest in expediting late-stage therapy development by efficiently conducting trial designs that encompass multiple therapies or multiple subpopulations simultaneously within a unified protocol. Such trial designs are referred to as master protocols, with specific designs characterized by the terms umbrella, basket, or platform. These designs, in contrast to the traditional trial designs, are full of complexity. What factors should be considered in designing a trial ensuring the safety of human subjects and demonstrating the efficacy of new therapy? This paper overviews the master protocol framework, comprehensively unifies the definitions, and illustrates essential design elements of representative example trials conducted in drugs and medical devices. Besides, to understand the master protocols deeply, it is also a need to summarize the commonly-used types of master protocols in various disease and treatment fields, along with the reasons for these phenomena by analyzing the characteristics of the diseases, the mechanism of therapeutic products, and the principles of various types of master protocols. Finally, we also propose practical considerations, including the design, ethical, statistics, and funding considerations that arise from implementing complex master protocols. This information serves to guide practitioners in designing more effective trials and identifying potentially valuable therapies.

Keywords: Design; Master protocol; Principle; Consideration; Clinical practice

†These authors contributed equally to this work.

***Corresponding authors:**
Fengyu Sun
(sun.129.com@163.com)
Yan Hou
(houyan@bjmu.edu.cn)

Citation: Song J, Rong Z, Zhong X, *et al.*, 2023, Practice and consideration of master protocol in clinical trials. *Tumor Discov*. https://doi.org/10.36922/td.342

Received: January 30, 2023
Accepted: April 18, 2023
Published Online: April 28, 2023

1. Introduction

Conventionally, the development of new therapeutic products has relied on a series of clinical trials, each testing one or two therapies for a single disease. This process is both time-consuming and expensive. Therefore, there is growing interest in accelerating therapy development through performing trials that simultaneously test multiple therapies or multiple subpopulations under a single protocol. Such trials, known as master protocols, have gained popularity and have been extensively researched in the fields of drugs and medical devices, especially in oncology. The Food and Drug

Administration (FDA) released guidance about master protocols in oncology drugs in 2022[1] and COVID-19 in 2019[2], representing the concerns and support of the regulatory authorities for master protocols. So far, over 100 master protocol trials have been initiated, leading to the marketing of several therapies, such as vemurafenib[3] and entrectinib[4].

In recent years, master protocol trials have proven to be more efficient in evaluating new targeted therapies, with a substantial increase in the number of clinical trials and research[5-10]. Woodcock *et al.* initiated the definition of master protocols and illustrated it with two examples in cancer[6]. Janiaud *et al.* reviewed the investigational drug clinical trials with master protocols in ClinicalTrials.gov and briefly summarized the advantages and limitations in oncology[11]. In contrast, only a few master protocol trials and research have been conducted in radiation oncology devices (RODs). Bitterman *et al.* summarized the examples with master protocols in RODs and demonstrated the shortcomings and challenges of clinical evaluation of RODs[12]. Couwenberg *et al.* explored the feasibility of a master protocol in techniques/software development for magnetic resonance (MR)-guided adaptive radiotherapy with the MR-Linac[13]. Due to the regulatory requirements for Class I and Class II devices[14], these devices often undergo less rigorous prospective assessment and have fewer clinical research studies conducted.

Despite the increasing number of clinical trials utilizing master protocols in both investigational drugs and medical devices, there are still a lot of challenges and varying degrees of insularity in the field. Published reviews have primarily focused on oncology drugs and devices, respectively, with limited comparisons and discussions across different fields, hindering a comprehensive understanding of master protocols. Besides, given the heightened scrutiny of medical devices, the application of the master protocols to identify the most high-value technologies more efficiently is necessary[12,15]. In addition, the development of *in vitro* diagnostics parallel to their corresponding therapeutic products in master protocols needs further investigation, as they can help identify populations with a higher likelihood of response and safety.

To synthetically understand how to identify the most valuable innovative drugs and medical devices more efficiently based on limited health-care resources using master protocols, this paper provides an overview of the master protocol framework, unifying definitions and illustrating essential design elements from representative example trials in both drugs and medical devices. Besides, to understand the master protocols deeply, it is also a need to summarize the commonly-used types of master protocols in various disease fields, along with the reasons for these phenomena by the characteristics of the diseases, the mechanism of therapeutic products, and the principles of various types of master protocols. Finally, we also propose practical considerations, including design, ethical, statistics, and funding aspects, to assist practitioners in better designing and identifying potentially valuable therapies using protocols.

2. Definition and types of master protocol trial design

A master protocol aims to explore or evaluate multiple therapies or multiple subpopulations in parallel under a single overarching protocol, with the characteristics of improving efficiency and establishing uniformity through standardization of procedures in clinical trials. In addition, the master protocols can be designed adaptively to modify the protocol flexibly, such as incorporating or terminating individual sub-studies, which are often classified into basket trials, umbrella trials, and platform trials (Figure 1).

2.1. Basket trial design

A basket trial is a type of clinical trial that tests how well a new drug or other substance works in patients who have different types of cancer that all have the same mutation or biomarker (Figure 1A). In basket trials, all patients receive the same treatment that targets the specific mutation or biomarker found in their cancer. In practice, the nonrandomized sub-studies within basket trials may be preferred because of their feasibility and close connection to the conventional single-arm Phase II designs. However, due to the absence of a comparator, non-randomized basket sub-studies should select an objective response as the primary endpoint for its interpretability. In addition, basket trials may also be useful for studying rare cancers and cancers with rare genetic changes. For example, the prevalence of many targets is too low to analyze by each target type with enough subjects, while pooling all subpopulations with homogeneity might be considered[16].

2.2. Umbrella trial design

An umbrella trial endeavors to study multiple therapies within a single disease (Figure 1B), in which patients with targets of interest are allocated to mutually exclusive therapeutic sub-studies. In terms of the allocation of patients, it is a necessity to prespecify and evaluate an explicit rule governing how to match subpopulations and candidate regimens, especially for patients who are positive for multiple biomarkers. Umbrella trials can employ either randomized or nonrandomized designs. For randomized umbrella sub-studies, FDA recommends a common control arm of the standard of care (SOC), which

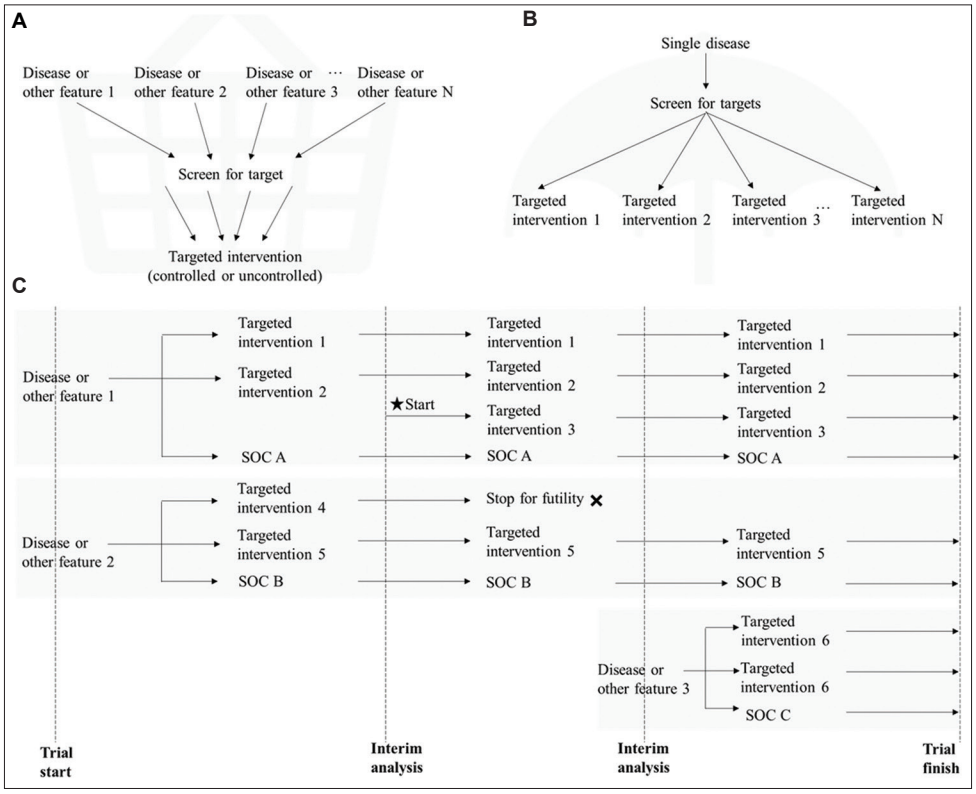

Figure 1. Master protocol trial design: basket trial, umbrella trial, and platform trial. (A) Schematic display of a basket trial. The same targeted intervention is investigated in populations with different diseases or other features in different sub-studies. (B) Schematic display of an umbrella trial. In the population with the same target or disease, several targeted interventions are investigated in different sub-studies. (C) Schematic display of a platform trial. Some sub-studies dedicated to a population with the particular same target or disease can be randomized clinical trials with the possibility to add up or remove treatment arms as data accrue.
SOC: Standard of care.

