



The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review

Elias Laurin Meyer, MSc¹; Peter Mesenbrink, PhD²;
Cornelia Dunger-Baldauf, PhD³; Hans-Jürgen Fülle, MD PhD³;
Ekkehard Glimm, PhD³; Yuhua Li, M.S.²; Martin Posch, PhD¹; and
Franz König, PhD¹

¹Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria; ²Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; and ³Novartis Pharma AG, Basel, Switzerland

ABSTRACT

Purpose: Recent years have seen a change in the way that clinical trials are being conducted. There has been a rise of designs more flexible than traditional adaptive and group sequential trials which allow the investigation of multiple substudies with possibly different objectives, interventions, and subgroups conducted within an overall trial structure, summarized by the term *master protocol*. This review aims to identify existing master protocol studies and summarize their characteristics. The review also identifies articles relevant to the design of master protocol trials, such as proposed trial designs and related methods.

Methods: We conducted a comprehensive systematic search to review current literature on master protocol trials from a design and analysis perspective, focusing on platform trials and considering basket and umbrella trials. Articles were included regardless of statistical complexity and classified as reviews related to planned or conducted trials, trial designs, or statistical methods. The results of the literature search are reported, and some features of the identified articles are summarized.

Findings: Most of the trials using master protocols were designed as single-arm ($n = 29/50$), Phase II trials ($n = 32/50$) in oncology ($n = 42/50$) using a binary endpoint ($n = 26/50$) and frequentist decision rules ($n = 37/50$). We observed an exponential increase in publications in this domain during the last few years in both planned and conducted trials, as well as relevant methods, which we assume has not yet reached its peak. Although many operational and statistical challenges associated with such trials

remain, the general consensus seems to be that master protocols provide potentially enormous advantages in efficiency and flexibility of clinical drug development.

Implications: Master protocol trials and especially platform trials have the potential to revolutionize clinical drug development if the methodologic and operational challenges can be overcome. (*Clin Ther.* 2020;42:1330–1360) © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Key words: adaptive design basket trial, master protocol, multi-arm multi-stage design, platform trial.

INTRODUCTION

Since the late 1940s, randomized controlled trials (RCTs) have served as the gold standard for establishing therapeutic efficacy.¹ However, recent advances in drug discovery and biotechnology have accelerated tremendously the detection of treatment candidates. In addition, diagnostics have become more refined, leading to more precisely defined disease descriptions and hence smaller patient populations for targeted therapies. The classic 2-arm parallel-group RCTs have thus become one of the rate-limiting factors in drug development, and more

Accepted for publication May 11, 2020

<https://doi.org/10.1016/j.clinthera.2020.05.010>

0149-2918/\$ - see front matter

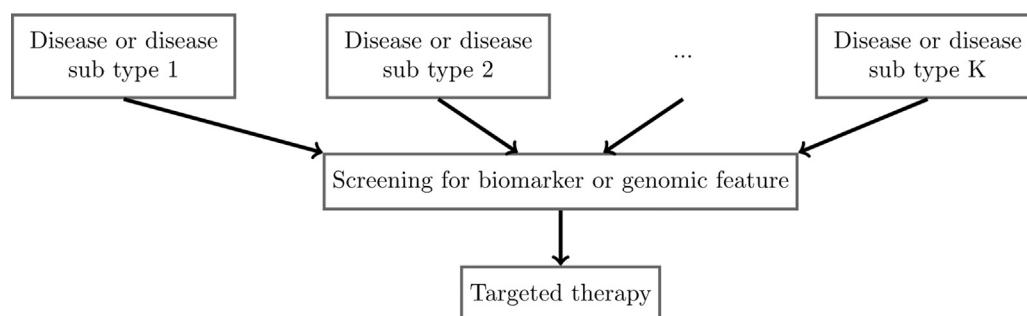
© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

flexible trial designs have been called for.^{2,3} Clinical trials conducted within the master protocol framework could remedy the problem because such trial designs allow for the evaluation of ≥ 1 investigational treatments in multiple subgroups of a study population within the same overall clinical trial structure compared with traditional randomized controlled trials, which mostly evaluate only one investigational drug in one study population. Furthermore, because of several subgroups running in parallel, the chance of patients meeting the inclusion criteria of at least one of the subgroups is increased. If inclusion and exclusion criteria are similar, sharing of patients across the whole study might be feasible (eg, by dynamic control arms). Although in practice planning and implementing a trial with a master protocol require more time to properly deal with operational and data-analytical complexities, Saville and Berry⁴ found, using simulation studies, that under certain assumptions such trials can greatly reduce the time and number of patients needed to successfully identify effective treatments. In many disease areas, such as remote damage control resuscitation,⁵ heart failure with preserved ejection fraction,⁶ pulmonary exacerbations of cystic fibrosis,⁷ colorectal cancer,⁸ squamous cell carcinoma of the head and neck,⁹ bladder cancer,¹⁰ nephrology,^{11–13} neonatal seizures,¹⁴ pediatric cancer,¹⁵ radiation oncology devices,¹⁶ schizophrenia,¹⁷ sepsis,¹⁸ tuberculosis,¹⁹ transplantation,²⁰ and multidrug-resistant organisms,²¹ master protocol trials are being considered to satisfy needs for the evaluation of new or targeted therapies, clinically validated targets, and predictive biomarkers, as well as facilitating faster clinical testing of available compounds. Although master protocol trials can also be designed using traditional design features, such as frequentist decision rules, fixed sample size, and allocation ratios, often innovative statistical methods, such as response-adaptive randomization, adaptive and seamless adaptive designs, sharing of common control arms, and/or Bayesian decision frameworks,^{22–36} are used in the design of master protocols. The debate concerning the actual benefits of some of these methods is still ongoing.^{37–45} The importance of adaptive trial designs and master protocols in the context of innovative trials and precision medicine has been highlighted by many authors.^{46–72} The Adaptive Platform Trials

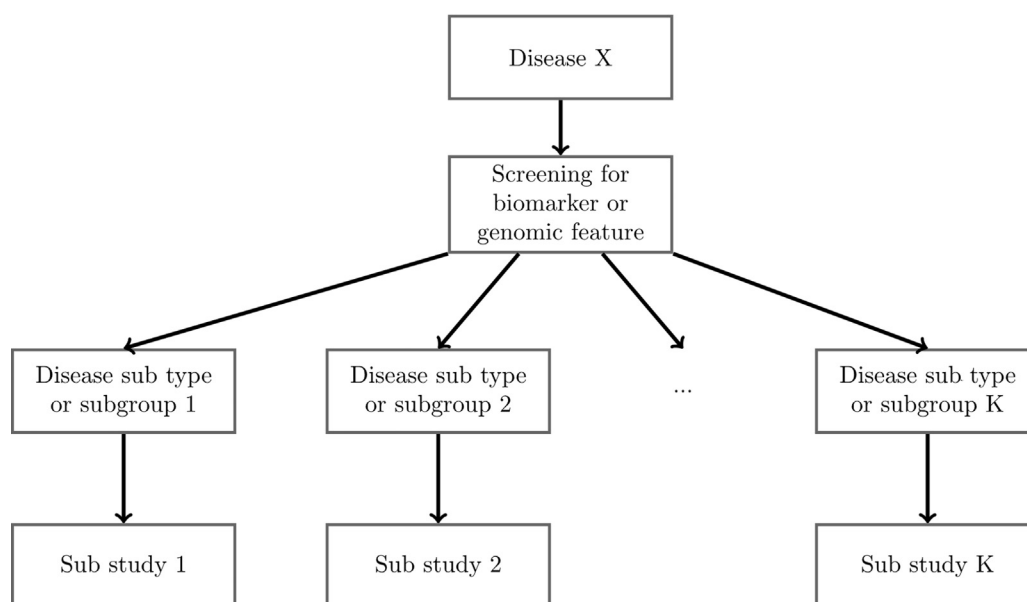
Coalition's opinion on design, conduct, oversight, and reporting of adaptive platform trials has recently been published.⁷³ For an overview of logistical and biostatistical considerations in the development of master protocol trials, see Yee et al.⁷⁴ For a comprehensive review of confirmatory adaptive clinical trials, see Bauer et al,⁷⁵ and Bothwell et al.⁷⁶ For a review of trial designs used in biomarker-guided adaptive trials, see Antoniou et al.⁷⁷

Within the group of master protocol clinical trials, 3 types of clinical trial designs can be differentiated: basket trials, umbrella trials, and platform trials. We call a master protocol trial a *basket trial* if one investigational treatment or treatment combination is evaluated in the context of multiple diseases or disease subtypes with a common biomarker or genetic feature linked to the therapeutic target of the treatment (Fig. 1A). If multiple investigational treatments or treatment combinations are evaluated in the context of a single disease, possibly within several substudies for different disease subtypes or patient subgroups, we call it an *umbrella trial* (Fig. 1B). A *platform trial* is a trial in which multiple investigational treatments or treatment combinations are evaluated in the context of a single disease, possibly within several substudies for different disease subtypes; furthermore, drugs or drug combinations within existing and new substudies may enter or leave the trial (e.g., if a new biomarker to identify disease subtypes becomes available), allowing the trial to run perpetually, in principle. In case a treatment is found to significantly outperform the existing control treatment, this treatment could become the new control treatment and serve as the new reference within the same trial structure (Fig. 2). Instead of considering a platform trial a distinct type of master protocol trial, it could also be seen as an adaptive form of an umbrella trial in which treatment arms and/or study populations may be added or dropped during the trial or as an overarching framework for substudies that can enter or leave the platform over time. However, for the remainder of this article, we use the above stated definitions.

Although several authors have observed that the definitions of basket, umbrella, and platform trials have been overlapping and inconsistent in the past,^{78–81} we used the definitions provided by Woodcock and LaVange,⁸² which are consistent with



(A) Schematic overview of a basket trial including K different diseases or disease sub types.

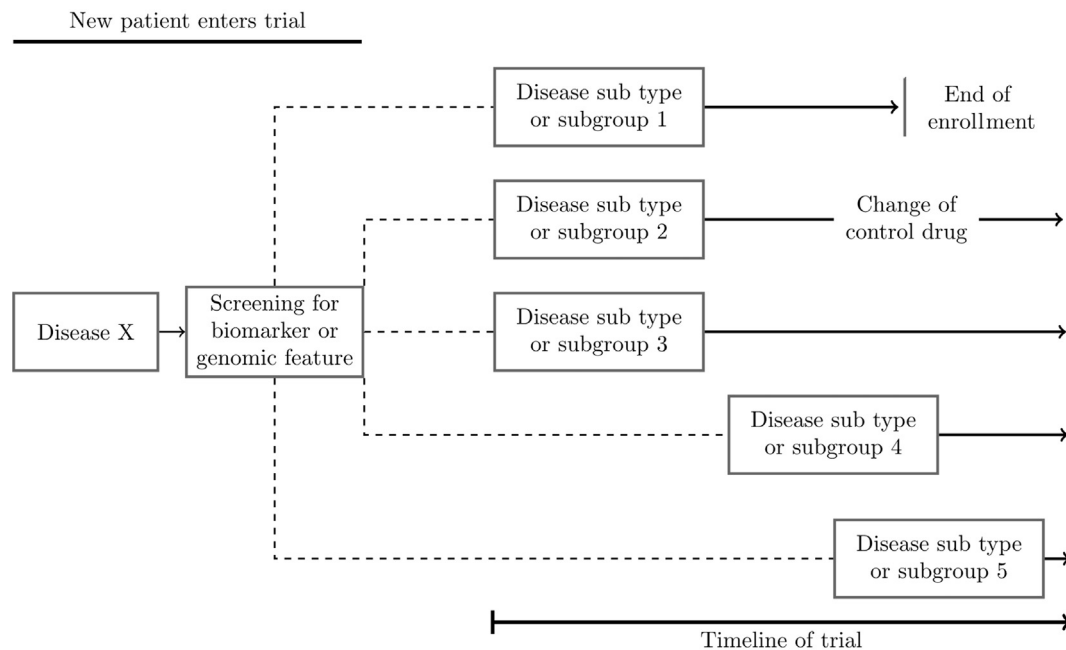


(B) Schematic overview of an umbrella trial including K different sub studies.

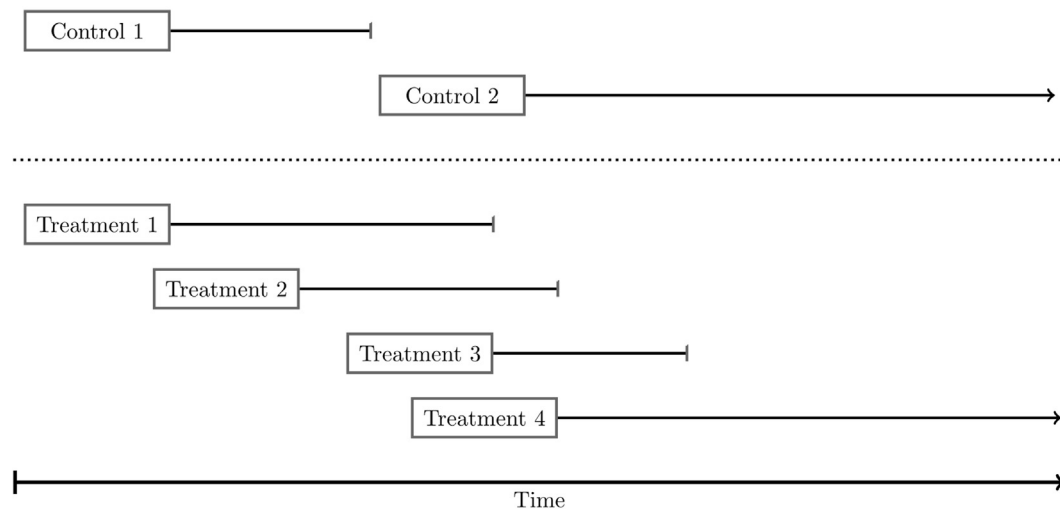
Figure 1. (A) Schematic overview of a basket trial, including K different diseases or disease subtypes.: Patients from K different diseases or disease subtypes are screened for the presence of a particular biomarker or genomic feature. After positive screening results, all patients, regardless of their disease or disease subtype, are treated with the same targeted therapy. An additional placebo arm could be included; however, single-arm basket trials tend to be more common. (B) Schematic overview of an umbrella trial, including K different substudies. Within the context of a single disease, patients are screened for the presence of a biomarker or genomic feature and accordingly enrolled or randomized to any of the K existing substudies, which can be independent and differ with respect to treatment, trial duration, and so on.

the definitions found in the recently released US Food and Drug Administration (FDA) draft guidance on master protocols⁸³ (October 2018), which is currently the only draft guidance available from a regulatory authority. A recommendation report on

the initiation and conduct of complex clinical trials by the Clinical Trials Facilitation and Coordination Group was released in 2019.⁸⁴ Siden et al,⁸⁵ who conducted a literature search similar to ours in terms of search strategy but with a different scope, found



(A) Schematic overview of a platform trial.



(B) Schematic overview of a single disease sub type or subgroup sub study of a platform trial.

Figure 2. (A) Schematic overview of a platform trial. Whenever new patients enter the trial, they are screened for the presence of a biomarker or genomic feature and enrolled in one of the existing substudies at that time. Substudies can enter and leave the trial at any time (e.g., when new biomarkers become available or futility criteria are met and no other candidate experimental drugs are available), the control arm within one substudy can change over time, and patient enrollment can continue perpetually. (B) Schematic overview of a single disease subtype or subgroup sub study of a platform trial. The control arm within one substudy can change over time, and patient enrollment can continue perpetually. Treatment arms can be dropped for futility or efficacy and be replaced by new treatment arms.

that only 57% of the self-reported master protocol trials they identified were consistent with the FDA's definitions. Janiaud et al⁶⁷ and Hirakawa et al⁸⁰ also give a comprehensive overview of conducted or currently ongoing trials with master protocols focusing on oncology only. The authors try to raise awareness that, although carrying tremendous hope, master protocol trials “should not be seen as a way to bypass rigorous clinical testing for expedited access to unproven treatment options.”⁶⁷ Another recent systematic review of master protocol trials by Park et al⁸⁶ found a similar exponential increase in master protocols over time. They also reported that most master protocols investigated experimental drugs in oncology in adult populations. A pooled analysis of published basket trials in cancer following a systematic review was recently published by Hazim and Prasad.⁸⁷ The authors found that at the time of article submission >1100 patients with >33 different tumor types had been enrolled in published basket trials, with 25% of patients having had partial or complete response to therapy.

