Systematic review of basket trials, umbrella trials, and platform trials: A landscape analysis of master protocols

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Abstract

Background: Master protocols, classified as basket trials, umbrella trials, and platform trials, are novel designs that investigate multiple hypotheses through concurrent sub-studies (e.g. multiple treatments or populations, or that allow adding/removing arms during the trial), offering enhanced efficiency and a more ethical approach to trial evaluation. Despite the many advantages of these designs, they are infrequently used. Methods: We conducted a landscape analysis of published master protocols using a systematic literature search to determine what trials have been conducted, with an overall goal of improving literacy in this emerging concept. On July 8th, 2019 English-language studies identified from MEDLINE, EMBASE, and CENTRAL databases and hand-searches of published reviews and registries. Results: We identified 83 master protocols (49 basket, 18 umbrella, 16 platform trials). The number of master protocols has increased rapidly over the last five years. Most have been conducted in the US (n=44/83) and investigated experimental drugs (n=82/83), in the field of oncology (n=76/83). The majority of basket trials were exploratory (i.e. phase I/II; n=47/49) and not randomized (n=44/49), with almost half (n=28/48) only investigating a single intervention. The median sample size of basket trials was 205 participants (Interquartile range, Q3-Q1 IQR: 500-90=410), with a median study duration of 22.3 (IQR: 74.1-42.9=31.1) months. Similar to basket trials, most umbrella trials were exploratory (n=16/18), but use of randomization was more common (n=8/18). The median sample size of umbrella trials was 346 participants (IQR: 565-252=313), with a median study duration of 60.9 (IQR: 81.3-46.9=34.4) months. The median number of interventions investigated in umbrella trials was 5 (IQR: 6-4=2). In platform trials, randomization
(n=15/16) and phase III investigation (n=7/15; one did not report information on phase), with four of them using seamless II/III design, were more common. The median sample size was 892 (IQR: 1835-255=1580), with median study duration of 58.9 (IQR: 101.3-36.9=64.4) months. Conclusions: We anticipate that the number of master protocols will continue to increase at a rapid pace over the upcoming decades. More efforts to improve awareness and training are needed to apply these innovative trial design methods to fields outside of oncology.

Background
Advancements in genomics, particularly in tumour sequencing, have improved our ability to differentiate cancers by their genetic mutations [1]. This has fueled the efforts towards “precision oncology”, where therapies are selected to specifically target cancers based on their genetic mutations. These innovative treatments are commonly referred to as targeted therapies [2]. However, it is unrealistic to investigate the broad spectrum of genetic sub-populations by conventional trial designs. Thus, “master protocol” frameworks have been proposed to provide a means of comprehensively and adaptively evaluating treatments from the field of oncology [3, 4].

The term master protocol refers to a single overarching design developed to evaluate multiple hypotheses, with the general goal of improving efficiency and establishing uniformity through standardization of procedures in the development and evaluation of different interventions [5, 6]. Under a common infrastructure, the master protocol may be differentiated into multiple parallel sub-studies to include standardized trial operational structures, patient recruitment and selection, data collection, analysis, and management [3-6].
Master protocols are often classified into ‘basket trials’, ‘umbrella trials’, and ‘platform trials’ [3-6]. Basket trials refer to designs where a targeted therapy is evaluated on multiple diseases that share common molecular alternations. Umbrella trials, on the other hand, evaluate multiple targeted therapies for a single disease that is stratified into subgroups by molecular alternation. Basket trials and umbrella trials employ a molecular screening protocol that allows for either recruitment of different diseases with the common molecular alteration(s), or that differentiates the single disease into different molecular subtypes. Platform trials, also referred to as multi-arm, multi-stage (MAMS) design trials [7-10], are trials that evaluate several interventions against a common control group and can be perpetual [3, 5, 11, 12]. This design has pre-specified adaptation rules to allow for dropping of ineffective intervention(s) and flexibility of adding new intervention(s) during the trial [3, 5, 11, 12].

Master protocols may be tailored and adapted to suit the research objectives of multiple clinical indications, but master protocols have not been well established in fields outside of oncology [4, 13]. There may be missed opportunities in research fields outside of oncology. Thus, an improved understanding and awareness of these research designs is important for the research community. Methodological summaries of master protocols to date have not been comprehensive, with a cursory review of the literature returning no systematic literature reviews. We conducted this comprehensive systematic literature review as a landscape analysis of master protocols, with the intent of improving literacy in this emerging field.

Methods

This systematic literature review was designed in accordance with the Preferred
Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [14].