will facilitate the trial results interpretable in the context of medical practice. In general, comparative analyses can be conducted between a test drug and the common control so that multiple drugs are evaluated simultaneously in a single disease (e.g., umbrella trials). It should be noted that the SOC in clinical practice may change over time if newer drugs are approved for marketing. In this case, the sponsor should suspend subject enrollment until the protocol and the protocol informed consent document are modified to include the new SOC as control[1].

2.3. Platform trial design

A platform trial refers to a design that studies multiple therapies perpetually, with therapies allowed to enter or leave the platform based on a decision algorithm (Figure 1C). Such a design provides substantial flexibility in terms of discontinuing unpromising therapeutic sub-studies, carrying forward favorable early results to definitive testing in the Phase II/III framework, and introducing new sub-studies as targets and agents. Therefore, platform trials usually incorporate adaptations to achieve flexibility. For example, Bayesian decision rules determine the discontinuation or further study of therapies, and response-adaptive randomization assigns patients to the most promising treatment.

3. Master protocol trials in oncology drugs

Due to the more profound advances in disease heterogeneity and molecular drivers of genesis, many master protocol trials have been designed and executed in the face of tumor subtypes, evaluating multiple therapies or multiple diseases in parallel. Table 1 lists the critical design elements of several representative master protocol cancer trials, illustrating their considerations and clinical practices. As we can see from Table 1, oncology drugs, mainly targeted therapies, account for the most extensive use of master protocols. This phenomenon is because a targeted therapy affecting one or more specific target(s) to control how cancer cells grow, divide, and spread is consistent with the principles of master protocols.

Specifically speaking, a basket trial in oncology drugs can access molecularly targeted agents for patients across

Table 1. Representative examples of master protocol design in oncology drugs

Trial	Registration number	Description	Design	Drug(s)	Target	Sample size	Primary endpoint
BRAF-V600[3]	NCT01524978	Basket trial to evaluate the efficacy of vemurafenib in non-melanoma cancers	Early Phase 2, multicenter, open-label, non-comparative, adaptive trial using Simon's two-stage design	1. Vemurafenib 2. Cetuximab	BRAF V600	122 planned for whole study	BORR
B2225[20]	NCT00154388	Basket trial to evaluate the efficacy of imatinib in hematologic malignancy and solid tumors	Phase 2, multicenter, open-label, non-comparative trial	Imatinib	Imatinib-sensitive tyrosine kinases	186 planned for whole study	Tumor response
Ace'[21]	NCT02304809	Basket trial to assess the efficacy and the safety of the targeted agent vemurafenib as a monotherapy in cohorts of patients with identified activating molecular alterations in BRAF gene	Phase 2, multicenter, open-label, non-comparative trial	Vemurafenib	BRAF mutation	216 actually enrolled	ORR
NCI-MATCH[22]	NCT02465060	Combination of a basket and umbrella trial to determine whether treating cancers according to molecular abnormalities is effective	Phase 2, open-label, non-randomized, parallel assignment trial	1. Dabrafenib+ trametinib 2. Nivolumab 3. Capivasertib 4. AZD4547 5. Ado-trastuzumab emtansine 6. AZD1775 7. Trametinib 8. Afatinib 9. GSK2636771 10 Taselisib 11. Palbociclib	1. BRAF/V600E/V600K 2. dMMR 3. AKT mutations 4. FGFR pathway aberrations 5. HER2 amplification 6. BRCA ½ 7. BRAF fusions, BRAF non-V600E 8. ERBB2 mutations 9. PTEN loss, PTEN mutations/deletions with PTEN IHC expression 10. PIK3A mutations without RAS co-mutations or PTEN loss 11. CCND1,2, and 3 amplification 12. Rb protein expression	6,452 planned for whole study	ORR
Lung-MAP[9,23]	NCT02154490	Umbrella trial to evaluate biomarker-matched therapies in subsets of stage IV or recurrent squamous cell NSCLC	Phase 2/3 randomized trial	1. Docetaxel 2. Durvalumab 3. Erlotinib hydrochloride 4. AZD4547 5. Ipilimumab 6. Nivolumab	1. PI3K PIK3CA mutation 2. CDK4/6 CCND1, 2,3 mutations CDK4 amplification 3. FGFR amplification, mutation, fusion 4. c-MET c-MET expression	1864 actually enrolled	PFS, ORR, OS

(Cont'd...)

Table 1. *(Continued)*

Trial	Registration number	Description	Design	Drug(s)	Target	Sample size	Primary endpoint
				7. Palbociclib 8. Rilotumumab 9. Talazoparib 10. Taselisib 11. Tremelimumab	5. Non-match study activity in a PD-L1+		
ALCHEMIST[24]	NCT02194738 NCT02193282 NCT02201992 NCT02595944	Umbrella trial to evaluate molecularly defined subsets of operable, early stage (Stage IB-IIIA) lung adenocarcinoma	Phase 2/3, multicenter, comparative, randomized trial	1. Erlotinib 2. Crizotinib 3. Nivolumab	1. EGFR mutation 2. ALK rearrangement 3. PD-L1 expression	6,000 – 8,000 planned for ALCHEMIST-Screening, 410 planned for ALCHEMIST-EGFR, 360 planned for ALCHEMIST- ALK, 903 planned for ALCHEMIST-PD-L1	OS, DFS
FOCUS4[25]	ISRCTN90061546	Umbrella trial in inoperable advanced or metastatic colorectal cancer to ascertain whether the proposed intervention improves PFS compared with the control group in the biomarker-defined cohort and whether the biomarkers used identify one or more patient cohorts with greater responsiveness to therapy than an unselected group	Phase 2/3, multi-site, multi-arm, multi-stage, double-blind, comparative trial	1. Specific BRAF mutated kinase inhibitor in combination with panitumumab (an EGFR targeted monoclonal antibody) with or without MEK inhibitor 2. Aspirin 3. AKT inhibitor and MEK inhibitor 4. HER1, 2 and 3 inhibitor 5. Capecitabine	1. BRAF mutation 2. PIK3CA mutation 3. KRAS or NRAS mutation 4. PTEN expression and wild type for BRAF, PIK3CA, KRAS, NRAS mutations	1,536 planned for whole study	PFS, OS
I-SPY 2[8,26]	NCT01042379	Platform trial to identify treatment regimens for locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures	Phase 2, multicenter, single-blind, comparative, adaptive randomization trial	1. AMG 386 with or without Trastuzumab 2. AMG 479 (Ganitumab) + metformin 3. MK-2206 with or without trastuzumab 4. AMG 386 and trastuzumab 5. T-DM1 and pertuzumab 6. Pertuzumab and trastuzumab	TNBC HER23. hormone receptor	4,000 planned for study	Pathological complete response

(Cont'd...)