In this systematic review, we aim to provide a comprehensive overview of the current literature on master protocols in terms of planned and conducted trials and trial design related methods, with a special focus on platform trials.

METHODS

We conducted a systematic literature search on PubMed using a prespecified set of keywords and further included suitable publications from the list of references in the identified articles and articles discovered via manual searches (Supplemental Appendix). This study was conducted in accordance with the PRISMA reporting guidelines for systematic literature reviews.⁸⁸

The key features of the identified planned and conducted trials were extracted and classified as basket, umbrella, or platform by the definitions provided above, which can differ from the reported self-classification. Some master protocol trials that we identified in our literature search do not exactly fit any of the previously mentioned definitions of basket, umbrella, and platform trials. Trials that included several indications (therefore by our definitions no umbrella or platform trials) and evaluated several treatments (therefore by our definitions no basket trials) were classified as other.

Identified trial design and methodologic articles were classified as follows: (1) articles that proposed new designs or methods relevant for basket trials, (2) articles that proposed new designs or methods relevant for umbrella and platform trial, (3) articles that discussed the issue of multiplicity in trial designs with master protocols, and (4) articles that investigate MAMS designs and related methods (Multi-arm, multi-stage [MAMS] designs have been suggested in the literature to compare several treatments while allowing for interim analyses; therefore, the statistical methods can be directly applied to umbrella and platform trials).

RESULTS

A word cloud based on the titles of the 286 identified articles (Fig. 3) reveals that many are in the fields of oncology and focus on adaptive elements of the designs concerned. On the basis of the titles, basket trials seem more popular than platform and umbrella trials. Fig. 4A shows the distribution of identified articles with respect to year of publication. Apart from an exceptional year 2018, we suspect that the exponential increase in publications because of increasing interest in this domain will still continue. Fig. 4B shows the number of identified articles with respect to publishing journal. Approximately 20% of all articles were published in *Journal of Clinical Oncology*, *Statistics in Medicine*, or *Clinical Trials*.

Planned and Conducted Trials

In Table I, the key features of the identified planned and conducted trials are summarized. In Fig. 4C and D, the originally planned sample size and the planned or actual number of study arms of the identified planned and conducted trials (in each figure we excluded one trial with a missing value) are summarized. Both the originally planned sample size and the planned or actual number of study arms have fairly skewed distributions. Table II lists the general features of the identified conducted or planned master protocol trials, indicating that most of the trials were designed as Phase II trials (n = 32/50) in oncology (n = 42/50). Table III lists some statistical features, indicating that most of the trials were single-arm (i.e., no control group but possibly many experimental arms; n = 29/50), using a binary endpoint (n = 26/50), no

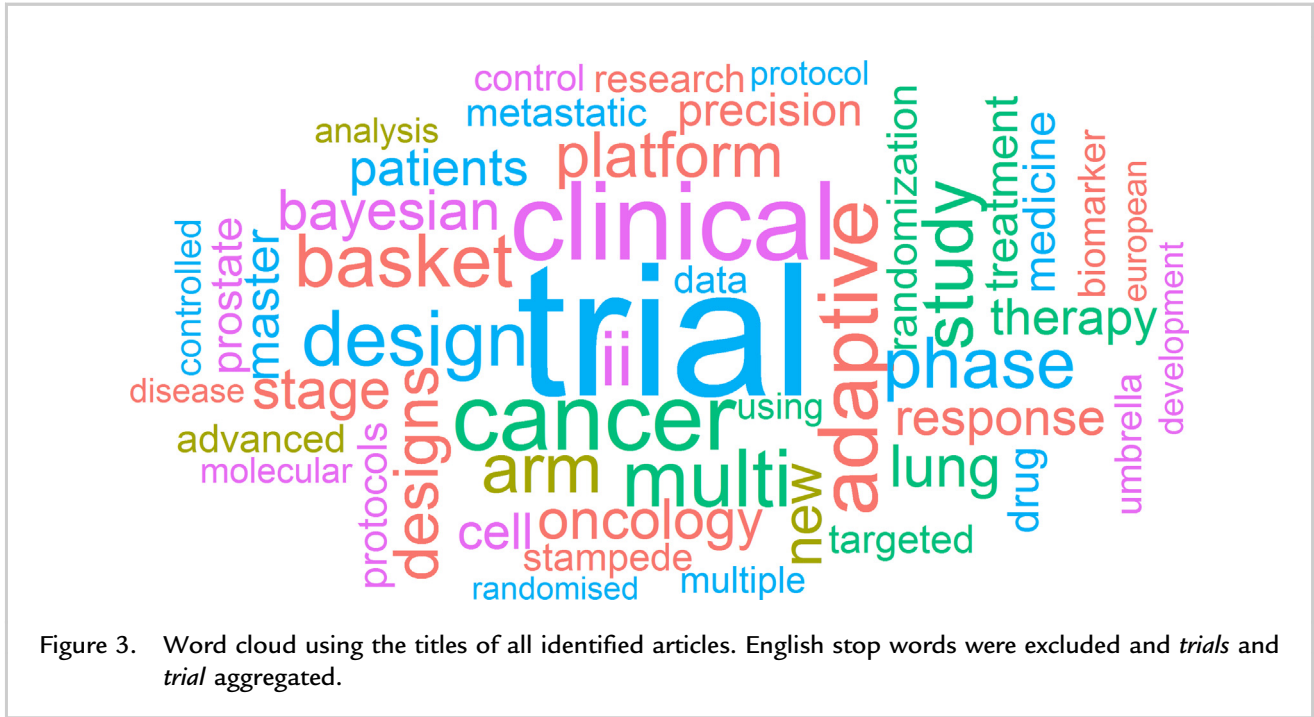


Figure 3. Word cloud using the titles of all identified articles. English stop words were excluded and *trials* and *trial* aggregated.

response-adaptive randomization ($n = 41/50$), and frequentist decision rules ($n = 37/50$).

In the following, we present the identified planned and conducted platform trials. Trials are ordered by year of first identified publication associated with it and within each year alphabetically by first author's last name. A verbal description highlighting the features of basket, umbrella, and other trials can be found in the Supplemental Appendix. The platform trials we identified in our literature search are as follows.

The **STAMPEDE** (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial^{107,148–152} is a multicenter, multi-arm, multi-stage, randomized, open-entry clinical trial assessing novel therapies in men with hormone-naïve prostate cancer. The primary endpoint is overall survival. Even though the trial has been running for nearly 15 years, it is still ongoing, and a multitude of results have already been published.^{153–161} Over time, some experimental arms have finished accrual, and new experimental arms have entered the trial.^{162–165} The investigators planned to include biomarker-stratified randomization in the future.¹⁵²

The **I-SPY2** (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And

moLecular Analysis 2) trial^{166–168} is an ongoing, Phase II, response-adaptive, randomized, multicenter trial evaluating new drugs or drug combinations in the context of neoadjuvant treatment for women with locally advanced breast cancer. The primary endpoint is pathologic complete response. Response-adaptive randomization of patients is used in 8 prospectively defined biomarker-based disease groups; however, efficacy is evaluated within 10 predefined clinically relevant biomarker signatures (that can be overlapping). If highly promising treatments are identified in the signatures, they will be graduated for further Phase III testing. Das and Lo¹⁶⁹ report that 6 drugs have already graduated^{170,171} and one study drug received accelerated FDA approval in one signature, seamlessly replacing the respective control drug.

The **FOCUS4** (Inhibition of EGFR, HER2, and HER3 Signalling in Patients With Colorectal Cancer Wild-Type for BRAF, PIK3CA, KRAS, and NRAS) trial^{107,172–174} was a randomized, multi-arm, multi-stage, seamless Phase II/III trial testing novel agents against placebo in several biomarker-defined subgroups of patients with colorectal cancer. The primary endpoints were progression-free survival and

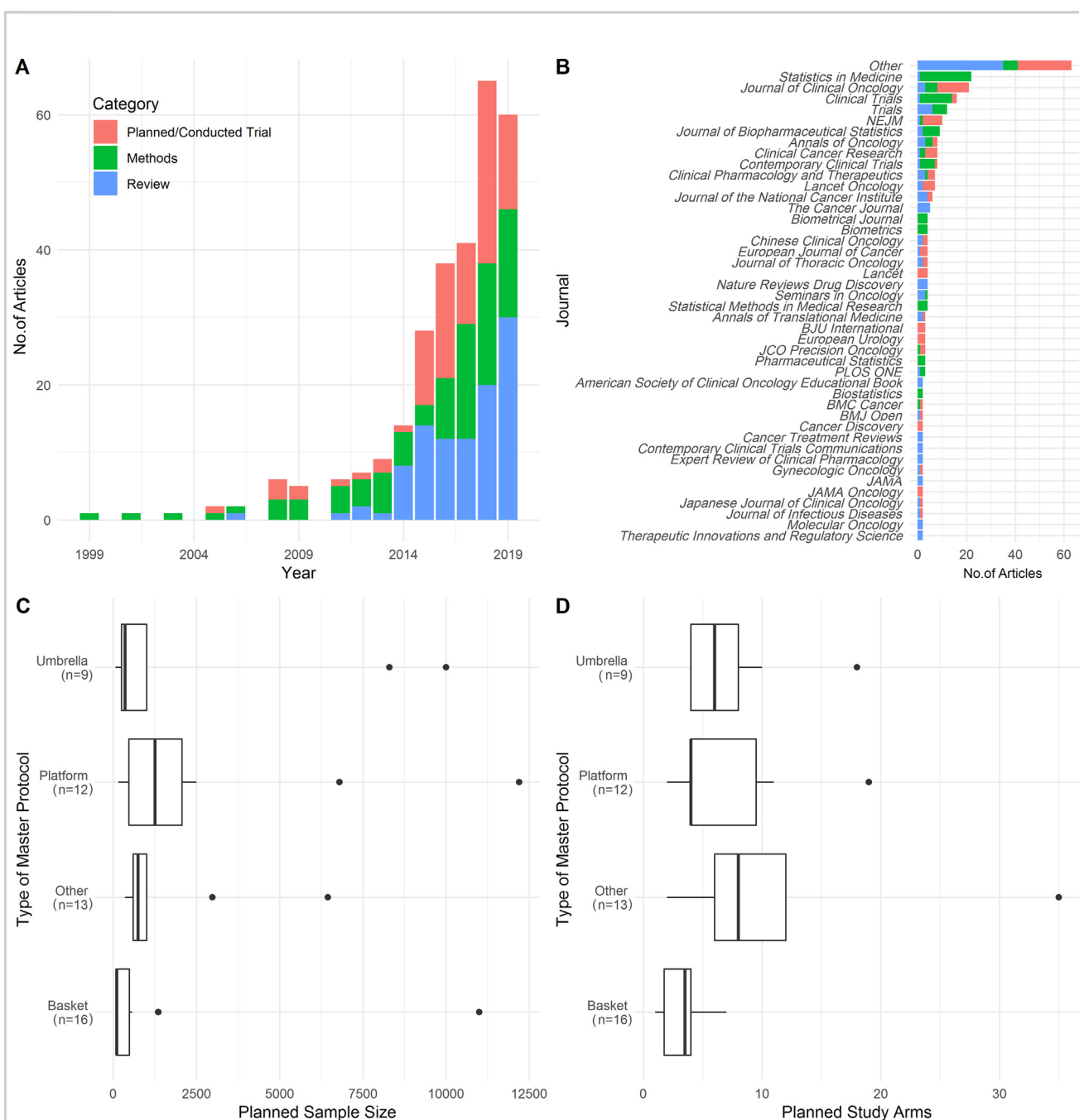


Figure 4. (A) Year of publication of identified articles. (B) Journal of publication of identified articles. Journals having published only one article were summarized as other. Journals are sorted firstly from highest to lowest number of publications and later alphabetically. (C) Originally planned sample size of included planned and conducted trials with respect to master protocol type. Master protocol types are sorted from lowest to highest number of associated trials. (D) Planned or actual number of study arms of included planned and conducted trials with respect to master protocol type. Master protocol types are sorted from lowest to highest number of associated trials.

Table I. Planned or conducted master protocol trials identified in the literature search.

Trial Name	Phase	Primary Endpoint	Type	Indication	Planned Sample Size	Planned Study Arms	Status as of January 2020	References	Registration Numbers
ADD-ASPIRIN	III	Time to event	Basket	Oncology	11,000	4	Recruiting	106,107	NCT02804815
Ado-Trastuzumab	II	Binary	Basket	Oncology	100	4	Active, not recruiting	117	NCT02675829
AZD5363	II	Safety/binary	Basket	Oncology	84	4	Active, not recruiting	109	NCT01226316
B2225	II	Binary	Basket	Oncology	NA	1	Completed	89–91	NCT00154388
IMPACT-2	I/II	Time to event	Basket	Oncology	1362	2	Recruiting	122	NCT02152254
INSPIRE	II	Metric	Basket	Oncology	100	1	Active, not recruiting	119	NCT02644369
KEYNOTE-012	I	Safety/binary	Basket	Oncology	90	5	Active, not recruiting	99–105	NCT01848834
KEYNOTE-016	II	Binary	Basket	Oncology	71	4	Recruiting	97–99	NCT01876511
KEYNOTE-158	II	Binary	Basket	Oncology	1350	1	Recruiting	99,118	NCT02628067
Larotrectinib	II	Binary	Basket	Oncology	570	3	Recruiting/active, not recruiting	110–112	NCT02576431, NCT02637687, NCT02122913
MINERVA	III	Metric	Basket	Ophthalmology	187	2	Completed	113,114	EudraCT2012-005417-38
Perifosine monotherapy	II	Binary	Basket	Oncology	96	3	Completed	108	Japic CTI-132287
SUMMIT	II	Binary	Basket	Oncology	392	4	Recruiting	115,116	NCT01953926
TOTEM2	II	Binary	Basket	Oncology	93	1	Completed	120	NCT00918320
TRAM-01	II	Binary	Basket	Oncology	150	4	Recruiting	121	NCT03363217
VE-BASKET	II	Binary	Basket	Oncology	101	7	Completed	92–96	NCT01524978
ALCHEMIST	III	Time to event	Umbrella	Oncology	8300	5	Recruiting/active, not recruiting	126,127,132,134,137,138	NCT02194738, NCT02595944, NCT02193282, NCT02201992
AMBITION	II	Binary	Umbrella	Oncology	68	4	Recruiting	146	NCT03699449
BATTLE	II	Binary	Umbrella	Oncology	250	4	Completed	123–125	NCT00409968, NCT00411671, NCT00411632, NCT00410059, NCT00410189
BATTLE-2	II	Binary	Umbrella	Oncology	450	4	Active, not recruiting	139–141	NCT01248247
CLUSTER	III	Binary	Umbrella	Autoinflammatory disease	180	6	Completed	144	NCT02059291
LUNG-MAP	II/III	Time to event	Umbrella	Oncology	10,000	18	Active, not recruiting	126–136	NCT02154490
N2M2	I/II	Safety/time to event	Umbrella	Oncology	350	8	Recruiting	142,143	NCT03158389

(continued on next page)

Table I. (Continued)

Trial Name	Phase	Primary Endpoint	Type	Indication	Planned Sample Size	Planned Study Arms	Status as of January 2020	References	Registration Numbers
UPSTREAM	II	Binary	Umbrella	Oncology	340	8	Recruiting	145	NCT03088059
VIKTORY	I/II	Binary/time to event	Umbrella	Oncology	1000	10	Completed/ recruiting/ unknown/ terminated	147	NCT02299648, NCT02448290, NCT02448329, NCT02451956, NCT02449551, NCT02447406, NCT02447380, NCT02449655, NCT02630199, NCT03082833, NCT02449655, NCT03061708
ALIC4E	IV	Time to event	Platform	Influenza	2500	2	completed	187,188	ISRCTN27908921
DIAN-TU	II/III	Metric	Platform	Alzheimer	490	5	recruiting	184	NCT01760005
EBOLA	II	Binary	Platform	Ebola	150	4	unknown	176	NCT02380625
EPAD-PoC	II	Binary	Platform	Alzheimer	1500	NA	NA	181–183	NCT02804789
FOCUS4	II/III	Time to event	Platform	Oncology	384	10	Completed	107,172–175	ISRCTN 90061546
GBM AGILE	II/III	Time to event	Platform	Oncology	550	4	Recruiting	185	NCT03970447
I-SPY2	II	Binary	Platform	Oncology	1920	19	Recruiting	166–171	NCT01042379
INSIGHt	II	Time to event	Platform	Oncology	280	4	Recruiting	142,186	NCT02977780
LEAP	II/III	Time to event	Platform	Oncology	1670	4	Suspended	189,190	NCT03092674
PREVAIL II	II	Binary	Platform	Ebola	1000	2	Completed	177–179	NCT02363322
REMAP-CAP	IV	Binary	Platform	Pneumonia	6800	9	Recruiting	18,180	NCT02735707
STAMPEDE	III	Time to event	Platform	Oncology	12,200	11	Recruiting	107,148–165	NCT00268476
CREATE	II	Binary	Other	Oncology	582	6	Active, not recruiting	200–203	NCT01524926
CUSTOM	II	Binary	Other	Oncology	600	6	Active, not recruiting	197	NCT01306045
ESMART	I/II	Binary/time to event	Other	Oncology	397	6	Recruiting	211	NCT02813135
FRACTION	II	Binary/time to event	Other	Oncology	1004	12	Recruiting/active, not recruiting	207	NCT02750514, NCT02996110, NCT02935634
MoST	I/II	Binary/time to event	Other	Oncology	1000	12	Recruiting	209	ACTRN12616000908437
MyPathway	II	Binary	Other	Oncology	765	6	Recruiting	204,205	NCT02091141

Table I. (Continued)

Trial Name	Phase	Primary Endpoint	Type	Indication	Planned Sample Size	Planned Study Arms	Status as of January 2020	References	Registration Numbers
National Lung Matrix Trial	II	Binary/time to event	Other	Oncology	620	9	Recruiting	198	NCT02664935, ISRCTN38344105
NCI-MATCH	II	Binary/time to event	Other	Oncology	6452	35	Recruiting	126,134,191–195	NCT02465060
PARAGON	II	Binary	Other	Oncology	350	7	Active, not recruiting	210	ACTRN12610000796088
Pediatric-MATCH	II	Binary	Other	Oncology	1000	10	Recruiting	134,199	NCT03155620
SHIVA	II	Time to event	Other	Oncology	742	2	Unknown	196	NCT01771458
SIGNATURE	II	Binary	Other	Oncology	620	8	Completed/terminated	208	NCT01885195, NCT01981187, NCT02002689, NCT02160041, NCT02186821, NCT02187783, NCT01833169, NCT01831726
TAPUR	II	Binary	Other	Oncology	2980	12	Recruiting	206	NCT02693535

NA = not applicable. Official expansion of trial titles can be found via clinicaltrials.gov or other registries.