**Data Sources and Searches**

Systematic searches were conducted on July 8th, 2019 in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. As no validated literature search strategy has been published, our strategies were developed based on a review of key papers, including the Draft Guidance of the United States Food and Drug Administration [FDA] [3-6, 15]. To improve the sensitivity of our search, we complemented the search terms on ‘master protocols’, ‘basket trials’, ‘umbrella trials’, and ‘platform trials’ with several search terms specific to ‘adaptive trial designs’. The search strategies for each database are presented in Appendix Tables 1-3. We supplemented our database searches with a review of bibliographies from included publications. In addition, we searched trial registries (Clinicaltrials.gov and ISRCTN registry) for registered master protocols. Search terms used for ClinicalTrials.gov are reported in Appendix Table 4. The list of published reviews related to master protocols that we reviewed are provided in Appendix Table 5.

**Study inclusion and exclusion criteria**

Complete study eligibility is described in Table 1. In brief, we included peer-reviewed publications, conference abstracts, and clinical registry records reporting on master protocols (basket trials, umbrella trials, and platform trials) that have been proposed, are ongoing, or already have been conducted. We defined ‘basket trials’ as any prospective clinical trials that investigated the utility (e.g. effectiveness, dosage, safety) of intervention(s) in a study population of multiple diseases with common predictive biomarkers and/or other common predictive patient characteristics that can be used to predict whether a patient will respond to a specific intervention, as the unifying eligibility criteria. We defined ‘umbrella
trials’ as any prospective clinical trials that investigated the utility of targeted interventions based on predictive biomarkers and/or other patient characteristics. In umbrella trials, the single disease population (e.g. single histology cancer) is stratified into multiple subgroups on predictive biomarkers and/or other characteristics. We defined ‘platform trials’ as any clinical trials that allowed for the intervention arm(s) to be dropped and the flexibility of introducing new intervention(s) during the trial. Graphical displays of basket trials, umbrella trials, and platform trials are provided in Figure 1. We excluded non-English language studies.

Two reviewers (JJHP and MJZ) independently reviewed all abstracts and proceedings identified in the literature searches. The full text publications of potentially relevant abstracts were then retrieved and assessed for eligibility. Two reviewers also screened the bibliographies of published literature reviews on master protocols (JJHP and ES) and trial registries (JJHP and LD). Discrepancies in study selection were resolved by discussion or, when necessary, by a third investigator (KT or EJM).

**Data Extraction**

Study design elements, patient characteristics, and outcomes were extracted independently by two investigators (JJHP and ES) using a standardized, piloted data extraction form. We recorded information on trial registry, trial recruitment status, phase, randomization, masking, number of clinical centers, sample size, trial duration, interventions and control, disease area, age of population, number of conventional diseases recruited, key eligibility for stratification, number of subgroups defined, and geographic location of the master protocols. Discrepancies were resolved by discussion.

**Data Synthesis**
A meta-analysis was not conducted for this study, and we present the findings of this landscape analysis descriptively. Organized by each classification (basket trials, umbrella trials, and platform trials), we report on temporal trends of master protocols, geographical representation, and trial and disease characteristics of each master protocol.

**Role of the Funding Source**

This study was not funded.

**Results**

**Literature search**

The study selection process is presented in Appendix Figure 1. We identified 5869 abstracts from our database searches, with an additional 140 records identified through hand-searches of bibliographies and trial registries. Of these, 639 records were selected for full-text review. In total, 214 publications describing 83 trials met our inclusion criteria. Thirty-four trials were only available through trial registries, with three trials in the pre-recruitment phase (NCT03339843, NCT03915678, and NCT03872427). A complete list of trials, with corresponding citations, is provided in Appendix Tables 6-8. In summary, we identified 49 basket trials, 18 umbrella trials, and 16 platform trials.

**Trends of master protocols**

There has been a rapid increase in the number of master protocols published in the last five years (Figure 2). From our literature search, we identified nine completed and published master protocol trials, including results. The Imatinib Target Exploration Consortium Study B2225 [16, 17], a basket trial, was the first master protocol to be conducted in 2001. This was followed by the platform trial STAMPEDE,
that was first proposed in 2005 [8, 9, 18-28]. We identified 68 ongoing master protocols (39 basket trials, 17 umbrella trials, and 12 platform trials) recruiting patients; of these, 11 basket trials [29-38], eight umbrella trials [39-46], and four platform trials [24, 47-50] have published results (Appendix Table 10).

At the time of writing (August 1st, 2019), one platform trial (LEAP; NCT03092674) is currently suspended for an unscheduled safety data review [51]. EBOLA (NCT02380625), a platform trial supported by the Bill and Melinda Gates Foundation in response to the 2014 West Africa Ebola outbreak, has been terminated, as it could not be launched in time in response to the outbreak [52].

**Trial characteristics of master protocols**

Trial characteristics of the master protocols are presented in Appendix Table 9, and the sample size distribution of these master protocols displayed as box plots is provided in Figure 3.