Table 1. *(Continued)*

Trial	Registration number	Description	Design	Drug(s)	Target	Sample size	Primary endpoint
				7. Ganetespib 8. ABT-888 9. Neratinib 10. PLX3397 11. Pembrolizumab-4 cycle 12. Talazoparib+ irinotecan 13. Patritumab and trastuzumab 14. Pembrolizumab-8 cycle 15. SGN-LIV1A 16. Durvalumab+ olaparib 17. SD-101+ pembrolizumab 18. Tucatinib+ trastuzumab and pertuzumab 19. Cemiplimab 20. Cemiplimab+ REGN3767 21. Trilaciclib with or without trastuzumab+ pertuzumab 22. SYD985 ([vic-] trastuzumab duocarmazine) 23. Oral paclitaxel+ encequidar+ dostarlimab (TSR-042) + carboplatin with or without trastuzumab 24. Oral paclitaxel+ encequidar+ dostarlimab (TSR-042) with or without trastuzumab 25. Amcenestrant			

(Cont'd...)

Table 1. *(Continued)*

Trial	Registration number	Description	Design	Drug(s)	Target	Sample size	Primary endpoint
				26. Amcenestrant+ abemaciclib 27. Amcenestrant+ letrozole			
NCI-MPACT[27]	NCT01827384	Platform trial to assess the utility of applying tumor DNA sequencing to treatment selection for patients with advanced, refractory cancer and somatic mutations in one of four signaling pathways by comparing the efficacy of four study regimens that were either matched to the patient's aberrant pathway (experimental arm) or not matched to that pathway (control arm)	Phase 2, multicenter, comparative, adaptive randomization trial	1. Adavosertib 2. Carboplatin 3. Everolimus 4. Temozolomide 5. Trametinib 6. Veliparib	1. DNA repair pathway 2. PI3K pathway 3. RAS/RAF/MEK pathway	208 actually enrolled	Number of participants with an objective response
BATTLE[28]	NCT00409968 NCT00410059 NCT00410189 NCT00411632 NCT00411671	Platform trial to evaluate targeted therapies in chemotherapy-refractory NSCLC	Phase 2, single-center, comparative, adaptive randomization trial using Bayesian design	1. Erlotinib 2. Vandetanib 3. Sorafenib 4. Erlotinib+ bexarotene	1. EGFR mutation 2. KRAS/BRAF mutation 3. VEGF expression 4. RXRs/CyclinD1 expression	255 actually enrolled	PFS, DCR
SHIVA[29]	NCT01771458	Platform trial to compare targeted therapy based on the molecular profile and conventional therapy based on investigator's choice for patients with refractory cancer	Phase 2, multicenter, open-label, comparative, crossover assignment, adaptive randomization trial	1. Imatinib 2. Everolimus 3. Vemurafenib 4. Sorafenib 5. Erlotinib 6. Lapatinib+ 7. trastuzumab 8. Dasatinib 9. Tamoxifen (or letrozole if contra-indication) 10. Abiraterone	1. Hormone receptor 2. PI3K/AKT/mTOR 3. RAF/MEK	742 actually enrolled	PFS

BORR: Confirmed best overall response rate; DCR: Disease control rate; DFS: Disease-free survival; IHC: Immunohistochemistry; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival

a broad range of tumor types, in which sample size within sub-studies is often small but yield quick results, given sufficient accrual[5]. For example, BRAF V600 is a basket trial evaluating vemurafenib, the selective BRAF V600 inhibitor, in patients with eight nonmelanoma cancers[3]. This study recruited only 122 adults but led the FDA to approve vemurafenib for treating BRAFV600-mutant Erdheim-Chester disease. In addition, an umbrella trial in cancer can evaluate multiple targeted drugs with corresponding biomarkers for patients in single cancer, of which biomarker-negative patients are usually enrolled into a "non-match" sub-study, thus evaluating the drug's purported mechanism of action more thoroughly. For example, lung-MAP is an umbrella trial evaluating four targeted agents with their corresponding molecular markers in squamous cell lung cancer. In this trial, patients with no targeted biomarkers of interest are assigned to the "nonmatch" sub-study, allowing a more thorough evaluation of the mechanism of drugs and more screened patients to participate[9]. Finally, for a platform trial, it can be more likely a specific form of a basket or an umbrella trial mentioned above with perpetual features and adaptation[17-19]. For instance, I-SPY 2 is a platform trial evaluating multiple neoadjuvant therapies for high-risk, locally advanced breast cancer with a trial network and informatics infrastructure, including adaptations of Bayesian decision rules and response-adaptive randomization for a more flexible design[8]. Therefore, the principles of master protocols closely match the mechanism of oncology drugs and will be further developed and applied to oncology drugs.

4. Master protocol trials in oncology devices

In evaluating oncology devices, the pertinent clinical question is which indications the new technology is better, to what extent, or whether it reduces toxicity[30]. To address these questions, some researchers use master protocol trials in oncology devices, which can test several clinical indications in a standardized fashion, allowing for more rapid and direct comparisons of different indications and technologies. Here, we list the critical information of several representative master protocol trials in oncology devices (including hardware and software) in Table 2, showing the considerations and clinical practices.

4.1. RODs

As is shown in Table 2, there are fewer master protocol trials in oncology devices reported than in oncology drugs, mainly focusing on RODs. This situation is large because drugs and devices have different FDA approval pathways, driving differences in clinical implementation and evaluation standards. In contrast to the high-quality evidence from Phases I, II, and III trials in oncology drug evaluation, most oncology devices classified as medium-risk (Class II) are approved via the premarket notification (510[k]) pathway to predicate devices and require only preclinical supporting data. As a result, we have often assumed the effectiveness of a novel device based on technical and physical parameters without evidence from clinical trials. This premarket notification pathway causes oncology device manufacturers' unwillingness to sponsor clinical studies of new oncology devices[12]. Consequently, the master protocol trials of oncology devices are usually after marketing approval and funded by academia. In addition, whereas oncology drugs primarily utilize biomarkers as targets in master protocols, oncology devices, especially RODs, use tumor sites as therapeutic targets to some extent. For instance, UMBRELLA-II trial evaluates the feasibility of various in-house developed techniques or software on the MR-Linac, in which various tumor sites are considered as therapeutic targets[13]. Furthermore, master protocol trials in oncology devices refer to single cancer type-agnostic protocols encompassing multiple cancer type-specific sub-studies, of which the most common trial design types are basket trials. For example, stereotactic MR-guided adaptive radiation therapy (SMART) is a basket trial evaluating the feasibility and efficacy of stereotactic MR-guided adaptive radiation therapy in patients with 13 different types of cancer[31].

4.2. *In vitro* diagnostic assays

Notably, *in vitro* diagnostic assays are classified as medical devices. Next generation sequencing (NGS) assays have been widely adopted in clinical oncology by utilizing the profiled genetic mutation information to select patients and guide the choice of target therapy. The NGS assays are essential in the master protocol trial of oncology drugs. For example, in NCI-MATCH mentioned above, a single NGS assay is used to screen for the actionable mutations in about 6000 patients who have relapsed or refractory solid tumors and lymphomas after standard systemic treatment, and assigned matched treatment[22]. As conducting prospective clinical trials is necessary to acquire FDA approval for a biomarker-targeting oncology drug, the development, and validation of NGS diagnostics assays that accurately and reliably report genetic mutation status from patient tumor biopsies to determine study eligibility are instrumental to the success of such clinical studies. NGS assays used in clinical trials for guiding therapy decisions were considered investigational devices and had to meet regulatory compliance for investigational device exemption, such as the code of federal regulations title 21 part 812 for investigational device exemption[32].