Table II. Overview of the phases of drug development and indications for the included master protocol trials.

Category	Basket	Other	Platform	Umbrella	Total
Phase					
I	1	0	0	0	1
I/II	1	2	0	2	5
II	12	11	5	4	32
II/III	0	0	4	1	5
III	2	0	1	2	5
IV	0	0	2	0	2
Indication					
Alzheimer disease	0	0	2	0	2
Autoinflammatory disease	0	0	0	1	1
Ebola	0	0	2	0	2
Influenza	0	0	1	0	1
Oncology	15	13	6	8	42
Ophthalmology	1	0	0	0	1
Pneumonia	0	0	1	0	1
Total	16	13	12	9	50

overall survival. The results of one of the subgroup analyses have recently been published.¹⁷⁵

Berry et al¹⁷⁶ proposed an adaptive trial ready to be activated in the event of a new Ebola pandemic that uses response-adaptive randomization and combinations of primary and secondary compounds.

Secondary compounds may be administered only in combination with a primary compound, but primary compounds may be administered as a single-agent regimen. The trial is intended to run perpetually, and new compounds may enter the trial throughout. A standard-of-care arm is to be included in the trial;

Table III. Overview of statistical features of the included master protocol trials.

Category	Basket	Other	Platform	Umbrella	Total
Primary endpoint					
Binary	10	6	5	5	26
Binary/TTE	0	5	0	1	6
Binary	0	1	0	0	1
Metric	2	0	1	0	3
Safety/binary	2	0	0	0	2
Safety/TTE	0	0	0	1	1
TTE	2	1	6	2	11
Type of control					
Concurrent	3	1	5	4	13
Includes nonconcurrent	0	1	6	1	8
No control	13	11	1	4	29
Primary analysis					
Frequentist	16	11	3	7	37
Bayesian	0	2	9	2	13
Response-adaptive randomization					
No	16	12	6	7	41
Yes	0	1	6	2	9

TTE = time to event.

however, it can be dropped or replaced. The primary endpoint is mortality after 14 days.

The **PREVAIL II** (Partnership for Research on Ebola Vaccines in Liberia II) trial^{177–179} was a Phase II trial evaluating the efficacy of ZMapp in the treatment of patients with known Ebola infection. The trial was originally planned as a randomized controlled trial with 2 study arms: standard of care and standard of care plus ZMapp. If throughout the trial a compound was found to be superior to the standard of care, this new standard of care could have been incorporated into the standard of care, thereby effectively changing the control in the middle of the trial. However, enrollment stopped after 72 patients because the Ebola outbreak ended. Results up to that point were very promising. The primary endpoint was mortality after 28 days.

The **REMAP-CAP** (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial^{18,180} is an ongoing, randomized, multifactorial trial embedded in clinical practice studying treatment of severe community-acquired pneumonia requiring admittance to an intensive care unit. Response-adaptive randomization is used; the primary endpoint is the 90-day all-cause mortality rate.

The **EPAD-PoC** (European Prevention of Alzheimer's Dementia—Proof of Concept) trial is part of the European Prevention of Alzheimer's Dementia project.^{181–183} Aims are first to find experimental drug candidates that can achieve clear, demonstrable clinical benefits and second to identify the (sub) population with maximal benefit from the intervention. Clinical status, biomarkers, and genetics are used to define patient subpopulations.

The **DIAN-TU** (Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia) trial¹⁸⁴ is a randomized, multicenter Phase II/III trial of potential disease-modifying therapies in individuals with Alzheimer disease. A longitudinal disease progression model is used, but the primary endpoint is change in the DIAN-TU cognitive composite score during 12 months.

The **GBM AGILE** (Glioblastoma Adaptive, Global, Innovative Learning Environment) trial¹⁸⁵ is a currently ongoing, multi-arm, response-adaptive, randomized, seamless Phase II/III trial in patients with newly diagnosed or recurrent glioblastoma. The primary endpoint is overall survival. In the first stage,

experimental arms are dropped or graduated using response-adaptive randomization and a maximum sample size per treatment of 150. Therapies graduating to the second stage will be tested in a 50 patient per arm, fixed randomization expansion cohort. For the primary analysis, data from both stages will be used.

The **INSIGHt** (Individualized Screening Trial of Innovative Glioblastoma Therapy) trial^{142,186} is an ongoing, randomized, adaptive Phase II trial in a subpopulation of patients with newly diagnosed glioblastoma. The primary endpoint is overall survival. Different experimental therapies, which may be added or dropped throughout the trial, are compared against a common control arms. Randomization ratios are updated throughout the trial based on progression-free survival.

The **ALIC⁴E** (Antivirals for influenza-Like Illness? An rCt of Clinical and Cost effectiveness in Primary Care) trial^{187,188} is a multinational, multicenter, response-adaptive randomized, open-label, perpetual trial. The goal is to determine whether antivirals should be routinely prescribed for influenza-like illness in primary care. New treatment arms may be added or dropped. A common control arm composed of the standard of care is added and might be replaced throughout the trial.

The Intergroup **LEAP** (Less Intense AML Therapy Platform) trial¹⁸⁹ is a randomized phase II/III trial in patients with acute myeloid leukemia using a rolling-arm trial designs similar to the one proposed by Ventz et al.¹⁹⁰ Throughout the trial, new *cassettes*, which describe a bundle of study arms, including a control, can be added. For the first *cassette* added to the trial, the Phase II objective was to determine the most promising experimental arm (with respect to overall survival), which should be further tested against control in the Phase III part. As of November 2019, the trial is suspended for an unscheduled safety data review.

Basket Designs and Methods

There exists a wide range of literature on basket trial designs. Beckman et al.²¹² proposed a general design concept for a confirmatory basket trial that uses short-term outcomes at early stages that inform adaptive decisions to continue or discontinue the trial. Li et al.²¹³ focused on the treatment effect estimation bias in a 2-stage oncology basket trial

setting where after the first stage a subset of cancer histologic types or a biomarker cutoff is chosen. Cunanan et al²¹⁴ developed an adaptive basket trial design that consists of 2 stages. After the first stage, the heterogeneity of treatment effects across patient subpopulations is evaluated. If the heterogeneity is too large (based on an exact test of a $K \times 2$ contingency table, with the critical value being a tuning parameter to tweak design operating characteristics), all subsequent analyses will be conducted independently for all subpopulations. If the heterogeneity is small, all subsequent analyses will be conducted with the pooled data. A simple, straightforward Bayesian basket design in which for every subpopulation the treatment effect space contains only 2 elements (corresponding to a null and an alternative hypothesis) was proposed in 2016 by Simon et al.²¹⁵ Xu et al²¹⁶ proposed a Bayesian basket trial design based on nonparametric Bayesian survival regression, which includes subpopulation identification and adaptive patient allocation based on model-based posterior predictive probabilities. A basket trial design using Bayesian hierarchical modeling to borrow information on the treatment effect across different patient subpopulations was proposed by Liu et al.²¹⁷ In a simulation study, Cunanan et al²¹⁸ found that the Bayesian hierarchical model as proposed by Berry et al²¹⁹ can have heavily inflated error rates. Cunanan et al²²⁰ further investigated the effect of different priors for the variance parameter in Bayesian hierarchical models, which is directly linked to how much information is shared across subpopulations, on the type 1 error rate. To better control the type 1 error in Bayesian hierarchical models attributable to inappropriately determining the degree of information borrowing, Chu and Yuan²²¹ proposed a calibrated Bayesian hierarchical model for basket trials in which the shrinkage parameter is defined as a (through simulation calibrated) function of a treatment effect similarity measure. Neuenschwander et al²²² proposed a robust approach for Bayesian hierarchical models in which the exchangeability assumption does not need to hold for every subpopulation, thus allowing some subpopulations to have similar treatment effects and some to have unique treatment effects. Hobbs and Landin²²³ also propose a Bayesian hierarchical model basket trial design that evaluates

the exchangeability for every pairwise combination of subpopulations. Another Bayesian trial design that aims to control for potential differences of treatment effects in subgroups is the Bayesian latent subgroup design by Chu and Yuan,²²⁴ which models the treatment response conditional on the latent variable of the subgroup being a treatment-sensitive or treatment-insensitive subgroup. Trippa and Alexander²²⁵ propose a Bayesian basket design that efficiently generates information on both the experimental agents under consideration and the predictive capabilities of putative biomarkers. Furthermore, Simon²²⁶ gives an overview of several basket trial designs in active use and generalizes the Bayesian basket design. Ventz et al²²⁷ proposed a general class of Bayesian basket trial designs using Bayesian hierarchical models and response-adaptive randomization, which facilitate both identification of a biomarker subpopulation, and identification of a subset of, for example, cancers within a biomarker-defined subpopulation that benefits from a treatment. The most recent design was proposed by Psioda et al,²²⁸ who proposed an adaptive Bayesian basket trial design using Bayesian model averaging, which allows for some baskets to share a similar efficacy and for some to have a unique efficacy. Using simulation studies and different scenarios, the authors found that compared with basket trial designs proposed earlier, their framework achieves steady performances with respect to certain operating characteristics, such as expected sample size and different error rates. Zhou et al²²⁹ proposed optimal and minimax 2-stage basket trial designs as a multi-arm basket extension of Simon's 2-stage design, which can, under a noninformative prior assumption on drug activity, control the global type 1 error and the expected power. Fujikawa et al²³⁰ proposed a Bayesian basket trial design for binary endpoints that incorporates predictive sample size determination, interim looks for efficacy and futility, and sharing of subpopulation data based on the similarity of the response rate posterior distributions. Li et al²³¹ discuss multi-stage enrichment and basket designs, whereby after the first stage only a subset of the subpopulations is continued and then pooled for further efficacy monitoring interim analyses before the final analysis. Ondra et al²³² conducted a systematic review on clinical trial designs for the

identification and confirmation of targeted subgroups. Ramsey et al.²³³ give an overview of limitations associated with basket trials. Freidlin et al.²³⁴ presented reasons why obtaining reliable evidence on clinical benefit of molecular profiling in multi-basket trials is challenging and proposed a 2-step procedure to facilitate more rigorous identification of clinically beneficial mutation and agent pairs.

Umbrella and Platform Designs and Methodology

The Bayesian hierarchical model-based trial design using response-adaptive randomization that was used in the **BATTLE** (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial¹²⁴ was described by Zhou et al.¹²³ alongside results from simulation studies under several different assumptions. The Bayesian 2-stage trial design of the **BATTLE 2** trial using biomarker-based response-adaptive randomization is described by Gu et al.¹⁴¹ alongside simulation studies investigating the operating characteristics. The trial design of the **PREVAIL II** Ebola trial is described by Proschan et al.¹⁷⁹ The authors use a Bayesian analysis strategy with the rationale that because of unpredictable decisions made by the data and safety monitoring board, stringent control of type 1 error is impossible in a frequentist setting. Kaizer et al.²³⁵ built on the PREVAIL II trial design and proposed a platform design using adaptive randomization and information borrowing across trial segments through Bayesian modeling that can greatly increase the power of the trial. A Phase II Bayesian adaptive platform trial that combines primary compounds with backbone regimens to find the best combination therapy has been proposed by Tang et al.²³⁶ The design allows for dropping, graduating, and adding new combinations during the trial, and the authors used simulation studies to indicate that it performs favorably under a set of assumptions on the combination effect compared with a fully Bayesian hierarchical model and other proposed designs. Normington et al.²³⁷ proposed a Bayesian adaptive platform trial design with time-to-event endpoints and a common control arm. Control data borrowing is facilitated using commensurate prior methods, which also adaptively adjust the randomization ratio at the interim analyses. Berry et al.¹⁷⁶ also proposed a platform design to test

combinations of primary and secondary compounds in the Ebola disease. Yuan et al.²³⁸ propose a Bayesian Phase II platform trial design with time-to-event endpoints that facilitates a shared control arm, response-adaptive randomization, interim analyses for futility and efficacy, and replacement of experimental arms throughout the trial. Ventz et al.¹⁹⁰ proposed an adaptive platform trial design with interim analyses and time-to-event endpoints that starts out as a 2-arm or multi-arm trial with a shared control and equal randomization. New experimental arms can be added any time, and all experimental arms have a maximum sample size, after which the final analysis will be conducted for this arm. Ventz et al.²³⁹ also investigated the effect of randomization procedures, both balanced and response-adaptive, on trial operating characteristics in the context of adding new treatment arms throughout an ongoing trial. Viele et al.²⁴⁰ investigated how different schemes for control allocation in multiple arm studies with response-adaptive randomization affect certain trial operating characteristics. Hobbs et al.²⁴¹ propose a Bayesian platform trial design that accepts new arms throughout the trial, facilitates a shared control arm, and allows for frequent interim looks for futility based on Bayesian predictive probabilities.^{242,243} Jiao et al.²⁴⁴ discussed various options of sharing control arms and incorporating historical data and proposed a procedure to incorporate these in a platform trial setting. Gajewski et al.²⁴⁵ investigated Bayesian response-adaptive designs in the context of multi-arm comparative effectiveness trials and found that they perform favorably compared with other Bayesian adaptive and fixed randomization trial designs. An R Shiny software (RStudio, Boston, Massachusetts) application that facilitates simulation of adaptive platform trials with limited complexity has been presented by Thorlund et al.²⁴⁶