Table 2. Representative examples of master protocol design in oncology devices

Trial	NCT number	Description	Design	Intervention	Sample size	Primary endpoint
SMART[31]	NCT04115254	Basket trial evaluating feasibility and efficacy of SMART in patients with 13 types of cancer	Phase I/II, open-label, non-randomized, parallel assignment trial	MR-guided Linac	1,000 planned for whole study	1. Delivery Success Rate for SMART across multiple tumors-Phase I 2. Tumor visualization-Phase I 3. Plan creation-Phase I 4. Rate of Improvement in Tumor Control-Phase II
EXTEND[33]	NCT03599765	Basket trial to assess the efficacy of upfront local consolidative therapy for oligometastatic disease	Phase II, open-label, randomized, parallel assignment trial	Systemic therapy with or without local consolidation therapy	367 planned for whole study	Incidence of adverse events
CIVO[34]	NCT04541108	Basket trial using the CIVO® platform to evaluate intratumoral microdoses of anti-cancer therapies in patients with different solid tumor types	Early Phase 0, open-label, parallel, non-randomized trial	The CIVO device	24 planned for whole study	Quantification of cell death and immune cell biomarkers by IHC and *in-situ* hybridization
SBRT[35]	NCT02239900	Basket trial to evaluate ipilimumab with concurrent or sequential stereotactic ablative radiation therapy to metastatic lesions in the liver or lung	Phase II, open-label, single-institution, Randomized, parallel assignment trial	Concurrent or sequential ipilimumab with SABR	143 actually enrolled	Toxicity
AGADIR[36]	NCT03915678	Basket trial to independently and simultaneously assess the effects of the association of atezolizumab+ BDB001+ radiotherapy in multiple solid tumors	Phase2, open-label, 6 independent single-arm, multicenter, based on 2-stage Simon's optimal design	Association atezolizumab+ BDB001+ RT	247 planned for whole study	Assessment of the antitumor activity
JUMP[37]	NCT04545957	Basket trial evaluating feasibility and efficacy of incorporating MRI simulation into the planning of radiation treatments in4 types of cancer	Phase I/II, open-label, non-randomized, parallel assignment trial	MRI Simulator	86 planned for whole study	1. Feasibility of acquiring MRI simulation prior to radiation therapy planning 2. Proportion of patients with quality of life decline exceeding 2× MID (minimal important differences)
CONFIRM[38]	NCT04368702	Basket trial evaluating magnetic resonance image-guided radiation in patients with gastric and breast cancer	Phase I/II, open-label, non-randomized, parallel assignment trial	Viewray MRIdian® Linac	86 planned for whole study	1. Number of patients and delivering MR-image guided radiation-Phase I 2. Tumor assessment with MR guidance-Phase I 3. Patient reported outcomes (PROMs)-Phase II

(Cont'd...)

Table 2. ***(Continued)***

Trial	NCT number	Description	Design	Intervention	Sample size	Primary endpoint
						4. 1-year tumor control-Phase II 5. Rate of pathologic complete response-Gastric
UMBRELLA-II[13]	NCT04351204	Combination of a basket and umbrella trial to evaluate the feasibility of various in-house developed techniques/ software on the MR-Linac in various tumor sites	Open-label, non-randomized, single-group assignment trial	Techniques/ software for MR-guided adaptive radiotherapy with the MR-Linac	Per sub-study, a maximum of 20 patients can be enrolled. No formal sample size calculation was performed because this is not a hypothesis-driven research. Rather, it is based on the needs of demonstrating feasibility of techniques/software	Feasibility
CONCORDE[39]	NCT04550104	Platform trial using the TiTE CRM design to find the RP2D of each DNA damage response inhibitor in combination with conventional radiotherapy in non-small cell lung cancer	Phase I, multi-institution, multi-arm, open-label, randomized trial	1. Radiotherapy only 2. Olaparib+ radiotherapy 3. AZD1390+ radiotherapy	200 planned for whole study	Dose limiting toxicities

MRI: Magnetic resonance imaging; CIVO: Comparative *in vivo* oncology; SMART: Stereotactic magnetic resonance-guided adaptive radiation therapy; MR: Magnetic resonance

We believe that the increased efficiency in trial administration and infrastructure, the most significant advantage of a master protocol trial design, will facilitate the complex systematic evaluation of innovations in oncology devices which is of great importance to patients, users, vendors, and society.

5. Master protocol trials in COVID-19

The COVID-19 pandemic threatens global security and the economy. Although safe and effective vaccines for COVID-19 have been developed and distributed, there is still a need to evaluate multiple treatments in clinical trials. However, unique challenges posed by COVID-19 have exposed inadequacies in the conventional phased investigational therapeutic development paradigm. To address the COVID-19 public health emergency, FDA issued a guidance in 2019, which describes the FDA's current recommendations to sponsors of master protocols evaluating drugs for the treatment or prevention of COVID-19[2]. The master protocols can unify resources and efforts for clinical research worldwide to initiate and coordinate COVID-19 clinical trials, which accelerate the treatment evaluation of COVID-19. Here, we summarize the key information of several representative master protocol trials in COVID-19 in Table 3.

Among the master protocol trials of COVID-19 published so far, the most common trial design is the platform trial, as it is relevant to the current need of developing COVID-19 drugs rapidly. In these trials, multiple interventions for COVID-19 are evaluated in different sub-studies with the addition and removal of interventions based on planned interim analyses, which can accelerate drug development and maximize the information obtained from the research effort. For example, RECOVERY is a platform trial to evaluate the effects of potential treatments in patients admitted to hospitals with COVID-19[40]. Consequently, effective treatment (dexamethasone) was quickly established in patients admitted to hospitals with COVID-19, which immediately changed clinical practice. Furthermore, compared with conducting separate stand-alone trials, conducting a master protocol trial can increase data quality and efficiency through shared infrastructure and reduce overall sample size by sharing a control arm. These efficiencies are of particular importance in the public health emergency with a critical need for efficient therapies, such as the current COVID-19 pandemic. Therefore, we expect master protocol trials to continue to play an important role in addressing the public health needs created by the current COVID-19 pandemic, and other emerging infectious diseases that might occur in the future.

Table 3. Representative examples of master protocol design in COVID-19

Trial	NCT number	Description	Design	Intervention	Sample size	Primary endpoint
RECOVERY[40]	NCT04381936	Platform trial to evaluate the effects of potential treatments in patients admitted to hospital with COVID-19	Phase 2/3, open-label, comparative, randomization trial	1. Lopinavir-Ritonavir 2. Corticosteroid 3. Hydroxychloroquine 4. Azithromycin 5. Convalescent plasma 6. Tocilizumab 7. Immunoglobulin 8. Synthetic neutralising antibodies 9. Aspirin 10. Colchicine 11. Baricitinib 12. Anakinra 13. Dimethyl fumarate 14. High Dose Corticosteroid 15. Empagliflozin 16. Sotrovimab 17. Molnupiravir 18. Paxlovid	50,000 planned for whole study	All-cause mortality within 28 days after randomization
PRINCIPLE[41]	ISRCTN86534580	Platform trial to assess the effectiveness of the respective interventions in reducing time to recovery and the incidence of hospitalization or death.	Multicenter, open-label, multi-arm, randomized, controlled trial	1. Azithromycin, hydroxychloroquine sulphate 2. Doxycycline 3. Inhaled budesonide (Pulmicort Turbohaler®) 4. Colchicine 5. Favipiravir 6. Ivermectin	12,000 planned for whole study	COVID-19-related hospital admission or death within 28 days
TOGETHER[42]	NCT04727424	Platform trial to assess the efficacy of fluvoxamine versus placebo in preventing hospitalization defined as either retention in a COVID-19 emergency setting or transfer to a tertiary hospital due to COVID-19	Phase 3, multicenter, prospective, adaptive, double-blind, randomized, placebo-controlled study	1. Fluvoxamine 2. Budesonide powder 3. Peginterferon lambda-1a	4,669 planned for whole study	Rate of fluvoxamine+ budesonide, peginterferon lambda, and fluvoxamine in changing the need for emergency care AND observation for more than 06 h due to the worsening of COVID-19 within 28 days Rate of fluvoxamine+ budesonide, peginterferon lambda and fluvoxamine in changing the need for hospitalization due to COVID-19 progression and related complications, including lower respiratory tract infection within 28 days
OPTIMISE-C19[43]	NCT04790786	Platform trial to evaluate the	Phase 4, open-label,	1. LillyBamlanivimab 2. Regeneron	60,000 planned for whole study	Alive and free from hospitalization

(Cont'd...)

Table 3. ***(Continued)***

Trial	NCT number	Description	Design	Intervention	Sample size	Primary endpoint
		comparative effectiveness of COVID-19-specific multiple monoclonal antibodies (mAbs) with Emergency Use Authorizations status	pragmatic, randomized trial	Casirivimab+ Imdevimab 3. Lilly Bamlanivimab+ Etesevimab 4. Sotrovimab 5. Bebtelovimab		
ACTIV[44]	NCT04593940	Platform trial to evaluate multiple investigational agents for the treatment of moderately or severely ill patients infected with SARS-CoV-2	Phase 3, randomized, triple-blind, placebo-controlled trial	1. Infliximab 2. Abatacept 3. Remdesivir 4. Cenicriviroc	1,971 actually enrolled	Number of patients that recovered from COVID-19
ACTT[45-48]	NCT04280705 NCT04401579 NCT04492475 NCT04640168	Platform trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19	Phase 3, multicenter, adaptive, randomized, double-blind, placebo-controlled trial	1. Remdesivir 2. Baricitinib 3. Interferon beta-1a 4. Dexamethasone	1062, 1033, 969, 1010 actually enrolled for ATCC-1, -2, -3, -4, respectively	Time to recovery (by race/ethnicity/sex)
CATCO[49]	NCT04330690	Platform trial to compare multiple agents against the currently available standard of care in adults admitted to participating hospitals with laboratory-confirmed SARS-CoV-2 infection	Phase 3, multicenter, adaptive, randomized, open-label, controlled trial	1. Artesunate 2. Imatinib 3. Infliximab 4. ARBs 5. Dexamethasone 6. LSALT Peptide	2,900 planned for whole study	28-day mortality Clinical status Respiratory support
DisCoVeRy[50]	NCT04315948	Platform trial to evaluate the safety and efficacy of possible therapeutic agents in hospitalized adult patients diagnosed with COVID-19	Phase 3, multicenter/ country, adaptive, randomized, open, or blinded	1. Remdesivir 2. Lopinavir/ritonavir 3. Interferon Beta-1A 4. Hydroxychloroquine 5. AZD7442	2,416 planned for whole study	Percentage of subjects reporting each severity rating on a 7-point ordinal scale

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

6. Master protocol trials in other fields

Besides, there are also some master protocol trials focusing on other disease domains. Herein, we summarize several kinds of diseases which may benefit a lot from master protocols, including hereditary and familial diseases, rare diseases, emerging infectious diseases, and in some drugs like Traditional Chinese Medicine (TCM), and establish the critical information of these trials in Table 4.

6.1. Hereditary and familial diseases

Hereditary and familial diseases are hereditary, which reside in a genetic mutation, and may pass on from one generation to the next. The development of hereditary and familial disease therapies targets specific genetic mutations. In practice, this process may include multiple therapies targeting multiple genetic mutations. Platform trials can lighten the complexity of this process by providing substantial flexibility, such as introducing new therapies to avoid undertaking other trials. For example, there is a type of early-onset Alzheimer's disease caused by a genetic mutation, and a platform trial named DIAN-TU evaluates potential treatments targeting this genetic mutation in patients at risk for or with this familial disease. Treatments of solanezumab and gantenerumab are currently under study, and additional therapies are planned[51].

Table 4. Representative examples of master protocol design in other fields

Field	Trial	NCT number	Description	Design	Intervention	Sample size	Primary endpoint
Traditional chinese medicine	BOSS[57]	NCT04408261	Basket trial to evaluate the efficacy and safety of Buqitongluo granule in treating qi deficiency and blood stasis syndrome and explore the effect of the improvement of qi deficiency and blood stasis syndrome on the prognosis of diseases	Phase 2, multicenter, randomized, double-blind, placebo-controlled trial	Buqitongluo granule	432 planned for whole study	Change in the syndrome score of qi deficiency and blood stasis
Rare diseases	CLUSTER[59]	NCT02059291	Umbrella trial to evaluate efficacy and safety of Canakinumab in patients with periodic fever syndromes	Phase 3, multicenter, open-label, comparative, randomized trial	Canakinumab (anti-interleukin-1β monoclonal antibody)	203 actually enrolled	Percentage of participants with resolution of initial flare and absence of new flares up to the end of the randomized treatment epoch (16 weeks)
Others	pNAAT[60]	NCT02870101	Combination of a basket and umbrella to evaluate diagnostic assays for pharyngeal and rectal NG and CT	Multicenter, open-label, single-group trial	Nucleic acid amplification tests 1, 2, 3 for NG and CT	2,767 actually enrolled	Number of participants with different tests relative to reference results
Hereditary and familial diseases, are diseases	DIAN-TU[51]	NCT01760005	Platform trial testing multiple drugs to slow or prevent the progression of Alzheimer's disease in autosomal dominant Alzheimer's disease families	phase 2/3, double-blind, randomized, pooled-placebo controlled 2-year biomarker trial	1. Solanezumab (an anti-soluble Aβ antibody) 2. Gantenerumab (an anti-fibrillar Aβ antibody)	490 planned for whole study	DIAN-TU cognitive composite
Rare diseases	INHIBIT[53]	NCT04303559	Platform trial comparing Eloctate versus Emicizumab to prevent inhibitor formation in patients with severe hemophilia A	Phase 3, multicenter, open-label, adaptive randomized trial using Bayesian design	1. Eloctate 2. Emicizumab	66 planned for whole study	The proportion developing anti-FVIII inhibitors
Emerging infectious diseases	REMAP-CAP[54]	NCT02735707	Platform trial to evaluate the effect of a range of interventions to improve the outcome	Phase 3, open-label, comparative, adaptive randomized trial using Bayesian design	Many kinds of drugs	10,000 planned for whole study	1. All-cause mortality at day 90 2. Days alive and not

(Cont'd...)

Table 4. *(Continued)*

Field	Trial	NCT number	Description	Design	Intervention	Sample size	Primary endpoint
			of patients admitted to intensive care with community-acquired pneumonia				receiving organ support in the intensive care unit at day 21 (primary endpoint for patients with suspected or proven COVID-19 pandemic infection)
Others	UPMC REMAP[61]	NCT03861767	Platform trial to determine the effect of various interventions to improve patient outcome as defined by hospital-free days at day 90 for adult patients undergoing elective surgery	Phase 3, triple-blind, comparative, randomized trial	Metformin ER	302 actually enrolled	Hospital free days

CT: Chlamydia trachomatis; NG: Neisseria gonorrhoeae

6.2. Rare diseases

Rare diseases affect only a small number of people, so trials for rare diseases tend to enroll fewer patients. Master protocols, especially umbrella or platform designs, can be chosen to address the rarity of the diseases using a common control, reducing the chance of assignment to placebo, comparing several treatments, and the ability to pool data across treatments[52]. Indeed, platform trials incorporate more adaptations for therapies to enter or leave the platform based on emerging treatments, sharing trial resources perpetually. INHIBIT is a platform trial investigating treatments to prevent and eliminate inhibitor formation in patients with hemophilia. It involves two trials within one protocol that capitalize on the same centers, laboratories, and visit timing while allowing other drugs to enter the trials if they emerge[53].

6.3. Emerging infectious diseases

As mentioned above, master protocol trials play an essential role in addressing the public health needs created by the current COVID-19 pandemic. Moreover, they are of great significance for the emerging infectious diseases that might occur in the future. Such trials can be constructed ahead of time with pre-prepared protocols, algorithms, and infrastructure, which are ready for an outbreak and enable the study of multiple therapies effectively and efficiently. For example, REMAP-CAP is a platform trial to test various interventions for patients admitted to intensive care with community-acquired pneumonia, which launches the pandemic COVID-19-specific domains now[54]. This trial shortens the time and cost of preparing a new clinical trial, thus accelerating the development of COVID-19 therapies.