Multiplicity

Multiplicity is an issue that arises from testing multiple hypotheses in the context of master protocol clinical trials. **Controlling the overall type 1 error rate becomes a difficult task when the trial is an open entry platform trial that allows for new cohorts to enter the trial over time.** Furthermore, it is not straightforward to determine which type 1 error rate should be controlled (eg, the family-wise

error rate, the per-comparison error rate, and so on) and to decide whether different substudies should be considered independent. Howard et al²⁴⁷ investigate multi-arm designs in which control group data are shared across several treatment arms. They define new type 1 error rates of interest and give recommendations for which type 1 error rates should be controlled with respect to the nature of the hypothesis tested. Stallard et al²⁴⁸ classified trials with multiplicity issues that arise from multiple subgroups and multiple treatments as treatment arms within subgroups, subgroups within treatment arms, or subgroups within treatment arms within subgroups and proposed that multiplicity corrections should be used in the second and third settings. Wason et al²⁴⁹ conducted a literature review of articles published in 2012 and found that there was no consensus on whether multiplicity corrections are needed if in a multi-arm trial the different arms are different treatments and not multiple doses of the same treatment. For multi-arm, response-adaptive, 2-stage designs, methods to control the family-wise type 1 error rate were proposed by Gutjahr et al.²⁵⁰ Robertson and Wason²⁵¹ proposed procedures to control the family-wise type 1 error rate in certain scenarios with response-adaptive randomization for normally distributed endpoints. Simulation studies can be performed to approximate error rates if no closed form is available for the calculation; however, regulatory agencies are reluctant to accept simulation-based justification of error rate control.²⁵² This reluctance might change in the future with the Complex Innovative Design Initiative of the FDA.²⁵³ Hlavin et al²⁵⁴ derive conditions under which the family-wise error rate can be controlled in multi-arm trials when performing many-to-one comparisons after safety selection. Dmitrienko et al²⁵⁵ discuss multiplicity considerations in exploratory and confirmatory subgroup analysis and emphasize the importance of prespecifying a small number of subgroups and using the correlations among the treatment effect tests in the confirmatory setting. For a comprehensive overview of multiplicity adjustment methods that strongly control the family-wise error rate, see Alosch et al²⁵⁶; for a recent general overview of multiplicity considerations in clinical trials, see Dmitrienko and D'Agostino.²⁵⁷

MAMS Designs and Methods

A MAMS, adaptive clinical trial design was proposed in the early 2000s²⁵⁸ with an interim look for futility after every stage. Intermediate or surrogate endpoints are used in the interim analyses, whereas the definitive endpoint is used in the final analysis. The trial design of the 5-stage STAMPEDE trial is based on this proposed design^{149–152}; although the trial originally incorporated 6 arms, several new treatment arms were added and old ones dropped throughout the ongoing trial. At every interim analysis except for the first one, which assessed only safety, experimental treatments can be dropped for futility based on a pair-wise comparison to the control arm. For comparisons with experimental arms added throughout the trial, only concurrent control patients are used. After the last stage, for every remaining experimental arm, a 1-sided test at level 0.025 was conducted to test the hypothesis of the hazard being smaller in the experimental arm. According to the authors, this resulted in an overall type 1 error for the pair-wise comparison of treatment versus control across the stages of approximately 0.015, depending on the correlation of the treatment effect on the intermediate and definitive endpoints. Royston et al²⁵⁹ and Bratton et al²⁶⁰ later extended the MAMS design to be more flexible and allow an arbitrary number of stages and binary outcomes. Extensive research exists on the properties and design of MAMS trials: Blenkinsop et al²⁶¹ investigated the effect of timing of interim analyses, allocation ratios, efficacy rules, and other design parameters on the pairwise and family-wise error rates under the MAMS framework and time-to-event endpoints. They included early stopping for efficacy and futility and provided methods to control the pairwise and family-wise error rates. Graf et al²⁶² investigated how the type 1 error is inflated in MAMS trials when selecting more promising treatments, changing randomization ratios, and performing naive tests not considering the adaptations accordingly. Bauer and Kieser²⁶³ proposed adaptive designs that allow for treatment selection at interim analyses and strictly control the type 1 error rate. Hommel²⁶⁴ extended the methods to allow for adding more treatments at an interim analysis. On the basis of the work by Bauer and Kieser²⁶³ and Hommel,²⁶⁴ Posch et al²⁶⁵ gave a general formulation of the adaptive testing procedure in the context of treatment selection

and proposed further methods, such as multiplicity-adjusted P values and simultaneous CIs. There has been extensive research on adaptive designs, but because this was not the scope of our research, we refer to Bretz et al²⁶⁶ and Bauer et al⁷⁵ for further information. Koenig et al²⁶⁷ proposed an adaptive Dunnett test that allowed for treatment selection at the interim analyses. Magirr et al²⁶⁸ generalized the Dunnett test for MAMS trials with treatment selection. Wason et al²⁶⁹ explore a range of statistical issues related to MAMS designs and give recommendations on how to deal with them. Using 3 cancer trials performed at the Medical Research Council Clinical Trials Unit, Barthel et al²⁷⁰ evaluated the performance of MAMS trials compared with traditional 2-arm parallel group designs. Wason and Jaki²⁷¹ propose a method to find the optimal design parameters for a MAMS design with respect to minimizing the expected sample size for chosen treatment effects. Bratton et al²⁷² investigate the pairwise and family-wise type 1 error rate of MAMS trials and propose methods to control the type 1 error rate under any scenario. Crouch et al²⁷³ provide an analytical method for calculating the family-wise error rate of a MAMS trial and propose a simple method to control the error rate. Magirr et al²⁷⁴ explored how flexibility can be added to MAMS designs and investigated the effect on the error rates. Ghosh et al²⁷⁵ provided algorithms that significantly reduce the computation needed to derive MAMS boundaries. Lin and Bunn²⁷⁶ compared MAMS designs using prespecified treatment selection and stopping rules with Bayesian response-adaptive randomization designs and found that both are comparable, with each of them being superior to the other, depending on the scenario. An earlier study on the same subject with slightly different assumptions but similar findings has been performed by Wason and Trippa.²⁷⁷ In a recently published article, Lee et al²⁷⁸ propose a decision-theoretic framework based on 2 utility functions: one that tries to maximize the number of rejected hypotheses and one that counts at least one rejected hypothesis as a trial success, to decide whether a new treatment arm should be added to a MAMS design. For a comparison of several MAMS designs with traditionally used trial designs in the context of an epidemic, such as Ebola, please refer to Brueckner et al.²⁷⁹

DISCUSSION

We conducted a comprehensive, systematic literature review on master protocol clinical trials that describes conducted and planned trials from all indications and relevant trial designs and methods. A similar search strategy was implemented by Siden et al⁸⁵ in their systematic review; however, the authors' primary aim was to illustrate the inconsistent use of the master protocol terms. The systematic search was performed using PubMed and augmented by articles of interest found from manual searches. **Although the level of skepticism toward master protocols differs considerably, especially with respect to their appropriateness for confirmatory clinical trials, we believe the general consensus in the identified literature is that master protocols provide potentially enormous advantages in efficiency and flexibility of clinical drug development.**

In a recently published commentary,²⁸⁰ the authors describe their experiences of clinical trial applications from 2 European medical regulators and highlight the risks and problems of master protocol trials from more than a statistical point of view. **They conclude that “master protocols should only be used when they are unavoidable for scientifically sound methodological reasons.”**²⁸⁰ This comment further illustrates that as more master protocols are designed the scientific community will have to educate regulators on the value that such trials will provide in potentially bringing new innovative treatments to patients in a short development timeline. Furthermore, the drug development process is also negatively affected if the application of new methods is handled too restrictively.^{281,282} We live in an era where polytherapy is becoming increasingly more common across chronic diseases as well as within oncology. When an open-entry platform trial is planned, it is understood that for each treatment being used in combination an investigational brochure needs to be submitted to health authorities. The protocol will also need to be amended for each new substudy or treatment arm added. Thus, the infrastructure in the master protocol needs to have the flexibility introduced from the beginning so that it is clear to health authorities, institutional review boards, and ethics committees what has changed by the adding of a new substudy. Operational obstacles of platform trials have been discussed by Schiavone

et al.²⁸³ Further challenges from investigator, sponsor, and regulatory views are discussed by Cecchini et al.²⁸⁴ Laage et al.²⁸⁵ reviewed ethical considerations of adaptive design elements potentially used in trials with master protocols, and Strzebonska and Waligora²⁸⁶ highlight ethical challenges in umbrella and basket trials. Klauschen et al.²⁸⁷ investigated the combinatorial complexity introduced by cancer precision medicine approaches and proposed a novel clinical trial design that combines elements of basket and umbrella trials to overcome this problem. A summary of trial management and data management teams involved in FOCUS4 and STAMPEDE, as well as data management challenges specific to adaptive platform protocols, is given by Morrell et al.²⁸⁸ and Hague et al.²⁸⁹ The European regulatory experience with adaptive designs has been discussed in the article by Elsässer et al.²⁹⁰ and Collignon et al,²⁹¹ who found that if innovative designs are properly implemented they are well accepted by regulatory authorities.

The number of conducted master protocol trials is still limited and largely restricted to oncology and exploratory trials. Although there is already quite a range of different trial designs, it remains speculative whether fully Bayesian designs or frequentist approaches are more favorable. Which statistical methods should be chosen will also depend on whether additional Phase III trials will follow or if the concept of a consecutive series of Phase I, II, and III trials is fading with the increase of master protocols. In the context of personalized medicine and targeted therapies with limited sample sizes, there is always the possibility that the evidence from a master protocol trial becomes the (only) pivotal basis for approval. Thus, the discussion of error rate control might not only be related to the master protocol trial itself but might also need to be put in the context of all trials eventually conducted.

In conclusion, master protocol trials and especially platform trials are appropriately considered to have the potential to revolutionize clinical drug development. However, in all the euphoria, the operational and statistical challenges associated with such trials must not be forgotten. These challenges need to be considered with utmost care, but if they can be overcome, a new era of clinical trials might be dawning.

DISCLOSURES

Drs Dunger-Baldauf, Fuelle, Glimm, Mesenbrink, and Li are employees of Novartis Pharmaceuticals. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

FUNDING SOURCES

The research of Elias Laurin Meyer was funded by Novartis. The sponsor played no role in the systematic selection of articles, the writing of the manuscript, or the decision to publish. The authors and not the sponsor have copyright of this article. The research of ELM was funded by Novartis on the university and not an individual level.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinthera.2020.05.010>.

REFERENCES

1. Redman Mary W, Allegra Carmen J. The master protocol concept. *Semin Oncol*. 2015;42:724–730. <https://doi.org/10.1053/j.seminoncol.2015.07.009>.
2. Berry Donald A. The Brave New World of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research. *Mol Oncol*. 2015;9: 951–959. <https://doi.org/10.1016/j.molonc.2015.02.011>.
3. Berry DA. Emerging innovations in clinical trial design. *Clin Pharmacol Ther*. 2016;99:82–91. <https://doi.org/10.1002/cpt.285>.
4. Saville Benjamin R, Berry Scott M. Efficiencies of platform clinical trials: a vision of the future. *Clin Trials*. 2016;13: 358–366. <https://doi.org/10.1177/1740774515626362>.
5. Tolles Juliana, Lewis Roger J. Adaptive and platform trials in remote damage control resuscitation. *J Trauma Acute Care Surg*. 2018;84(1). <https://doi.org/10.1097/ta.0000000000001904>.
6. Shah Sanjiv J. Innovative clinical trial designs for precision medicine in heart failure with preserved ejection fraction. *J Cardiovasc Translational Res*. 2017;10:322–336. <https://doi.org/10.1007/s12265-017-9759-8>.
7. Schultz Andre, Marsh Julie A, Saville Benjamin R, et al. Trial refresh: a case for an adaptive platform trial for pulmonary exacerbations of cystic fibrosis. *Front Pharmacol*. 2019;10(March):1–8. <https://doi.org/10.3389/fphar.2019.00301>.

8. Lam Michael, Jonathan M, Loree Allan, Pereira Lima Anderson, Chun Yun Shin, Scott Kopetz. Accelerating therapeutic development through innovative trial design in colorectal cancer. *Curr Treat Options Oncol*. 2018;19. <https://doi.org/10.1007/s11864-018-0524-2>.
9. Saada-Bouزيد Esma, Le Tourneau Christophe. Beyond EGFR targeting in SCCHN: angiogenesis, PI3K, and other molecular targets. *Front Oncol*. 2019;9(February):1–8. <https://doi.org/10.3389/fonc.2019.00074>.
10. Felsenstein Kenneth M, Theodorescu Dan. Precision medicine for urothelial bladder cancer: update on tumour genomics and immunotherapy. *Nat Rev Urol*. 2018;15:92.
11. Heerspink Hiddo JL, Perkovic Vlado. Trial design innovations to accelerate therapeutic advances in chronic kidney disease: moving from single trials to an ongoing platform. *Clin J Am Soc Nephrol*. 2018;13:946–948. <https://doi.org/10.2215/CJN.01290118>.
12. Kovesdy Csaba P. Clinical trials in end-stage renal disease—priorities and challenges. *Nephrol Dial Transplant*. Jun 2019;1–6. <https://doi.org/10.1093/ndt/gfz088>.
13. Paul Perco, Pena Michelle, Heerspink Hiddo JL, Mayer Gert. Multimarker panels in diabetic kidney disease: the way to improved clinical trial design and clinical practice? *Kidney Int Rep*. 2019;4:212–221. <https://doi.org/10.1016/j.ekir.2018.12.001>.
14. Soul Janet S, Pressler Ronit, Allen Marilee, et al. Recommendations for the design of therapeutic trials for neonatal seizures. *Pediatr Res*. 2019;85:943–954. <https://doi.org/10.1038/s41390-018-0242-2>.
15. Khan Tahira, Stewart Mark, Blackman Samuel, et al. Accelerating pediatric cancer drug development: challenges and opportunities for pediatric master protocols. *Ther Innovation Regul Sci*. 2019;53:270–278. <https://doi.org/10.1177/2168479018774533>.
16. Bitterman Danielle S, Cagney Daniel N, Singer Lisa, Nguyen Paul L, Catalano Paul J, Mak Raymond H. Master protocol trial design for efficient and rational evaluation of novel therapeutic oncology devices. *JNCI: J Natl Cancer Inst*. 2020;112(3):229–237. Oxford University Press.
17. Joshi Yash B, Light Gregory A. Using EEG-guided basket and umbrella trials in psychiatry: a precision medicine approach for cognitive impairment in schizophrenia. *Front Psychiatr*. 2018;9(November):1–9. <https://doi.org/10.3389/fpsyt.2018.00554>.
18. Talisa Victor B, Yende Sachin, Seymour Christopher W, Angus Derek C. Arguing for adaptive clinical trials in sepsis. *Front Immunol*. 2018;9:1–8. <https://doi.org/10.3389/fimmu.2018.01502>.
19. Phillips Patrick PJ, Gillespie Stephen H, Martin Boeree, et al. Innovative trial designs are practical solutions for improving the treatment of tuberculosis. *J Infect Dis*. 2012;205(SUPPL. 2). <https://doi.org/10.1093/infdis/jis041>.
20. Stegall Mark D, Smith Byron, Bentall Andrew, Schinstock Carrie. The need for novel trial designs, master protocols, and research consortia in transplantation. *Clin Transplant*. 2020;34(1). e13759, Wiley Online Library.
21. de Kraker Marlieke EA, Sommer Harriet, Femke de Velde, et al. Optimizing the design and analysis of clinical trials for antibacterials against multidrug-resistant organisms: a white paper from COMBACTE's STAT-net. *Clin Infect Dis*. 2018;67:1922–1931. <https://doi.org/10.1093/cid/ciy516>.
22. Spiegelhalter David J, Abrams Keith R, Myles Jonathan P. *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. vol. 13. John Wiley & Sons; 2004.
23. Berry Donald A. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5:27–36. <https://doi.org/10.1038/nrd1927>.
24. Freidlin Boris, Korn Edward L, Gray Robert, Martin Alison. Multi-arm clinical trials of new agents: some design considerations. *Clin Cancer Res*. 2008;14:4368–4371. <https://doi.org/10.1158/1078-0432.CCR-08-0325>.
25. Berry Donald A. Adaptive clinical trials in oncology. *Nat Rev Clin Oncol*. 2012;9:199–207. <https://doi.org/10.1038/nrclinonc.2011.165>.
26. Haines Linda M, Hassan Sadiq. Start-up designs for response-adaptive randomization procedures with sequential estimation. *Stat Med*. 2015;34:2958–2970. <https://doi.org/10.1002/sim.6528>.
27. Du Yining, Wang Xuan, Jack Lee J. Simulation study for evaluating the performance of response-adaptive randomization. *Contemp Clin Trials*. 2015;40:15–25. <https://doi.org/10.1016/j.cct.2014.11.006>.
28. Gajewski Byron J, Berry Scott M, Barsan William G, et al. Hyperbaric oxygen brain injury treatment (HOBIT) trial: a multifactor design with response adaptive randomization and longitudinal modeling. *Pharm Stat*. 2016;15:396–404. <https://doi.org/10.1002/pst.1755>.
29. Du Yining, Cook John D, Jack Lee J. Comparing three regularization methods to avoid extreme allocation probability in response-adaptive randomization. *J Biopharm Stat*. 2018;28:309–319. <https://doi.org/10.1080/10543406.2017.1293077>.
30. Cellamare Matteo, Ventz Steffen, Baudin Elisabeth, Mitnick Carole D, Trippa Lorenzo. A Bayesian response-adaptive trial in tuberculosis: the endTB trial. *Clin Trials*. 2017;14:17–28. <https://doi.org/10.1186/s13063-017-1922-1>.

- doi.org/10.1177/1740774516665090.
31. Saville Benjamin R, Berry Scott M. Balanced covariates with response adaptive randomization. *Pharm Stat*. 2017;16:210–217. <https://doi.org/10.1002/pst.1803>.
 32. Nowacki Amy S, Zhao Wenle, Yuko Y, Palesch. A surrogate-primary replacement algorithm for response-adaptive randomization in stroke clinical trials. *Stat Methods Med Res*. 2017;26:1078–1092. <https://doi.org/10.1177/0962280214567142>.
 33. Jiang Yunyun, Zhao Wenle, Durkalski-Mauldin Valerie. Impact of adaptation algorithm, timing, and stopping boundaries on the performance of Bayesian response adaptive randomization in confirmative trials with a binary endpoint. *Contemp Clin Trials*. 2017;62(March):114–120. <https://doi.org/10.1016/j.cct.2017.08.019>.
 34. Butler Christopher C, Connor Jason T, Lewis Roger J, et al. Answering patient-centred questions efficiently: response-adaptive platform trials in primary care. *Br J Gen Pract*. jun 2018;68:294–295. <https://doi.org/10.3399/bjgp18x696569>.
 35. Kim Mi Ok, Harun Nusrat, Liu Chunyan, Khoury Jane C, Broderick Joseph P. Bayesian selective response-adaptive design using the historical control. *Stat Med*. 2018;37:3709–3722. <https://doi.org/10.1002/sim.7836>.
 36. Jiang Yunyun, Zhao Wenle, Durkalski-Mauldin Valerie. Time-trend impact on treatment estimation in two-arm clinical trials with a binary outcome and Bayesian response adaptive randomization. *J Biopharm Stat*. 2019;1–20. <https://doi.org/10.1080/10543406.2019.1607368>.
 37. Korn Edward L, Freidlin Boris. Outcome-adaptive randomization: is it useful? *J Clin Oncol*. 2011;29:771–776. <https://doi.org/10.1200/JCO.2010.31.1423>.
 38. Yuan Ying, Yin Guosheng. On the usefulness of outcome-adaptive randomization. *J Clin Oncol*. may 2011;29:e390–e392. <https://doi.org/10.1200/JCO.2010.34.5330>.
 39. Freidlin Boris, Korn Edward L. Borrowing information across subgroups in phase II trials: is it useful? *Clin Cancer Res*. 2013;19:1326–1334. <https://doi.org/10.1158/1078-0432.CCR-12-1223>.
 40. Freidlin Boris, Korn Edward L. Adaptive randomization versus interim monitoring. *J Clin Oncol*. 2013;31:969–970. <https://doi.org/10.1200/jco.2012.45.0254>.
 41. Lipsky Ari M, Lewis Roger J. Response-adaptive decision-theoretic trial design: operating characteristics and ethics. *Stat Med*. 2013;32:3752–3765.
 42. Thall Peter F, Fox P, Wathen J. Statistical controversies in clinical research: scientific and ethical problems with adaptive randomization in comparative clinical trials. *Ann Oncol*. 2015;26:1621–1628. <https://doi.org/10.1093/annonc/mdv238>.
 43. Korn Edward L, Freidlin Boris. Adaptive clinical trials: advantages and disadvantages of various adaptive design elements. *J Natl Cancer Inst*. 2017;109:1–6. <https://doi.org/10.1093/jnci/djx013>.
 44. Wathen J Kyle, Thall Peter F. A simulation study of outcome adaptive randomization in multi-arm clinical trials. *Clin Trials*. 2017;14:432–440.
 45. Piccorelli Annalisa V, Fraker Sarah A. Balancing statistical and ethical considerations in planning clinical trials: recommendations for response-adaptive randomization urn designs. *J Biopharm Stat*. 2018;28:1105–1118.
 46. Menis Jessica, Hasan Baktiar, Besse Benjamin. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. *Eur Respir Rev*. 2014;23:367–378. <https://doi.org/10.1183/09059180.00004214>.
 47. Catenacci Daniel VT. Next-generation clinical trials: novel strategies to address the challenge of tumor molecular heterogeneity. *Mol Oncol*. 2015;9:967–996.
 48. Hollingsworth Simon J. Precision medicine in oncology drug development: a pharma perspective. *Drug Discov Today*. 2015;20:1455–1463. <https://doi.org/10.1016/j.drudis.2015.10.005>.
 49. Kummar Shivaani, Mickey Williams P, Jian Lih Chih, et al. Application of molecular profiling in clinical trials for advanced metastatic cancers. *J Natl Cancer Inst*. 2015;107:1–6. <https://doi.org/10.1093/jnci/djv003>.
 50. Mandrekar Sumithra J, Dahlberg Suzanne E, Simon Richard. Improving clinical trial efficiency: thinking outside the box. *Am Soc Clin Oncol Educ Book*. 2015;35:e141–e147. <https://doi.org/10.14694/EdBookAM.2015.35.e141>.
 51. Redig Amanda J, Janne Pasi A. Basket trials and the evolution of clinical trial design in an era of genomic medicine. *J Clin Oncol*. 2015;33:975–977.
 52. Zardavas Dimitrios, Piccart-Gebhart Martine. Clinical trials of precision medicine through molecular profiling: focus on breast cancer. *Am Soc Clin Oncol Educ Book*. 2015;35:e183–e190.
 53. Billingham Lucinda, Malottki Kinga, Steven Neil. Research methods to change clinical practice for patients with rare cancers. *Lancet Oncol*. 2016;17:e70–e80.
 54. Renfro Lindsay A, Mallick Himel, Wen An Ming, Sargent Daniel J, Mandrekar Sumithra J. Clinical trial designs incorporating predictive biomarkers. *Cancer Treat Rev*. 2016;43:74–82. <https://doi.org/10.1016/j.ctrv.2015.12.008>.

55. Simon Richard. Genomic alteration-driven clinical trial designs in oncology. *Ann Intern Med.* 2016;165:270–278. <https://doi.org/10.7326/M15-2413>.
56. Trusheim MR, Shrier AA, Antonijevic Z, et al. PIPELINES: creating comparable clinical knowledge efficiently by linking trial platforms. *Clin Pharmacol Ther.* 2016;100:713–729. <https://doi.org/10.1002/cpt.514>.
57. Zardavas Dimitrios, Piccart-Gebhart Martine. New generation of breast cancer clinical trials implementing molecular profiling. *Cancer Biol Med.* 2016;13:226–235. <https://doi.org/10.20892/j.issn.2095-3941.2015.0099>.
58. Hyman David M, Taylor Barry S, Baselga Jose. Implementing genome-driven oncology. *Cell.* 2017;168:584–599.
59. Simon Richard. Critical review of umbrella, basket, and platform designs for oncology clinical trials. *Clin Pharmacol Ther.* 2017;102:934–941. <https://doi.org/10.1002/cpt.814>.
60. Renfro Lindsay A, An Ming Wen, Mandrekar Sumithra J. Precision oncology: a new era of cancer clinical trials. *Cancer Lett.* 2017;387:121–126. <https://doi.org/10.1016/j.canlet.2016.03.015>.
61. Balevic Stephen J, Cohen-Wolkowicz Michael. Innovative study designs optimizing clinical pharmacology research in infants and children. *J Clin Pharmacol.* 2018;58(September 2017):S58–S72. <https://doi.org/10.1002/jcph.1053>.
62. Bui Nam Q, Kummar Shivaani. Evolution of early phase clinical trials in oncology. *J Mol Med.* 2018;96:31–38.
63. Fountzilas Elena, Tsimberidou Apostolia M. Overview of precision oncology trials: challenges and opportunities. *Expert Rev Clin Pharmacol.* 2018;11:797–804. <https://doi.org/10.1080/17512433.2018.1504677>.
64. Heerspink Hiddo JL, List James, Perkovic Vlado. New clinical trial designs for establishing drug efficacy and safety in a precision medicine era. *Diabetes Obes Metab.* 2018;20:14–18. <https://doi.org/10.1111/dom.13417>.
65. Park Jay JH, Thorlund Kristian, Mills Edward J. Critical concepts in adaptive clinical trials. *Clin Epidemiol.* 2018;10:343–351. <https://doi.org/10.2147/CLEP.S156708>.
66. Tao Jessica J, Schram Alison M, Hyman David M. Basket studies: redefining clinical trials in the era of genome-driven oncology. *Annu Rev Med.* 2018;69:319–331. <https://doi.org/10.1146/annurev-med-062016-050343>.
67. Janiaud Perrine, Serghiou Stylianos, John P, Ioannidis A. New clinical trial designs in the era of precision medicine: an overview of definitions, strengths, weaknesses, and current use in oncology. *Cancer Treat Rev.* 2019;73(December 2018):20–30. <https://doi.org/10.1016/j.ctrv.2018.12.003>.
68. Harris Courtney J, Waters Alicia M, Tracy Elisabeth T, et al. Precision oncology: a primer for pediatric surgeons from the apsa cancer committee. *J Pediatr Surg.* 2019. Elsevier, [in press].
69. Amy Burd, Schilsky Richard L, Byrd John C, et al. Challenges and approaches to implementing master/basket trials in oncology. *Blood Adv.* 2019;3:2237–2243.
70. Leonetti Alessandro, Boyd Lenka, Giuliani Jacopo, Giovannetti Elisa, Garajová Ingrid. Light and shadow on innovative clinical trial designs: reflections from the eortc-pamm course on “preclinical and early-phase clinical pharmacology”. *Expert Rev Clin Pharmacol.* 2019;12(11):1033–1036. Taylor & Francis.
71. Sotelo-Rodríguez Diana Carolina, Ruíz-Patino Alejandro, Ricaurte Luisa, Arrieta Oscar, Lucia Zatarain-Barrón Zyanya, Cardona Andrés F. Challenges and shifting paradigms in clinical trials in oncology: the case for immunological and targeted therapies. *ecancermedicallscience.* 2019;13.
72. Deborah B Doroshow, James H Doroshow. From the broad phase ii trial to precision oncology: a perspective on the origins of basket and umbrella clinical trial designs in cancer drug development. *Cancer J.* 2019;25:245–253.
73. Angus Derek C, Alexander Brian M, Scott Berry, et al. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov.* 2019;12:797–807. <https://doi.org/10.1038/s41573-019-0034-3>.
74. Yee Laura M, McShane Lisa M, Freidlin Boris, Mooney Margaret M, Korn Edward L. Biostatistical and logistical considerations in the development of basket and umbrella clinical trials. *Cancer J.* 2019;25:254–263.
75. Bauer Peter, Frank Bretz, Dragalin Vladimir, Franz König, Wassmer Gernot. Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls. *Stat Med.* 2016;35:325–347. <https://doi.org/10.1002/sim.6472>.
76. Bothwell Laura E, Avorn Jerry, Khan Nazleen F, Kesselheim Aaron S. Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov. *BMJ Open.* 2018;8:1–11. <https://doi.org/10.1136/bmjopen-2017-018320>.
77. Antoniou Miranta, Jorgensen Andrea L, Kolamunnage-Dona Ruwanthi. Biomarker-guided adaptive trial designs in phase II and phase III: a methodological review. *PLoS ONE.* 2016;11:1–30. <https://doi.org/10.1371/journal.pone.0149803>.

78. Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. *Ann Oncol*. 2017;28:34–43. <https://doi.org/10.1093/annonc/mdw413>.
79. Cunanen Kristen M, Gonen Mithat, Shen Ronglai, et al. Basket trials in oncology: a trade-off between complexity and efficiency. *J Clin Oncol*. 2017;35:271–273. <https://doi.org/10.1200/JCO.2016.69.9751>.
80. Hirakawa Akihiro, Asano Junichi, Sato Hiroyuki, Teramukai Satoshi. Master protocol trials in oncology: review and new trial designs. *Contemp Clin Trials Commun*. 2018;12(April):1–8. <https://doi.org/10.1016/j.conctc.2018.08.009>.
81. Renfro Lindsay A, Mandrekar Sumithra J. Definitions and statistical properties of master protocols for personalized medicine in oncology. *J Biopharm Stat*. 2018;28:217–228. <https://doi.org/10.1080/10543406.2017.1372778>.
82. Woodcock Janet, LaVange Lisa M. Master protocols to study multiple therapies, multiple diseases, or both. *New Engl J Med*. 2017;377:62–70. <https://doi.org/10.1056/NEJMr1510062>.
83. Master Protocols FDA. *Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics. Guidance for Industry, DRAFT GUIDANCE*; October 2018. <https://www.fda.gov/media/120721/download>, 2019-05-02.
84. Clinical Trials Facilitation and Coordination Group (CTFG). Recommendation paper on the initiation and conduct of complex clinical trials. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf, 2019-08-05.
85. Siden EG, Park JJ, Zoratti MJ, et al. Reporting of master protocols towards a standardized approach: a systematic review. *Contemp Clin Trials Commun*. 2019;15:100406. <https://doi.org/10.1016/j.conctc.2019.100406>.
86. Park Jay JH, Siden Ellie, Zoratti Michael J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials*. 2019;20:1–10. <https://doi.org/10.1186/s13063-019-3664-1>.
87. Hazim Antonious, Prasad Vinay. A pooled analysis of published, basket trials in cancer medicine. *Eur J Cancer*. 2018;101:244–250. <https://doi.org/10.1016/j.ejca.2018.06.035>.
88. Liberati Alessandro, Altman Douglas G, Tetzlaff Jennifer, et al. The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6, e1000100.
89. McArthur Grant A, Demetri George D, Allan Van Oosterom, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: imatinib target exploration consortium study B2225. *J Clin Oncol*. 2005;23:866–873. <https://doi.org/10.1200/JCO.2005.07.088>.
90. Heinrich Michael C, Joensuu Heikki, Demetri George D, et al. 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*. 2008;14:2717–2725. <https://doi.org/10.1158/1078-0432.CCR-07-4575>.
91. Chugh Rashmi, Kyle Wathen J, Maki Robert G, et al. Phase II multicenter trial of imatinib in 10 histologic subtypes of sarcoma using a bayesian hierarchical statistical model. *J Clin Oncol*. 2009;27:3148–3153. <https://doi.org/10.1200/JCO.2008.20.5054>.
92. Hyman David M, Puzanov Igor, Subbiah Vivek, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *New Engl J Med*. 2015;373:726–736. <https://doi.org/10.1056/NEJMoa1502309>.
93. Diamond Eli L, Subbiah Vivek, Lockhart A Craig, et al. Vemurafenib for BRAF V600-mutant erdheim-chester disease and langerhans cell histiocytosis analysis of data from the histology-independent, phase 2, open-label VE-BASKET study. *JAMA Oncol*. 2018;4:384–388. <https://doi.org/10.1001/jamaoncol.2017.5029>.
94. Kaley Thomas, Touat Mehdi, Subbiah Vivek, et al. BRAF inhibition in BRAF V600 -mutant gliomas: results from the VE-BASKET study. *J Clin Oncol*. 2018;36:3477–3484. <https://doi.org/10.1200/JCO.2018.78.9990>.
95. Hobbs BP, Kane MJ, Hong DS, Landin R. Statistical challenges posed by uncontrolled master protocols: sensitivity analysis of the vemurafenib study. *Ann Oncol*. 2018;29:2296–2301.
96. Carroll Molly J, Parent Carl R, Page David, Kreeger Pamela K. Tumor cell sensitivity to vemurafenib can be predicted from protein expression in a braf-v600e basket trial setting. *BMC Cancer*. 2019;19:1–13.
97. Dung T Le, Uram Jennifer N, Wang Hao, et al. Pd-1 blockade in tumors with mismatch-repair deficiency. *New Engl J Med*. 2015;372:2509–2520.
98. Le Dung T, Durham Jennifer N, Smith Kellie N, et al. Mismatch repair deficiency predicts response of solid tumors to pd-1 blockade. *Science*. 2017;357:409–413.