6.4. Traditional Chinese medicine

In TCM, multiple diseases in different people with the same syndrome (Zheng) may be treated in the same manner[55,56], which is consistent with the design of a basket trial. Therefore, basket trials are good choices to study a single TCM among different diseases with the same syndrome (Zheng). BOSS is the first TCM basket trial evaluating the BuqiTongluo for qi deficiency and blood stasis syndrome consisting of stable angina pectoris, ischemic stroke, and diabetic peripheral neuropathy[57,58]. This study accurately evaluated the independent clinical efficacy of treatment for each disease and innovatively embodied the advantage in TCM of "treating different diseases with the same treatment"[55].

Master protocols can increase the efficiency in trial administration and infrastructure, facilitating the evaluation of multiple therapies or diseases. Therefore, in our future research, we would sincerely refer to

master protocols in these particular areas, such as multiple treatments investigated in a single rare disease using a common control arm, the TCM treatment of different diseases with the same syndrome, to promote the development of master protocols and therapies for patients.

7. The practical considerations in master protocol trial

7.1. Design considerations

7.1.1. A common control arm

When a sponsor tends to evaluate multiple therapies simultaneously in a single disease, such as umbrella trials, FDA recommends that the sponsor use a common control arm of SOC to improve efficiency in randomized trials[1]. The SOC may change over time as newer drugs develop, possibly affecting a long-running master protocol. This occurred in Lung-MAP when nivolumab was approved, which is superior to the SOC (docetaxel) selected for the biomarker-matched sub-studies. When comparing several therapies to a common control group, the test statistics will be correlated, which will lead to a lower probability of at least one false positive rejection than independent trials with a dedicated control group for each comparison[62,63]. Therefore, consistent with the standard setting of a series of separate studies, the multiplicity adjustment as regards the Type I error rate would not be a need for sub-studies comparing several active therapies to the same control group. This would be reinforced by the fact that different therapies would support separate and specific claims of efficacy even investigated globally within the same trial[62].

However, another type of error rate led using a common control group should be recognized. In master protocol sub-studies comparing multiple therapies to a common control group, corresponding regulatory decisions are correlated using a common control group, which may inflate the chance of simultaneous multiple false positive regulatory decisions[62]. For example, if the control group obtained weak results by chance, the statistical tests may then be significant for many of the therapy comparisons, even with no treatment effect for these therapies; if the control group obtained overoptimistic results by chance, few of the therapies could exhibit a statistically significant effect, even in the case of true efficacy[19]. In summary, the chance of multiple simultaneous false positive regulatory decisions might increase in the case of a common control group. To reduce it, there are some strategies such as lower individual values of the Type I error rate for each comparison, and more randomized patients to the control arm[62].

7.1.2. Subjects with multiple biomarkers

In master protocols designed to investigate therapies targeting multiple biomarkers, a challenge may arise if patients have positive results for multiple biomarkers of interest. The multi-biomarkers patients are eligible for more than one subgroup but can only be allocated to one of them. FDA recommends, in this case, that the protocol should contain a prespecified plan for allocation of these multi-biomarkers subjects[1], such as the pragmatic allocation to the eligible sub-study with the currently fewest included patients, the random allocation to one of the eligible sub-studies[64]. In practice, Lung-MAP trial assigned patients using a prespecified plan that the groups for biomarkers with lower prevalence receive more patients[23]. Notably, some researchers argue that patients with multiple biomarkers might be underrepresented in some sub-studies, and the variety of schemes for allocation could hamper the interpretation, thus proposing some methods to handle this problem, such as using random or pragmatic sub-study allocation[64].

7.2. Ethical consideration

Patients tend to give their informed consent early in the clinical trial, which is usually based on scarce protocol information. With more complicated informed consent caused by the increasing complexity and length of the master protocol trial, patients cannot thoroughly understand these documents and the trial concept to give truly informed consent. As the trial progresses, the settings not yet fully established might change because of the characteristics of master protocol designs[65]. The Declaration of Helsinki considers it crucial and ethically obligatory that each informed consent document guarantee that if new information having an impact on benefits or risks becomes available, this information is shared with the patients, and patients are asked to re-consent[66]. One approach is that patients could be informed about recruitment status during the informed consent process and choose another sub-study with an already established setting. Such an approach would involve the patients more in the decision-making process, which will challenge both patients and investigators[65].

7.3. Statistics considerations

7.3.1. The multiplicity issue

Multiplicity is the Type I error rate inflation from a multiple-testing problem. From the regulatory perspective, it has to be adjusted at an acceptable level when several tests are performed simultaneously for decision-making about efficacy. In master protocol trials, the master protocol-wise error (MPWE) rate is referred to as the probability of declaring at least one of the sub-studies of the master

protocol optimistic when none is, which will be at least as large as the type I error rate of each sub-study and will increase with the number of sub-studies included[19].

In a basket trial, a given therapy would successively be submitted to regulators for marketing authorization in different indications. MPWE would mean that at least one of the indications of therapy is declared efficacious when there is no treatment effect in any of the indications. In an umbrella trial, several therapies would successively be submitted to regulators for marketing authorization for a similar indication. MPWE would mean that at least one therapy is wrongly declared efficacious in the subgroup of interest. In practice, it is logical to design a study in which the MPWE rate is not more significant than the equivalent error rate obtained within a series of separate studies. Otherwise, the correction of the MPWE rate across different sub-studies could be needed, such as using smaller values of the Type I error rate in each sub-study.

7.3.2. The homogeneity and pooling

The subgroups of a master protocol can be considered homogeneous if they share important clinical characteristics such that the interpretation of the treatment effect and the assessment of the benefit/risk is meaningful for the overarching target population as a whole[19]. In practice, when target populations are too small to provide a conclusive sample size and power, such as rare diseases, it is of great significance to make use of preplanned pooling among homogeneous sub-studies after an interim analysis. Homogeneity assessment depends on the strength of scientific and clinical evidence, which would influence the execution and decision-making of the trial. For example, in a basket trial that investigates a single therapy in different patients, if the subgroups cannot be seen as homogeneous according to the assessment, the design will run a series of independent sub-studies, which leads to separate indications and benefit/risk assessments for the same treatment. Otherwise, the target populations are homogeneous enough to be considered as a whole overarching population so that it would support a global indication and benefit/risk assessment for a target population. Notably, the adequacy of pooling the sub-studies and the similarity of expected responses across sub-studies would need to discuss based on biological and clinical grounds.

7.4. Funding limitation

In clinical trials, sample size and trial duration are often limited due to budget constraints. Therefore, the treatment effects or event rates might be picked with optimistic assumptions to calculate the sample size suitable for the budget and can stay competitive for the marketing decision. Master protocol trials require more costs than the budget in traditional clinical trials to establish the needed trial infrastructure and the increased upfront planning and coordination[67]. For example, Lung-MAP is a multi-drug, multi-sub-study Master Protocol in previously treated patients with squamous advanced non-small cell lung cancer. Funding for this study is shared between the National Cancer Institute (NCI) and the pharmaceutical companies at a total expected cost of $160 – 170 million over 5 years[68]. Therefore, the feasibility of master protocol trials is limited even though they have lots of advantages, such as improving efficiency, and introducing other benefits to the staff of the trial location and local infrastructure. However, it is important to fund long-term master protocol trials, because they can harbor data-driven techniques and improve the quality of clinical trial research by building research infrastructure and improving medicine development opportunities.

8. Concluding remarks

Master protocols expedite the process of trials in late-stage drug development by testing multiple therapies or multiple subpopulations simultaneously under a single protocol efficiently. This work aims to deepen the understanding of master protocols across various diseases and therapies, providing useful information when designing and conducting master protocols. Oncology is the most prevalent field of master protocols. Thereinto, the largest proportion is oncology drugs, which can use all types of master protocols due to the mechanism of oncology drug action. Namely, an oncology drug usually affects one or more specific target(s), which is consistent with the principles of master protocols. While the demand for clinical trials of devices is not as strong as that of drugs, thus the master protocol trials in oncology devices are less, in which radiotherapy is the most concerned.