99. Baretta Marina, Azad Nilofer Saba. Precision cancer trials with immunomodulatory agents: personalizing histology agnostic approaches. *Cancer J.* 2019;25:287–295.
100. Chow Laura QM, Haddad Robert, Gupta Shilpa, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol.* 2016;34:3838–3845. <https://doi.org/10.1200/JCO.2016.68.1478>.
101. Muro Kei, Chung Hyun Cheol, Shankaran Veena, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol.* jun 2016;17:717–726. <https://doi.org/10.1016/S1470-204500175-3>.
102. Nanda Rita, Laura Q, Chow M, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib keynote-012 study. *J Clin Oncol.* 2016;34:2460–2467. <https://doi.org/10.1200/JCO.2015.64.8931>.
103. Seiwert Tanguy Y, Burtneß Barbara, Mehra Rane, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol.* 2016;17:956–965. <https://doi.org/10.1016/S1470-204530066-3>.
104. Plimack Elizabeth R, Bellmunt Joaquim, Gupta Shilpa, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. *Lancet Oncol.* 2017;18:212–220. <https://doi.org/10.1016/S1470-204530007-4>.
105. Tahara Makoto, Muro Kei, Hasegawa Yasuhisa, et al. Pembrolizumab in Asia-Pacific patients with advanced head and neck squamous cell carcinoma: analyses from KEYNOTE-012. *Cancer Sci.* 2018;109:771–776. <https://doi.org/10.1111/cas.13480>.
106. Coyle Christopher, Cafferty Fay H, Rowley Samuel, et al. ADDASPIRIN: a phase III, double-blind, placebo controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours. *Contemp Clin Trials.* 2016;51:56–64. <https://doi.org/10.1016/j.cct.2016.10.004>.
107. Parmar Mahesh KB, Sydes Matthew R, Cafferty Fay H, et al. Testing many treatments within a single protocol over 10 years at MRC Clinical Trials Unit at UCL: multi-arm, multi-stage platform, umbrella and basket protocols. *Clin Trials.* 2017;14:451–461. <https://doi.org/10.1177/1740774517725697>.
108. Hasegawa Kosei, Kagabu Masahiro, Mizuno Mika, et al. Phase II basket trial of perifosine monotherapy for recurrent gynecologic cancer with or without PIK3CA mutations. *Investig New Drugs.* 2017;35:800–812. <https://doi.org/10.1007/s10637-017-0504-6>.
109. Hyman David M, Smyth Lillian M, Mark T, et al. AKT inhibition in solid tumors with AKT1 mutations. *J Clin Oncol.* 2017;35:2251–2259. <https://doi.org/10.1200/JCO.2017.73.0143>.
110. Alexander Drilon, Laetsch Theodore W, Kummar Shivaani, et al. Efficacy of larotrectinib in TRK fusion—positive cancers in adults and children. *New Engl J Med.* 2018;378:731–739. <https://doi.org/10.1056/nejmoa1714448>.
111. Chen Yu, Chi Ping. Basket trial of TRK inhibitors demonstrates efficacy in TRK fusion-positive cancers. *J Hematol Oncol.* 2018;11:1–5. <https://doi.org/10.1186/s13045-018-0622-4>.
112. Jørgensen Jan Trøst. A paradigm shift in biomarker guided oncology drug development. *Ann Translational Med.* 2019;7:148. <https://doi.org/10.21037/atm.2019.03.36>, 148.
113. Hykin Philip G, Staurengi Giovanni, Wiedemann Peter, et al. Ranibizumab 0.5 mg treatment in adolescents with choroidal neovascularization: subgroup analysis data from the Minerva study. *Retin Cases Brief Rep.* 2019. <https://doi.org/10.1097/ICB.0000000000000825>.
114. Lai Timothy YY, Staurengi Giovanni, Lanzetta Paolo, et al. Efficacy and safety of ranibizumab for the treatment of choroidal neovascularization due to uncommon cause: twelve-Month Results of the MINERVA Study. *Retina.* 2017;1464–1477. <https://doi.org/10.1097/IAE.0000000000001744>.
115. Hyman David M, Piha-Paul Sarina A, Won Helen, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature.* 2018;554:189–194. <https://doi.org/10.1038/nature25475>.
116. Ulaner Gary A, Saura Cristina, Piha-Paul Sarina A, et al. Impact of fdg pet imaging for expanding patient eligibility and measuring treatment response in a genome-driven basket trial of the pan-her kinase inhibitor, neratinib. *Clin Cancer Res.* 2019;25(24):7381–7387. AACR.
117. Li Bob T, Shen Ronglai, Buonocore Darren, et al. Ado-trastuzumab emtansine for patients with HER2-mutant lung cancers: results from a phase II basket trial. *J Clin Oncol.* 2018;36:2532–2537.

- <https://doi.org/10.1200/JCO.2018.77.9777>.
118. Chung Hyun Cheol, Ros Willeke, Delord Jean-Pierre, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2019;37. <https://doi.org/10.1200/JCO.18.01265>. JCO.18.01265.
 119. Clouthier Derek L, Lien Scott C, Cindy Yang SY, et al. An interim report on the investigator-initiated phase 2 study of pembrolizumab immunological response evaluation (inspire). *J Immunother Cancer*. 2019;7:72. <https://doi.org/10.1186/s40425-019-0541-0>.
 120. Le Teuff Gwénäel, Castaneda-Heredia Alicia, Dufour Christelle, et al. Phase II study of temozolomide and topotecan (totem) in children with relapsed or refractory extracranial and central nervous system tumors including medulloblastoma with post hoc bayesian analysis: a European itcc study. *Pediatr Blood Cancer*. 2019, e28032.
 121. Perreault Sébastien, Larouche Valérie, Tabori Uri, et al. A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with refractory tumor and activation of the mapk/erk pathway: tram-01. *BMC Cancer*. 2019;19:1–9.
 122. Said Rabih, Apostolia-Maria Tsimberidou. Basket trials and the md anderson precision medicine clinical trials platform. *Cancer J*. 2019;25:282–286.
 123. Zhou Xian, Liu Suyu, Kim Edward S, Herbst Roy S, Lee J Jack. Bayesian adaptive design for targeted therapy development in lung cancer — a step toward personalized medicine. *Clin Trials: J Soc Clin Trials*. jun 2008;5:181–193. <https://doi.org/10.1177/1740774508091815>.
 124. Kim Edward S, Herbst Roy S, Wistuba Ignacio I, et al. The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov*. jun 2011;1:44–53. <https://doi.org/10.1158/2159-8274.CD-10-0010>.
 125. Liu Suyu, Lee J Jack. An overview of the design and conduct of the battle trials. *Chin Clin Oncol*. 2015;4.
 126. Abrams Jeffrey, Conley Barbara, Mooney Margaret, et al. National cancer institute's precision medicine initiatives for the new national clinical trials Network. *Am Soc Clin Oncol Educ Book*. 2014;34:71–76. <https://doi.org/10.14694/edbookam.2014.34.71>.
 127. Malik Shakun M, Pazdur Richard, Abrams Jeffrey S, et al. Consensus report of a joint NCI Thoracic Malignancies Steering Committee: FDA workshop on strategies for integrating biomarkers into clinical development of new therapies for lung cancer leading to the inception of "Master Protocols" in lung cancer. *J Thorac Oncol*. 2014;9:1443–1448. <https://doi.org/10.1097/JTO.0000000000000314>.
 128. Herbst RS, Gandara DR, Hirsch FR, et al. Lung master protocol (Lung-MAP)—A biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res*. apr 2015;21:1514–1524. <https://doi.org/10.1158/1078-0432.CCR-13-3473>.
 129. Steuer CE, Papadimitrakopoulou V, Herbst RS, et al. Innovative clinical trials: the LUNG-MAP study. *Clin Pharmacol Ther*. 2015;97:488–491. <https://doi.org/10.1002/cpt.88>.
 130. Ferrarotto R, Redman MW, Gandara DR, Herbst RS, Papadimitrakopoulou VA. Lung-MAP—framework, overview, and design principles. *Chin Clin Oncol*. 2015;4:36. <https://doi.org/10.3978/j.issn.2304-3865.2015.09.02>.
 131. Wright Gavin Michael, Russell Prudence Anne. The promise of lung master protocol for squamous cell carcinoma: one trial to rule them all, one trial to find them...? *Ann translational Med*. 2015;3.
 132. Tsao Anne S, Scagliotti Giorgio V, Bunn Jr Paul A, et al. Scientific advances in lung cancer 2015. *J Thorac Oncol*. 2016;11:613–638.
 133. Lam Vincent K, Papadimitrakopoulou Vassiliki. Master protocols in lung cancer: experience from lung master protocol. *Curr Opin Oncol*. 2018;30:92–97. <https://doi.org/10.1097/CCO.0000000000000433>.
 134. Chen Alice P, Eljanne Mariam, Harris Lyndsay, Malik Shakuntala, Seibel Nita L. National cancer institute basket/umbrella clinical trials: match, lungmap, and beyond. *Cancer J*. 2019;25:272–281.
 135. Edelman Martin J, Redman Mary W, Albain Kathy S, et al. Swog s1400c (nct02154490)—a phase ii study of palbociclib for previously treated cell cycle gene alteration —positive patients with stage iv squamous cell lung cancer (lung-map substudy). *J Thorac Oncol*. 2019;14:1853–1859.
 136. Langer Corey J, Redman Mary W, Wade James L, et al. SWOG S1400B (NCT02785913), a phase II study of GDC-0032 (Taselisib) for previously treated PI3K-positive patients with stage IV squamous cell lung cancer (lung-MAP sub-study). *J Thorac Oncol*. 2019;14(10):1839–1846. Elsevier.
 137. Govindan Ramaswamy, Mandrekar Sumithra J, Gerber David E, et al. Alchemist trials: a golden opportunity to transform outcomes in early-stage non-small cell lung cancer. *Clin Cancer Res*. 2015;21:5439–5444. <https://doi.org/10.1158/1078-0432.CCR-15-0354>.
 138. Gerber DE, Oxnard GR, Govindan R. ALCHEMIST: bringing genomic discovery and targeted therapies to early-stage lung cancer. *Clin Pharmacol Ther*. 2015;97:447

- 450. <https://doi.org/10.1002/cpt.91>.
139. Papadimitrakopoulou Vassiliki, Lee J Jack, Wistuba Ignacio I, et al. The BATTLE-2 study: a biomarker-integrated targeted therapy study in previously treated patients with advanced non—small-cell lung cancer. *J Clin Oncol*. oct 2016;34: 3638–3647. <https://doi.org/10.1200/JCO.2015.66.0084>.
 140. Kim Chul, Giaccone Giuseppe. Lessons learned from battle-2 in the war on cancer: the use of bayesian method in clinical trial design. *Ann translational Med*. 2016;4.
 141. Gu Xuemin, Chen Nan, Wei Caimiao, et al. Bayesian two-stage biomarker-based adaptive design for targeted therapy development. *Stat Biosciences*. jun 2016;8:99–128. <https://doi.org/10.1007/s12561-014-9124-2>.
 142. Alexander Brian M, Cloughesy Timothy F. Platform trials arrive on time for glioblastoma. *Neuro-Oncology*. 04 2018;20:723–725. <https://doi.org/10.1093/neuonc/noy040>.
 143. Wick Wolfgang, Dettmer Susan, Berberich Anne, et al. N 2 M 2 (NOA-20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma. *Neuro-Oncology*. 2019;21:95–105. <https://doi.org/10.1093/neuonc/noy161>.
 144. De Benedetti Fabrizio, Gattorno Marco, Anton Jordi, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *New Engl J Med*. 2018;378:1908–1919. <https://doi.org/10.1056/NEJMoa1706314>.
 145. Galot R, Le Tourneau C, Guigay J, et al. Personalized biomarker-based treatment strategy for patients with squamous cell carcinoma of the head and neck: EORTC position and approach. *Ann Oncol*. 2018;29: 2313–2327. <https://doi.org/10.1093/annonc/mdy452>.
 146. Jung-Yun Lee, Yi Ju Yeon, Kim Hyun-Soo, et al. An umbrella study of biomarker-driven targeted therapy in patients with platinum-resistant recurrent ovarian cancer: a Korean gynecologic oncology group study (kgog 3045), ambition. *Jpn J Clin Oncol*. 2019;49:789–792.
 147. Lee Jeeyun, Kim Seung Tae, Kim Kyung, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: the viktory umbrella trial. *Cancer Discov*. 2019;9: 1388–1405.
 148. James Nicholas D, Sydes Matthew R, Clarke Noel W, et al. Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm, multistage randomized controlled trial. *BJU Int*. 2008;103: 464–469. <https://doi.org/10.1111/j.1464-410X.2008.08034.x>.
 149. Parmar Mahesh KB, Barthel Friederike MS, Sydes Matthew, et al. Speeding up the evaluation of new agents in cancer. *J Natl Cancer Inst*. 2008;100: 1204–1214. <https://doi.org/10.1093/jnci/djn267>.
 150. Sydes Matthew R, Mahesh K, Parmar B, et al. Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial. *Trials*. 2009;10:1–16. <https://doi.org/10.1186/1745-6215-10-39>.
 151. Sydes Matthew R, Parmar Mahesh KB, Mason Malcolm D, et al. Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. *Trials*. 2012;13:1–14. <https://doi.org/10.1186/1745-6215-13-168>.
 152. Gilson C, Chowdhury S, Parmar MKB, Sydes MR. Incorporating biomarker stratification into STAMPEDE: an adaptive multi-arm, multi-stage trial platform. *Clin Oncol*. 2017;29: 778–786. <https://doi.org/10.1016/j.clon.2017.10.004>.
 153. James Nicholas D, Sydes Matthew R, Mason Malcolm D, et al. Celecoxib plus hormone therapy versus hormone therapy alone for hormone-sensitive prostate cancer: first results from the STAMPEDE multiarm, multistage, randomised controlled trial. *Lancet Oncol*. 2012;13:549–558. <https://doi.org/10.1016/S1470-204570088-8>.
 154. James Nicholas David, Spears Melissa R, Clarke Noel W, et al. Survival with newly diagnosed metastatic prostate cancer in the docetaxel era: data from 917 patients in the control arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). *Eur Urol*. 2015;67: 1028–1038. <https://doi.org/10.1016/j.eururo.2014.09.032>.
 155. James Nicholas D, Sydes Matthew R, Clarke Noel W, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *The Lancet*. 2016;387:1163–1177. <https://doi.org/10.1016/S0140-673601037-5>.
 156. James Nicholas D, Spears Melissa R, Clarke Noel W, et al. Failure-free survival and radiotherapy in patients with newly diagnosed nonmetastatic prostate cancer. *JAMA Oncol*. 2016;2:348–357. <https://doi.org/10.1001/jamaoncol.2015.4350>.
 157. Vale Claire L, Burdett Sarah, Larysa H, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol*. 2016;17:243–256. [https://doi.org/10.1016/S1473-3099\(16\)00000-0](https://doi.org/10.1016/S1473-3099(16)00000-0).

- doi.org/10.1016/S1470-204500489-1.
158. James Nicholas D, de Bono Johann S, R Spears Melissa, et al, STAMPEDE Investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. *New Engl J Med*. 2017;377:338–351. <https://doi.org/10.1056/NEJMoa1702900>.
 159. Mason Malcolm D, Clarke Noel W, James Nicholas D, et al. Adding celecoxib with or without zoledronic acid for hormone-naïve prostate cancer: long-term survival results from an adaptive, multiarm, multistage, platform, randomized controlled trial. *J Clin Oncol*. 2017;35:1530–1541. <https://doi.org/10.1200/JCO.2016.69.0677>.
 160. Parker Christopher C, James Nicholas D, Brawley Christopher D, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *The Lancet*. 2018;392:2353–2366. <https://doi.org/10.1016/S0140-673632486-3>.
 161. Sydes MR, Spears MR, Mason MD, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. *Ann Oncol*. 2018;29:1235–1248. <https://doi.org/10.1093/annonc/mdy072>.
 162. Parker Christopher C, Sydes Matthew R, Mason Malcolm D, et al. Prostate radiotherapy for men with metastatic disease: a new comparison in the systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy (STAMPEDE) trial. *BJU Int*. 2013;111:697–699. <https://doi.org/10.1111/bju.12087>.
 163. Attard Gerhardt, Sydes Matthew R, Mason Malcolm D, et al. Combining enzalutamide with abiraterone, prednisone, and androgen deprivation therapy in the STAMPEDE trial. *Eur Urol*. 2014;66:799–802. <https://doi.org/10.1016/j.eururo.2014.05.038>.
 164. Gillessen Silke, Gilson Clare, James Nick, Adler Amanda, Sydes Matthew R, Clarke Noel. Repurposing metformin as therapy for prostate cancer within the STAMPEDE trial platform. *Eur Urol*. 2016;70:906–908. <https://doi.org/10.1016/j.eururo.2016.07.015>.
 165. Gilbert Duncan C, Duong Trinh, Sydes Matthew, et al. Transdermal oestradiol as a method of androgen suppression for prostate cancer within the STAMPEDE trial platform. *BJU Int*. 2018;121:680–683. <https://doi.org/10.1111/bju.14153>.
 166. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther*. 2009;86:97–100. <https://doi.org/10.1038/clpt.2009.68>.
 167. Esserman Laura J, Woodcock Janet. Accelerating identification and regulatory approval of investigational cancer drugs. *JAMA - J Am Med Assoc*. 2011;306:2608–2609. <https://doi.org/10.1001/jama.2011.1837>.
 168. Berry Scott M, Connor Jason T, Lewis Roger J. The platform trial an efficient strategy for evaluating multiple treatments. *JAMA*. 2015. <https://doi.org/10.1001/jama.2015.2316>.
 169. Das Sonya, Lo Andrew W. Re-inventing drug development: a case study of the I-SPY 2 breast cancer clinical trials program. *Contemp Clin Trials*. 2017;62:168–174. <https://doi.org/10.1016/j.cct.2017.09.002>.
 170. Rugo Hope S, Olopade Olufunmilayo I, DeMichele Angela, et al. Adaptive randomization of veliparib—carboplatin treatment in breast cancer. *New Engl J Med*. jul 2016;375:23–34. <https://doi.org/10.1056/NEJMoa1513749>.
 171. Park John W, Liu Minetta C, Douglas Yee, et al. Adaptive randomization of neratinib in early breast cancer. *New Engl J Med*. jul 2016;375:11–22. <https://doi.org/10.1056/NEJMoa1513750>.
 172. Kaplan Richard, Maughan Timothy, Crook Angela, et al. Evaluating many treatments and biomarkers in oncology: a new design. *J Clin Oncol*. 2013;31:4562–4568. <https://doi.org/10.1200/JCO.2013.50.7905>.
 173. Kaplan Richard. The FOCUS4 design for biomarker stratified trials. *Chin Clin Oncol*. 2015;4:1–10. <https://doi.org/10.3978/j.issn.2304-3865.2015.02.03>.
 174. FOCUS4. Focus4-n protocol: a randomised controlled comparison of capecitabine against active monitoring after first-line treatment for patients with colorectal cancer. http://www.focus4trial.org/media/1470/focus4-n-protocolv40-05apr2018_final-clean.pdf, 2019-05-02.
 175. Adams Richard, Brown Ewan, Brown Louise, et al. Inhibition of EGFR, HER2, and HER3 signalling in patients with colorectal cancer wild-type for BRAF, PIK3CA, KRAS, and NRAS (FOCUS4-D): a phase 2—3 randomised trial. *Lancet Gastroenterol Hepatol*. 2018;3:162–171. <https://doi.org/10.1016/S2468-125330394-1>.
 176. Berry Scott M, Petzold Elizabeth A, Dull Peter, et al. A response adaptive randomization platform trial for efficient evaluation of Ebola virus treatments: a model for pandemic response. *Clin Trials: J Soc Clin Trials*. 2016;13:22–30. <https://doi.org/10.1177/1740774515621721>.
 177. PREVAIL II Writing Group. A randomized, controlled trial of

- zmapp for ebola virus infection. *New Engl J Med*. 2016;375:1448–1456. <https://doi.org/10.1056/NEJMoa1604330>.
178. Dodd Lori E, Proschan Michael A, Neuhaus Jacqueline, et al. Design of a randomized controlled trial for ebola virus disease medical countermeasures: PREVAIL II, the ebola MCM study. *J Infect Dis*. 2016;213:1906–1913. <https://doi.org/10.1093/infdis/jiw061>.
 179. Proschan Michael A, Dodd Lori E, Price Dionne. Statistical considerations for a trial of Ebola virus disease therapeutics. *Clin Trials*. 2016;13:39–48. <https://doi.org/10.1177/1740774515620145>.
 180. Lewis Roger J. The pragmatic clinical trial in a learning health care system. *Clin Trials*. 2016;13:484–492. <https://doi.org/10.1177/1740774516655097>.
 181. Ritchie Craig W, Molinuevo José Luis, Truyen Luc, Satlin Andrew, Van der Geyten Serge, Lovestone Simon. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. *The Lancet Psychiatry*. 2016;3:179–186. <https://doi.org/10.1016/S2215-036600454-X>.
 182. Solomon Alina, Kivipelto Miia, Molinuevo José Luis, Tom Brian, Ritchie Craig W. European prevention of Alzheimer's dementia longitudinal cohort study (EPAD LCS): study protocol. *BMJ Open*. 2018;8:1–12. <https://doi.org/10.1136/bmjopen-2017-021017>.
 183. William Ritchie Craig, Muniz-Terrera G, Kivipelto M, Solomon A, Tom B, Molinuevo JL. The European Prevention of Alzheimer's Dementia (EPAD) longitudinal cohort study: baseline data release v500. 0. *J Prev Alzheimer's Dis*. 2019;1–6.
 184. Bateman Randall J, Benzinger Tammie L, Scott Berry, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model. *Alzheimer's Dement*. 2017;13:8–19. <https://doi.org/10.1016/j.jalz.2016.07.005>.
 185. Alexander Brian M, Ba Sujuan, Berger Mitchel S, et al. Adaptive global innovative learning environment for glioblastoma: GBM AGILE. *Clin Cancer Res*. 2018;24:737–743. <https://doi.org/10.1158/1078-0432.CCR-17-0764>.
 186. Alexander Brian M, Trippa Lorenzo, Gaffey Sarah, et al. Individualized screening trial of innovative glioblastoma therapy (insight): a bayesian adaptive platform trial to develop precision medicines for patients with glioblastoma. *JCO Precision Oncol*. 2019;3:1–13.
 187. Butler Christopher C, Coenen Samuel, Saville Benjamin R, Cook Johanna, van der Velden Alike, Homes Jane. A trial like ALIC 4 E: why design a platform, response-adaptive, open, randomised controlled trial of antivirals for influenza-like illness? *ERJ Open Res*. apr 2018;4. <https://doi.org/10.1183/23120541.00046-2018>, 00046–2018.
 188. Bongard Emily, van der Velden Alike W, Cook Johanna, Saville Ben, Beutels Philippe. Antivirals for influenza-Like Illness? A randomised Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC 4 E): the ALIC 4 E protocol. *BMJ Open*. 2018;8, e021032. <https://doi.org/10.1136/bmjopen-2017-021032>.
 189. Walter Roland B, Michaelis Laura C, Othus Megan, et al. Intergroup LEAP trial (S1612): a randomized phase 2/3 platform trial to test novel therapeutics in medically less fit older adults with acute myeloid leukemia. *Am J Hematol*. 2018;93: E49–E52. <https://doi.org/10.1002/ajh.24980>.
 190. Ventz Steffen, Alexander Brian M, Parmigiani Giovanni, Gelber Richard D, Trippa Lorenzo. Designing clinical trials that accept new arms: an example in metastatic breast cancer. *J Clin Oncol*. 2017;35: 3160–3168. <https://doi.org/10.1200/JCO.2016.70.1169>.
 191. Conley Barbara A, Doroshow James H. Molecular analysis for therapy choice: NCI MATCH. *Semin Oncol*. 2014;41:297–299. <https://doi.org/10.1053/j.seminoncol.2014.05.002>. ISSN 15328708.
 192. Do K, Coyne G O'Sullivan, Chen AP. An overview of the NCI precision medicine trials-NCI MATCH and MPACT. *Chin Clin Oncol*. 2015;4:31. <https://doi.org/10.3978/j.issn.2304-3865.2015.08.01>.
 193. Bando Hideaki, Takebe Naoko. Perspectives on research activity in the USA on cancer precision medicine. *Jpn J Clin Oncol*. 2016;46: 106–110. <https://doi.org/10.1093/jjco/hyv162>.
 194. Moore Kathleen N, Mannel Robert S. Is the NCI MATCH trial a match for gynecologic oncology? *Gynecol Oncol*. 2016;140:161–166. <https://doi.org/10.1016/j.ygyno.2015.11.003>.
 195. Barroilhet Lisa, Matulonis Ursula. The NCI-MATCH trial and precision medicine in gynecologic cancers. *Gynecol Oncol*. 2018;148:585–590. <https://doi.org/10.1016/j.ygyno.2018.01.008>.
 196. Le Tourneau Christophe, Delord Jean Pierre, Goncalves Anthony, et al. 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*. 2015;16: 1324–1334. <https://doi.org/10.1016/S1470-204500188-6>.

197. Lopez-Chavez Ariel, Thomas Anish, Rajan Arun, et al. Molecular profiling and targeted therapy for advanced thoracic malignancies a biomarker-derived, multiarm, multihistology phase ii basket trial. *J Clin Oncol*. 2015;33:1000–1007. <https://doi.org/10.1200/JCO.2014.58.2007>.
198. Middleton G, Crack LR, Popat S, et al. The National Lung Matrix Trial: translating the biology of stratification in advanced non-small-cell lung cancer. *Ann Oncol*. 2015;26:2464–2469. <https://doi.org/10.1093/annonc/mdv394>.
199. Allen Carl E, Laetsch Theodore W, Mody Rajen, et al. Target and agent prioritization for the children's oncology group—national cancer institute pediatric match trial. *J Natl Cancer Inst*. 2017;109:djw274.
200. Schöffski Patrick, Wozniak A, Stacchiotti S, et al. Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European Organization for Research and Treatment of Cancer phase II trial 90101 'CREATE'. *Ann Oncol*. 2017;28:3000–3008. <https://doi.org/10.1093/annonc/mdx527>.
201. Schöffski Patrick, Wozniak Agnieszka, Michael G, et al. The tyrosine kinase inhibitor crizotinib does not have clinically meaningful activity in heavily pre-treated patients with advanced alveolar rhabdomyosarcoma with FOXO rearrangement: European Organisation for Research and Treatment of Cancer phase 2 trial. *Eur J Cancer*. 2018;94:156–167. <https://doi.org/10.1016/j.ejca.2018.02.011>.
202. Schöffski Patrick, Sufliarsky Jozef, Gelderblom Hans, et al. Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prosp. *Lancet Respir Med*. 2018;6:431–441. <https://doi.org/10.1016/S2213-260030116-4>.
203. Péron Julien, Marreaud Sandrine, Staelens Dominiek, et al. A multinational, multi-tumour basket study in very rare cancer types: the European Organization for Research and Treatment of Cancer phase II 90101 "CREATE" trial. *Eur J Cancer*. 2019;109:192–195. Elsevier.
204. Hainsworth John D, Meric-Bernstam Funda, Swanton Charles, et al. Targeted therapy for advanced solid tumors on the basis of molecular profiles: results from mypathway, an open-label, phase IIA multiple basket study. *J Clin Oncol*. 2018;36:536–542. <https://doi.org/10.1200/JCO.2017.75.3780>.
205. Meric-Bernstam Funda, Hurwitz Herbert, Raghu Kanwal Pratap Singh, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, openlabel, phase 2a, multiple basket study. *Lancet Oncol*. 2019;20:518–530. <https://doi.org/10.1016/S1470-204530904-5>.
206. Mangat Pam K, Halabi Susan, Suanna S Bruinooge, et al. Rationale and design of the targeted agent and profiling utilization registry study. *JCO precision Oncol*. 2018;2:1–14. <https://doi.org/10.1200/PO.18.00122>.
207. Simonsen Katy L, Fracasso Paula M, Bernstein Steven H, et al. The Fast Real-time Assessment of Combination Therapies in ImmunOncology (FRACTION) program: innovative, high-throughput clinical screening of immunotherapies. *Eur J Cancer*. 2018;103:259–266. <https://doi.org/10.1016/j.ejca.2018.07.127>.
208. Slosberg Eric D, Kang Barinder P, Peguero Julio, et al. Signature program: a platform of basket trials. *Oncotarget*. 2018;9:21383–21395. <https://doi.org/10.18632/oncotarget.25109>.
209. Thavaneswaran Subotheni, Sebastian Lucille, Ballinger Mandy, et al. Cancer Molecular Screening and Therapeutics (MoST): a framework for multiple, parallel signal-seeking studies of targeted therapies for rare and neglected cancers. *Med J Aust*. oct 2018;209:354–355. <https://doi.org/10.5694/mja18.00227>.
210. Kok Peey-Sei, Beale Philip, O'Connell Rachel L, et al. Paragon (anzgog-0903): a phase 2 study of anastrozole in asymptomatic patients with estrogen and progesterone receptor-positive recurrent ovarian cancer and ca125 progression. *J Gynecol Oncol*. 2019;30.
211. Rossoni Caroline, Bardet Aurélie, Geoerger Birgit, Paoletti Xavier. Sequential or combined designs for phase i/ii clinical trials? a simulation study. *Clin Trials*. 2019;16(6):635–644. SAGE Publications Sage UK: London, England.
212. Beckman RA, Antonijevic Z, Kalamegham R, Chen C. Adaptive design for a confirmatory basket trial in multiple tumor types based on a putative predictive biomarker. *Clin Pharmacol Ther*. 2016;100:617–625. <https://doi.org/10.1002/cpt.446>.
213. Wen Li, Chen Cong, Li Xiaoyun, Robert A, Beckman. Estimation of treatment effect in two-stage confirmatory oncology trials of personalized medicines. *Stat Med*. 2017;36:1843–1861. <https://doi.org/10.1002/sim.7272>.
214. Cunanen Kristen M, Iasonos Alexia, Shen Ronglai, Begg Colin B, Gönen Mithat. An efficient basket trial design. *Stat Med*. 2017;36:1568