Besides oncology, several kinds of diseases and therapies may greatly benefit from master protocols, that is, emerging infectious diseases (notably the COVID-19 pandemic), rare diseases, and TCM. Relative scarce master protocol trials focus on fields other than oncology devices reported. Each master protocols have specific principles and can be applied to various fields. For example, the platform trial accelerates the treatment evaluation for COVID-19, which is a good way to meet the urgent needs for emerging infectious diseases without effective treatment. Umbrella or platform designs are suitable for rare diseases to address the rarity of the patients. Basket designs can evaluate a single Traditional Chinese Medicine among multiple diseases with the same syndrome (Zheng).

However, due to the complexity of master protocols, many problems and risks that are neither new nor

fundamental problems in traditional trials have become apparent and difficult to handle. Therefore, master protocols should be prudently used when they are unavoidable for scientific reasons. It is unethical and inappropriate to consider master protocols as a vehicle that can simplify authorization or shorten review timelines. The abuse of over-complex clinical trial designs might result in unethical conduct of studies and weaken regulatory independence. In practice, master protocol design and execution require careful consideration of time and resources for establishing trial infrastructure, predefining planning, and collaborating among different parties involved in the conduct to agree on trial details. Therefore, a master protocol should be carefully designed and restricted to ensure trial subject safety, data integrity, or quality of trial conduct.

Nevertheless, it has been argued that master protocol trials could enhance clinical trial efficiency and reduce trial time and cost from a long-term perspective. First, master protocols increase the benefits of patients in clinical trials because these designs aim to treat patients with the most rational therapy based on their characteristics. Besides, master protocols are long-term with trial infrastructure shared and common standardized operating procedures established between sub-studies. Therefore, they can collect a large amount of high-quality data, and recruit and train clinical trial staff into secure roles. In addition, master protocols allow adding a new therapeutic discovery after a clinical trial begins, rather than launching a new clinical trial, and better adopting the new changes in clinical practices. Finally, as precision medicine develops, the therapies become more and more stringent to evaluate rapidly, there is no alternative but to move forward with current research efforts to simultaneously test multi-treatments or multi-diseases within master protocols.

Acknowledgments

None.

Funding

This work was supported by the National Natural Science Foundation (grant number: 82173615) of China.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Conceptualization: Jiali Song, Zhiwei Rong, Fengyu Sun, Yan Hou
Supervision: Kang Li, Fengyu Sun, Yan Hou
Writing – original draft: Xinwen Zhong, Jiali Song, Yuhong Lu
Writing – review & editing: Jike Huang, Yipei Yu, Zhilin Liu, Xuyuan Quan, Nana Chen

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. FDA, 2022, Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry. Silver Spring, Maryland: The United States Food and Drug Administration.
2. FDA, 2019. COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention Guidance for Industry. Silver Spring, Maryland: The United States Food and Drug Administration.
3. Hyman DM, Puzanov I, Subbiah V, *et al*., 2015, Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*, 373(8): 726–736.
4. Demetri GD, Paz-Ares L, Farago AF, *et al*., 2018, Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: Pooled analysis of STARTRK-2, STARTRK-1, and ALKA-372-001. *Ann Oncol*, 29: 175–175.
5. Renfro LA, Sargent DJ, 2017, Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: A review and examples. *Ann Oncol*, 28(1): 34–43.
6. Woodcock J, LaVange LM, 2017, Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med*, 377(1): 62–70.
7. Park JJ, Hsu G, Siden EG, *et al*., 2020, An overview of precision oncology basket and umbrella trials for clinicians. *CA Cancer J Clin*, 70(2): 125–137.
8. Barker AD, Sigman CC, Kelloff GJ, *et al*., 2009, I-SPY 2: An adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther*, 86(1): 97–100.
9. Herbst RS, Gandara DR, Hirsch FR, *et al*., 2015, Lung master protocol (Lung-MAP)-a biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res*, 21(7): 1514–1524.
10. Hirakawa A, Asano J, Sato H, *et al*., 2018, Master protocol trials in oncology: Review and new trial designs. *Contemp Clin Trials Commun*, 12: 1–8.

11. Janiaud P, Serghiou S, Ioannidis JPA, 2019, New clinical trial designs in the era of precision medicine: An overview of definitions, strengths, weaknesses, and current use in oncology. *Cancer Treat Rev*, 73: 20–30.

12. Bitterman DS, Cagney DN, Singer LL, *et al*., 2020, Master protocol trial design for efficient and rational evaluation of novel therapeutic oncology devices. *J Natl Cancer Inst*, 112(3): 229–237.

13. Couwenberg A, van der Heide U, Janssen T, *et al*., 2022, Master protocol trial design for technical feasibility of MR-guided radiotherapy. *Radiother Oncol*, 166: 33–36.

14. Chetty IJ, Martel MK, Jaffray DA, *et al*., 2015, Technology for innovation in radiation oncology. *Int J Radiat Oncol Biol Phys*, 93(3): 485–492.

15. Kavanagh B, 2019, Radiation oncology APM: Why us? Why now? *Int J Radiat Oncol Biol Phys*, 105(1): 22–24.

16. Hu C, Dignam JJ, 2019, Biomarker-driven oncology clinical trials: Key design elements, types, features, and practical considerations. *JCO Precis Oncol,* 1: 1-12.

17. Saville BR, Berry SM, 2016, Efficiencies of platform clinical trials: A vision of the future. *Clin Trials*, 13(3): 358–366.

18. Berry SM, Connor JT, Lewis RJ, 2015, The platform trial: An efficient strategy for evaluating multiple treatments. JAMA, 313(16): 1619–1620.

19. Collignon O, Gartner C, Haidich AB, *et al*., 2020, Current statistical considerations and regulatory perspectives on the planning of confirmatory basket, umbrella, and platform trials. *Clin Pharmacol Ther*, 107(5): 1059–1067.

20. Heinrich MC, Joensuu H, Demetri GD, *et al*., 2008, Phase II, open-label study evaluating the activity of imatinib in treating life-threatening malignancies known to be associated with imatinib-sensitive tyrosine kinases. *Clin Cancer Res*, 14(9): 2717–2725.

21. Moro-Sibilot D, Cozic N, Pérol M, *et al*., 2019, Crizotinib in c-MET-or ROS1-positive NSCLC: Results of the AcSé phase II trial. *Ann Oncol*, 30(12): 1985–1991.

22. Murciano-Goroff YR, Drilon A, Stadler ZK, 2021, The NCI-MATCH: A national, collaborative precision oncology trial for diverse tumor histologies. *Cancer Cell*, 39(1): 22–24.

23. Redman MW, Papadimitrakopoulou VA, Minichiello K, *et al*., 2020, Biomarker-driven therapies for previously treated squamous non-small-cell lung cancer (Lung-MAP SWOG S1400): A biomarker-driven master protocol. *Lancet Oncol*, 21(12): 1589–1601.

24. Gerber DE, Oxnard GR, Govindan R, 2015, ALCHEMIST: Bringing genomic discovery and targeted therapies to early-stage lung cancer. *Clin Pharmacol Ther*, 97(5): 447–450.

25. Schmoll HJ, 2018, FOCUS4: A new trial design for evaluation of targeted drugs in colorectal cancer? *Lancet Gastroenterol Hepatol*, 3(3): 143–145.

26. Wang H, Yee D, 2019, I-SPY 2: A neoadjuvant adaptive clinical trial designed to improve outcomes in high-risk breast cancer. *Curr Breast Cancer Rep*, 11(4): 303–310.

27. Chen AP, Kummar S, Moore N, *et al*., 2021, Molecular profiling-based assignment of cancer therapy (NCI-MPACT): A randomized multicenter phase II trial. *JCO Precis Oncol*, 5: 133–144.

28. Kim ES, Herbst RS, Wistuba II, *et al*., 2011, The BATTLE trial: Personalizing therapy for lung cancer. *Cancer Discov*, 1(1): 44–53.

29. Le Tourneau C, Delord JP, Gonçalves A, *et al*., 2015, Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): A multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol*, 16(13): 1324–1334.

30. Kunkler IH, Ward C, Langdon SP, 2015, Technical innovation in adjuvant radiotherapy: Evolution and evaluation of new treatments for today and tomorrow. *Breast*, 24(Suppl 2): S114–S119.