- 1579. <https://doi.org/10.1002/sim.7227>.
215. Simon Richard, Geyer Susan, Subramanian Jyothi, Roychowdhury Sameek. The Bayesian basket design for genomic variant-driven phase II trials. *Semin Oncol.* 2016;43:13–18. <https://doi.org/10.1053/j.seminoncol.2016.01.002>.
 216. Xu Yanxun, Müller Peter, Tsimberidou Apostolia M, Berry Donald. A nonparametric Bayesian basket trial design. *Biometrical J.* 2018;(April):1–15. <https://doi.org/10.1002/bimj.201700162>.
 217. Liu Rong, Liu Zheyu, Ghadessi Mercedeh, Vonk Richardus. Increasing the efficiency of oncology basket trials using a Bayesian approach. *Contemp Clin Trials.* 2017;63:67–72. <https://doi.org/10.1016/j.cct.2017.06.009>.
 218. Cunanan Kristen M, Iasonos Alexia, Shen Ronglai, et al. Specifying the true- and false-positive rates in basket trials. *JCO Precision Oncol.* 2017;1–5. <https://doi.org/10.1200/PO.17.00181>.
 219. Berry Scott M, Broglio Kristine R, Groshen Susan, Berry Donald A. Bayesian hierarchical modeling of patient subpopulations: efficient designs of Phase II oncology clinical trials. *Clin Trials.* 2013;10:720–734. <https://doi.org/10.1177/1740774513497539>.
 220. Cunanan Kristen M, Iasonos Alexia, Shen Ronglai, Gönen Mithat. Variance prior specification for a basket trial design using Bayesian hierarchical modeling. *Clin Trials.* 2019;16:142–153. <https://doi.org/10.1177/1740774518812779>.
 221. Chu Yiyi, Yuan Ying. A Bayesian basket trial design using a calibrated Bayesian hierarchical model. *Clin Trials.* 2018;15:149–158. <https://doi.org/10.1177/1740774518755122>.
 222. Neuenschwander Beat, Simon Wandel, Roychoudhury Satrajit, Bailey Stuart. Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharm Stat.* 2016;15:123–134. <https://doi.org/10.1002/pst.1730>.
 223. Hobbs Brian P, Landin Rick. Bayesian basket trial design with exchangeability monitoring. *Stat Med.* 2018;37:3557–3572. <https://doi.org/10.1002/sim.7893>.
 224. Chu Yiyi, Yuan Ying. BLAST: bayesian latent subgroup design for basket trials accounting for patient heterogeneity. *J R Stat Soc Ser C: Appl Stat.* 2018;67:723–740. <https://doi.org/10.1111/rssc.12255>.
 225. Trippa Lorenzo, Michael Alexander Brian. Bayesian baskets: a novel design for biomarker-based clinical trials. *J Clin Oncol.* 2017;35:681–687. <https://doi.org/10.1200/JCO.2016.68.2864>.
 226. Simon Richard. New designs for basket clinical trials in oncology. *J Biopharm Stat.* 2018;28:245–255. <https://doi.org/10.1080/10543406.2017.1372779>.
 227. Ventz Steffen, Barry William T, Parmigiani Giovanni, Trippa Lorenzo. Bayesian response-adaptive designs for basket trials. *Biometrics.* 2017;73:905–915. <https://doi.org/10.1111/biom.12668>.
 228. Psioda Matthew A, Xu Jiawei, Jiang Qi, Ke Chunlei, Zhao Yang, Ibrahim Joseph G. Bayesian adaptive basket trial design using model averaging. *Biostatistics.* 2019: 1–16. <https://doi.org/10.1093/biostatistics/kxz014>.
 229. Zhou Heng, Liu Fang, Wu Cai, Rubin Eric H, Giranda Vincent L, Chen Cong. Optimal two-stage designs for exploratory basket trials. *Contemp Clin Trials.* 2019;85: 105807.
 230. Fujikawa Kei, Teramukai Satoshi, Yokota Isao, Daimon Takashi. A bayesian basket trial design that borrows information across strata based on the similarity between the posterior distributions of the response probability. *Biometrical J.* 2019;62:330–338.
 231. Wen Li, Zhao Jing, Li Xiaoyun, Chen Cong, Beckman Robert A. Multi-stage enrichment and basket trial designs with population selection. *Stat Med.* 2019;38:5470–5485.
 232. Ondra Thomas, Alex Dmitrienko, Tim Friede, et al. Methods for identification and confirmation of targeted subgroups in clinical trials: a systematic review. *J Biopharm Stat.* 2016;26:99–119. <https://doi.org/10.1080/10543406.2015.1092034>.
 233. Ramsey Scott D, Shankaran Veena, Sullivan Sean D. Basket cases: how real-world testing for drugs approved based on basket trials might lead to false diagnoses, patient risks, and squandered resources. *J Clin Oncol.* 2019;37: 3472–3474. <https://doi.org/10.1200/JCO.18.02320>.
 234. Freidlin Boris, Carmen J Allegra, Korn Edward L. Moving molecular profiling to routine clinical practice: a way forward? *J Natl Cancer Inst.* 2019 (corrected proof).
 235. Kaizer Alexander M, Hobbs Brian P, Koopmeiners Joseph S. A multi-source adaptive platform design for testing sequential combinatorial therapeutic strategies. *Biometrics.* 2018;74:1082–1094. <https://doi.org/10.1111/biom.12841>.
 236. Tang Rui, Shen Jing, Yuan Ying. ComPAS: a Bayesian drug combination platform trial design with adaptive shrinkage. *Stat Med.* 2018;1–15. <https://doi.org/10.1002/sim.8026>.
 237. James Normington, Zhu Jiawen, Mattiello Federico, Sarkar Somnath, Carlin Brad. An efficient bayesian platform trial design for borrowing adaptively from historical control data in

- lymphoma. *Contemp Clin Trials*. 2019;105890.
238. Yuan Ying, Guo Beibei, Mark Munsell, Lu Karen, Jazaeri Amir. MIDAS: a practical Bayesian design for platform trials with molecularly targeted agents. *Stat Med*. 2016;35:3892–3906. <https://doi.org/10.1002/sim.6971>.
 239. Ventz Steffen, Cellamare Matteo, Parmigiani Giovanni, Trippa Lorenzo. Adding experimental arms to platform clinical trials: randomization procedures and interim analyses. *Biostatistics*. 2018;19:199–215. <https://doi.org/10.1093/biostatistics/kxx030>.
 240. Viele Kert, Broglio Kristine, Anna McGlothlin, Saville Benjamin R. Comparison of methods for control allocation in multiple arm studies using response adaptive randomization. *Clin Trials*. 2020;17(1):52–60. SAGE Publications Sage UK: London, England.
 241. Hobbs Brian P, Chen Nan, Jack Lee J. Controlled multi-arm platform design using predictive probability. *Stat Methods Med Res*. 2018;27:65–78. <https://doi.org/10.1177/0962280215620696>.
 242. Dmitrienko Alexei, Dauh Wang Ming. Bayesian predictive approach to interim monitoring in clinical trials. *Stat Med*. 2006;25:2178–2195. <https://doi.org/10.1002/sim.2204>.
 243. Saville Benjamin R, Connor Jason T, Ayers Gregory D, Alvarez Joann. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. *Clin Trials: J Soc Clin Trials*. 2014;11:485–493. <https://doi.org/10.1177/1740774514531352>.
 244. Jiao Feiran, Tu Wenda, Jimenez Sara, Crentsil Victor, Chen Yeh-Fong. Utilizing shared internal control arms and historical information in small-sized platform clinical trials. *J Biopharm Stat*. 2019;29:845–859.
 245. Gajewski Byron J, Statland Jeffrey, Barohn Richard. Using adaptive designs to avoid selecting the wrong arms in multiarm comparative effectiveness trials. *Stat Biopharm Res*. 2019;11:375–386. <https://doi.org/10.1080/19466315.2019.1610044>.
 246. Thorlund Kristian, Golchi Shirin, Jonas Haggstrom, Mills Edward. Highly efficient clinical trials simulator (hect): software application for planning and simulating platform adaptive trials. *Gates Open Res*. 2019;3.
 247. Howard Dena R, Brown Julia M, Todd Susan, Gregory Walter M. Recommendations on multiple testing adjustment in multi-arm trials with a shared control group. *Stat Methods Med Res*. 2018;27:1513–1530. <https://doi.org/10.1177/0962280216664759>.
 248. Stallard N, Todd S, Parashar D, Kimani PK, Renfro LA. On the need to adjust for multiplicity in confirmatory clinical trials with master protocols. *Ann Oncol*. 2019;30:506–509. <https://doi.org/10.1093/annonc/mdz038>.
 249. Wason James MS, Stecher Lynne, Mander Adrian P. Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? *Trials*. 2014;15:364. <https://doi.org/10.1186/1745-6215-15-364>.
 250. Gutjahr Georg, Posch Martin, Werner Brannath. Familywise error control in multi-armed response-adaptive two-stage designs. *J Biopharm Stat*. 2011;21:818–830. <https://doi.org/10.1080/10543406.2011.551337>.
 251. Robertson DS, Wason JMS. Familywise error control in multi-armed response-adaptive trials. *Biometrics*. 2019;1–10. <https://doi.org/10.1111/biom.13042>.
 252. Benda Norbert, Brandt Andreas. Regulatory issues with multiplicity in drug approval: principles and controversies in a changing landscape. *J Biopharm Stat*. 2018;28:3–9. <https://doi.org/10.1080/10543406.2017.1378669>.
 253. FDA. Complex innovative trial designs pilot program. <https://www.fda.gov/drugs/development-resources/complexinnovative-trial-designs-pilot-program>, 2019-08-05.
 254. Hlavin Gerald, Lisa V. Hampson, and Franz Koenig. Many-to-one comparisons after safety selection in multi-arm clinical trials. *PLoS ONE*. 2017;12:1–23. <https://doi.org/10.1371/journal.pone.0180131>.
 255. Alex Dmitrienko, Millen Brian, Lipkovich Ilya. Multiplicity considerations in subgroup analysis. *Stat Med*. 2017;36:4446–4454. <https://doi.org/10.1002/sim.7416>.
 256. Alosch Mohamed, Frank Bretz, Huque Mohammad. Advanced multiplicity adjustment methods in clinical trials. *Stat Med*. 2013;33:693–713. <https://doi.org/10.1002/sim.5974>.
 257. Alex Dmitrienko, Ralph B. D'Agostino. Multiplicity considerations in clinical trials. *New Engl J Med*. 2018;378:2115–2122. <https://doi.org/10.1056/nejmra1709701>.
 258. Royston Patrick, Mahesh K, Parmar B, Qian Wendi. Novel designs for multi-arm clinical trials with survival outcomes with an application in ovarian cancer. *Stat Med*. 2003;22:2239–2256. <https://doi.org/10.1002/sim.1430>.
 259. Royston Patrick, Barthel Friederike MS, Parmar Mahesh KB, Choodari-Oskoei Babak, Isham Valerie. Designs for clinical trials with time-to-event outcomes based on stopping guidelines for lack of benefit. *Trials*. 2011;12:1–18. <https://doi.org/10.1186/1745-6215-12-81>.
 260. Bratton Daniel J, Phillips Patrick PJ, Parmar Mahesh KB. A multi-arm multi-stage clinical trial design for binary outcomes with application

- to tuberculosis. *BMC Med Res Methodol.* 2013;13. <https://doi.org/10.1186/1471-2288-13139>.
261. Alexandra Blenkinsop, Mahesh K, Parmar B, Choodari-Oskooei Babak. Assessing the impact of efficacy stopping rules on the error rates under the multi-arm multi-stage framework. *Clin Trials.* 2019;16:132–141. <https://doi.org/10.1177/1740774518823551>.
 262. Graf Alexandra C, Bauer Peter, Glimm Ekkehard, Koenig Franz. Maximum type 1 error rate inflation in multiarmed clinical trials with adaptive interim sample size modifications. *Biometrical J.* 2014;56:614–630. <https://doi.org/10.1002/bimj.201300153>.
 263. Bauer Peter, Kieser Meinhard. Combining different phases in the development of medical treatments within a single trial. *Stat Med.* 1999;18:1833–1848. [https://doi.org/10.1002/\(SICI\)1097-0258\(19990730\)18:14h1833::AIDSIM221i3.0.CO;2-3](https://doi.org/10.1002/(SICI)1097-0258(19990730)18:14h1833::AIDSIM221i3.0.CO;2-3).
 264. Hommel Gerhard. Adaptive modifications of hypotheses after an interim analysis. *Biometrical J.* 2001;43:581–589. <https://doi.org/10.1002/1521-403643:5h581::AID-BIMJ581i3.0.CO;2-J>.
 265. Posch Martin, Koenig Franz, Branson Michael, Werner Brannath, Dunger-Baldauf Cornelia, Bauer Peter. Testing and estimation in flexible group sequential designs with adaptive treatment selection. *Stat Med.* 2005;24:3697–3714. <https://doi.org/10.1002/sim.2389>.
 266. Frank Bretz, Koenig Franz, Werner Brannath, Glimm Ekkehard, Posch Martin. Adaptive designs for confirmatory clinical trials. *Stat Med.* apr 2009;28:1181–1217. <https://doi.org/10.1002/sim.3538>.
 267. Koenig Franz, Werner Brannath, Frank Bretz, Posch Martin. Adaptive Dunnett tests for treatment selection. *Stat Med.* 2008;27:1612–1625. <https://doi.org/10.1002/sim.3048>.
 268. Magirr D, Jaki T, Whitehead J. A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection. *Biometrika.* 2012;99:494–501. <https://doi.org/10.1093/biomet/ass002>.
 269. James Wason, Magirr Dominic, Law Martin, Jaki Thomas. Some recommendations for multi-arm multi-stage trials. *Stat Methods Med Res.* 2012;25:716–727. <https://doi.org/10.1177/0962280212465498>.
 270. Sophie Barthel FM, Parmar MKB, Royston P. How do multi-stage, multi-arm trials compare to the traditional two-arm parallel group design - a reanalysis of 4 trials. *Trials.* 2009;10. <https://doi.org/10.1186/1745-6215-10-21>.
 271. Wason James MS, Jaki Thomas. Optimal design of multi-arm multi-stage trials. *Stat Med.* 2012;31:4269–4279. <https://doi.org/10.1002/sim.5513>.
 272. Bratton Daniel J, Mahesh K, Parmar B, Phillips Patrick PJ, Choodari-Oskooei Babak. Type I error rates of multi-arm multi-stage clinical trials: strong control and impact of intermediate outcomes. *Trials.* 2016;17:1–8. <https://doi.org/10.1186/s13063-016-1382-5>.
 273. Crouch Luis A, Dodd Lori E, Proschan Michael A. Controlling the family-wise error rate in multi-arm, multi-stage trials. *Clin Trials.* 2017;14:237–245. <https://doi.org/10.1177/1740774517694130>.
 274. Magirr D, Stallard N, Jaki T. Flexible sequential designs for multi-arm clinical trials. *Stat Med.* 2014;33:3269–3279. <https://doi.org/10.1002/sim.6183>.
 275. Ghosh Pranab, Liu Lingyun, Senchaudhuri P, Gao Ping, Mehta Cyrus. Design and monitoring of multi-arm multi-stage clinical trials. *Biometrics.* 2017;73:1289–1299. <https://doi.org/10.1111/biom.12687>.
 276. Lin Jianchang, Bunn Veronica. Comparison of multi-arm multi-stage design and adaptive randomization in platform clinical trials. *Contemp Clin Trials.* 2017;54:48–59. <https://doi.org/10.1016/j.cct.2017.01.003>.
 277. Wason James MS, Trippa Lorenzo. A comparison of Bayesian adaptive randomization and multi-stage designs for multi-arm clinical trials. *Stat Med.* 2014;33:2206–2221. <https://doi.org/10.1002/sim.6086>.
 278. Kim May Lee, James Wason, Nigel Stallard. To add or not to add a new treatment arm to a multiarm study: a decision-theoretic framework. *Stat Med.* 2019;1–17. <https://doi.org/10.1002/sim.8194>.
 279. Brueckner Matthias, Titman Andrew, Jaki Thomas, Rojek Amanda, Peter Horby. Performance of different clinical trial designs to evaluate treatments during an epidemic. *PLOS ONE.* 2018;13, e0203387. <https://doi.org/10.1371/journal.pone.0203387>.
 280. Sudhop Thomas, Brun Nikolai Constantin, Riedel Claudia, Rosso Aldana, Broich Karl, Senderovitz Thomas. Master protocols in clinical trials: a universal Swiss Army knife? *The Lancet. Oncology.* 2019;20:e336–e342. <https://doi.org/10.1016/S1470-204530271-2>.
 281. Eichler Hans Georg, Bloechl-Daum Brigitte, Brasseur Daniel, et al. The risks of risk aversion in drug regulation. *Nat Rev Drug Discov.* 2013;12:907–916. <https://doi.org/10.1038/nrd4129>.
 282. Bauer Peter, Franz König. The risks of methodology aversion in drug regulation. *Nat Rev Drug Discov.* 2014;13:317–318. <https://doi.org/10.1038/nrd4319>.
 283. Schiavone Francesca, Bathia Riya, Krishna Letchemanan, et al. This is a platform alteration: a trial management perspective on the operational aspects of adaptive and

- platform and umbrella protocols. *Trials*. dec 2019;20:264. <https://doi.org/10.1186/s13063-019-3216-8>.
284. Cecchini Michael, Rubin Eric H, Blumenthal Gideon M, et al. Challenges with novel clinical trial designs: master protocols. *Clin Cancer Res*. 2019;25:2049–2057. <https://doi.org/10.1158/1078-0432.CCR-18-3544>.
285. Laage Thomas, Loewy John W, Menon Sandeep, et al. Ethical considerations in adaptive design clinical trials. *Ther Innovation Regul Sci*. 2017;51:190–199. <https://doi.org/10.1177/2168479016667766>.
286. Strzebonska Karolina, Waligora Marcin. Umbrella and basket trials in oncology: ethical challenges. *BMC Med Ethics*. 2019;20:58.
287. Klauschen Frederick, Andreeff Michael, Ulrich Keilholz, Dietel Manfred, Albrecht Stenzinger. The combinatorial complexity of cancer precision medicine. *Oncoscience*. 2014;1:504. <https://doi.org/10.18632/oncoscience.66>.
288. Morrell Liz, Hordern Joshua, Brown Louise, et al. Mind the gap? The platform trial as a working environment. *Trials*. 2019;20:297. <https://doi.org/10.1186/s13063-019-3377-5>.
289. Hague Dominic, Townsend Stephen, Masters Lindsey, et al. 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;20:294.
290. Elsässer Amelie, Jan Regnstrom, Vetter Thorsten, et al. Adaptive clinical trial designs for European marketing authorization: a survey of scientific advice letters from the European Medicines Agency. *Trials*. 2014;15:1–10. <https://doi.org/10.1186/1745-6215-15-383>.
291. Collignon Olivier, Koenig Franz, Koch Armin, et al. Adaptive designs in clinical trials: from scientific advice to marketing authorisation to the European Medicine Agency. *Trials*. 2018;19:1–14. <https://doi.org/10.1186/s13063-018-3012-x>.

Address correspondence to: Franz König, Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria. E-mail: franz.koenig@meduniwien.ac.at