31. Stereotactic Magnetic Resonance Guided Radiation Therapy. Available from: https://clinicaltrials.gov/ct2/show/nct04115254?term=nct04115254&draw=2&rank=1 [Last accessed on 2023 Apr 26].

32. Lih CJ, Takebe N, 2017, Considerations of developing an NGS assay for clinical applications in precision oncology: The NCI-MATCH NGS assay experience. *Curr Probl Cancer*, 41(3): 201–211.

33. Systemic Therapy with or without Local Consolidative Therapy in Treating Patients with Oligometastatic Solid Tumor. Available from: https://clinicaltrials.gov/ct2/show/nct03599765?term=nct03599765&draw=2&rank=1 [Last accessed on 2023 Apr 26].

34. Ow TJ, Mehta V, Gersten AJ, *et al*., 2022, A phase 0 master protocol utilizing a novel intratumoral microdosing approach for simultaneously evaluating multiple drugs and drug combinations in patients with solid tumors. *Int J Radiat Oncol Biol Phys*, 112(5): e48.

35. Welsh JW, Tang C, de Groot P, *et al*., 2019, Phase II trial of ipilimumab with stereotactic radiation therapy for metastatic disease: Outcomes, toxicities, and low-dose radiation-related abscopal responses. *Cancer Immunol Res*, 7(12): 1903–1909.

36. Atezolizumab Combined with BDB001 and Immunogenic Radiotherapy in Patients with Advanced Solid Tumors (AGADIR). Available from: https://clinicaltrials.gov/ct2/show/nct03915678?term=nct03915678&draw=2&rank=1 [Last accessed on 2023 Apr 26].

37. Jump: MR Simulation For Radiation Therapy Master Protocol (JUMP). Available from: https://clinicaltrials.gov/ct2/show/nct04545957?term=nct04545957&draw=2&rank=1 [Last accessed on 2023 Apr 26].

38. CONFIRM: Magnetic Resonance Guided Radiation Therapy (CONFIRM). Available from: https://clinicaltrials.gov/ct2/show/nct04368702?term=nct04368702&draw=2&rank=1 [Last accessed on 2023 Apr 26].

39. Walls GM, Oughton JB, Chalmers AJ, *et al*., 2020, CONCORDE: A phase I platform study of novel agents in combination with conventional radiotherapy in non-small-cell lung cancer. *Clin Transl Radiat Oncol*, 25: 61–66.

40. RECOVERY Collaborative Group, 2020, Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. *Lancet*, 396(10259): 1345–1352.

41. Yu LM, Bafadhel M, Dorward J, *et al*., 2021, Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): A randomised, controlled, open-label, adaptive platform trial. *Lancet*, 398(10303): 843–855.

42. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, *et al*., 2022, Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: The TOGETHER randomised, platform clinical trial. *Lancet Global Health*, 10(1): e42–e51.

43. Huang DT, McCreary EK, Bariola JR, *et al*., 2021, The UPMC OPTIMISE-C19 (OPtimizing Treatment and Impact of Monoclonal antIbodieS through Evaluation for COVID-19) trial: A structured summary of a study protocol for an open-label, pragmatic, comparative effectiveness platform trial with response-adaptive randomization. *Trials*, 22(1): 363.

44. LaVange L, Adam SJ, Currier JS, *et al*., 2021, Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV): Designing master protocols for evaluation of candidate COVID-19 therapeutics. *Ann Intern Med*, 174(9): 1293–1300.

45. Beigel JH, Tomashek KM, Dodd LE, *et al*., 2020, Remdesivir for the treatment of Covid-19-final report. *N Engl J Med*, 383(19): 1813–1826.

46. Kalil AC, Mehta AK, Patterson TF, *et al*., 2021, Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: A double-bind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med*, 9(12): 1365–1376.

47. Kalil AC, Patterson TF, Mehta AK, *et al*., 2021, Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med*, 384(9): 795–807.

48. Wolfe CR, Tomashek KM, Patterson TF, *et al*., 2022, Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): A randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med*, 10(9): 888–899.

49. Ali K, Azher T, Baqi M, *et al*., 2022, Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: A randomized controlled trial. *CMAJ*, 194(7): E242–E251.

50. Ader F, Discovery French Trial Management Team, 2020, Protocol for the DisCoVeRy trial: Multicentre, adaptive, randomised trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults. *BMJ Open*, 10(9): e041437.

51. Bateman RJ, Benzinger TL, Berry S, *et al*., 2017, The DIAN-TU next generation Alzheimer's prevention trial: Adaptive design and disease progression model. *Alzheimers Dement*, 13(1): 8–19.

52. Kidwell KM, Roychoudhury S, Wendelberger B, *et al*., 2022, Application of Bayesian methods to accelerate rare disease drug development: Scopes and hurdles. *Orphanet J Rare Dis*, 17(1): 186.

53. Bertolet M, Brooks MM, Ragni MV, 2020, The design of a Bayesian platform trial to prevent and eradicate inhibitors in patients with hemophilia. *Blood Adv*, 4(21): 5433–5441.

54. Angus DC, Berry S, Lewis RJ, *et al*., 2020, The REMAP-CAP (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study. Rationale and design. *Ann Am Thorac Soc*, 17(7): 879–891.

55. Zhai X, Wang X, Wang L, *et al*., 2020, Treating different diseases with the same method-a traditional Chinese medicine concept analyzed for its biological basis. *Front Pharmacol*, 11: 946.

56. Jiang M, Zhang C, Zheng G, *et al*., 2012, Traditional chinese medicine zheng in the era of evidence-based medicine: A literature analysis. *Evid Based Complement Alternat Med*, 2012: 409568.

57. Liu W, Zhou L, Feng L, *et al*., 2021, BuqiTongluo granule for ischemic stroke, stable angina pectoris, diabetic peripheral neuropathy with qi deficiency and blood stasis syndrome: Rationale and novel basket design. *Front Pharmacol*, 12: 764669.

58. Yuan B, 2021, Towards a clinical efficacy evaluation system adapted for personalized medicine. *Pharmgenomics Pers Med*, 14: 487–496.

59. De Benedetti F, Gattorno M, Anton J, *et al*., 2018, Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N Engl J Med*, 378(20): 1908–1919.

60. Doernberg SB, Komarow L, Tran TTT, *et al*., 2020, Simultaneous evaluation of diagnostic assays for pharyngeal and rectal neisseria gonorrhoeae and chlamydia trachomatis using a master protocol. *Clin Infect Dis*, 71(9): 2314–2322.

61. Reitz KM, Seymour CW, Vates J, *et al*., 2020, Strategies to promote ResiliencY (SPRY): A randomised embedded multifactorial adaptative platform (REMAP) clinical trial protocol to study interventions to improve recovery after surgery in high-risk patients. *BMJ Open*, 10(9): e037690.

62. Howard DR, Brown JM, Todd S, *et al*., 2018, Recommendations on multiple testing adjustment in multi-arm trials with a shared control group. *Stat Methods Med*

Res, 27(5): 1513–1530.

63. Dunnett CW, 1955, A multiple comparison procedure for comparing several treatments with a control. *J Am Stat Assoc*, 50(272): 1096–1121.

64. Kesselmeier M, Benda N, Scherag A, 2020, Effect size estimates from umbrella designs: Handling patients with a positive test result for multiple biomarkers using random or pragmatic subtrial allocation. *PLoS One*, 15(8): e0237441.

65. Sudhop T, Brun NC, Riedel C, *et al*., 2019, Master protocols in clinical trials: A universal Swiss Army knife? *Lancet Oncol*, 20(6): e336–e342.

66. World Medical Association, 2013, World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*, 310(20): 2191–2194.

67. Park JJH, Ford N, Xavier D, *et al*., 2021, Randomised trials at the level of the individual. *Lancet Glob Health*, 9(5): e691–e700.

68. Redman MW, Allegra CJ, 2015, The master protocol concept. *Semin Oncol*, 42(5): 724–730.