The majority of master protocols were basket designs, with 49 identified in the current review. Among basket trials, all except for one trial involved a drug investigation (n = 48/49); NCT03003195 was the exception as a proposed vaccine basket trial. The majority of basket trials were exploratory (i.e. phase I or phase II; n = 47/49) and were not blinded, including of their outcome assessors (i.e. open-label; n = 46/49); almost half of the included basket trials only investigated a single intervention arm (n = 28/48; one did not report information on the number of interventions), with the majority not involving a control group or randomization (n = 44/49). The median sample size of basket trials was 205 participants (Interquartile range, Q3-Q1 [IQR]: 500-90=410), with a median study duration of 22.3 (IQR: 74.1-42.9=31.1) months. ALCHEMIST (NCT02193282; NCT02595944; NCT02201992) and CLUSTER (NCT02059291) [57-59] were the only phase III basket trials, which were
comprised of three interventions arms and were of an open-label design.

Eighteen umbrella trials were identified. All umbrella trials investigated experimental drugs, with eight out of the 18 trials having used randomization to assign patients into different arms. The median sample size of umbrella trials was 346 participants (IQR: 565-252=313), with a median study duration of 60.9 (IQR: 81.3-46.9=34.4) months. The median number of interventions investigated in umbrella trials was 5 (IQR: 6-4=2). Similar to basket trials, the majority of umbrella trials were also exploratory (n = 16/18;) and open-label (n = 16/17; one did not report information on blinding).

Our review returned 16 platform trials. All of the platform trials involved investigation of experimental drugs. The median sample size was 892 (IQR: 1835-255=1580), with median study duration of 58.9 (IQR: 101.3-36.9=64.4) months. Nearly all platform trials were of open-label design (n = 12/14; two trials did not report information on blinding), similar to basket and umbrella trials. In contrast to basket and umbrella trials, however, phase III investigation was more common among platform trials (n = 7/15; one did not report information on phase); four of these 7 platform trials were seamless II/III trials. In the majority of platform trials, patients were assigned by randomization (n = 15/16). PRISM (NCT03527147) was the only non-randomized platform trial, though this is currently a phase I study. However, the trial registry of PRISM indicates that future arms may be added. In STAMPEDE [8, 9, 18-28] and I-SPY2 [49, 50, 53, 60-64], several agents have graduated from the phase II evaluation with seamless transitions into phase III evaluations. The phase III evaluation for the I-SPY program is called I-SPY3.

**Disease characteristics of master protocols**

The patient and disease characteristics of master protocols are provided in
Appendix Table 10. Most studies were in adult populations (n = 69/83), with nearly all in the field of oncology (n = 76/83). No umbrella trials were conducted outside of oncology. Notably, two basket trials were conducted for other clinical indications, namely hereditary periodic fevers (CLUSTER; NCT02059291) [57-59] and complement-mediated disorders (TNT0009 Basket trial). Additionally, five platform trials have been designed for influenza (ALIC4E; ISRCTN27908921) [65], Ebola (EBOLA) [52], pneumonia (REMAP-CAP; NCT02735707), pre-operative surgery (UPMC REMAP; NCT03861767) and Alzheimer’s disease (The DIAN-TU platform; NCT01760005) [48].

**Geographic representation of master protocols**

The information on the geographical representation of the current master protocols are provided in Appendix Table 11. The majority of current master protocols have taken place in the United States (n = 44/83) (Figure 4). Other high-income countries such as the UK (n = 25), France (n = 23), Spain (n = 17), and Canada (n = 13) were the next most common countries. There were no master protocols observed from low-income countries, though the EBOLA (NCT02380625) trial had been proposed for Guinea, Sierra Leone, and Liberia [52]. Two upper-middle-income countries, Brazil and Mexico, were involved in the DIAN-TU platform trial (NCT01760005), but these countries only accounted for three of 36 study sites [48]. China, an upper-middle income country, has centres participating in FUTURE (NCT03805399), GBM AGILE [47, 53, 54], TRUMP (NCT03574402), and VE-BASKET (NCT01524978) [55, 56] trials, but it should be noted that in China only accounts for a minority of study sites in GBM AGILE and VE-BASKET.

**Discussion**
To our knowledge, this is the first landscape analysis of master protocols. This was achieved through a methodologically robust and rigorous systematic literature review, that included queries of medical literature databases, reference lists of included studies, and clinical trial registries. Unlike previous publications on master protocols that have been limited in scope to select only specific studies, this review catalogues all master protocols that have been conducted and/or proposed to date. Of the 83 master protocols (49 basket trials, 18 umbrella trials, and 16 platform trials), the majority have involved investigation of experimental drugs in adult patients for the field of oncology.

Our study may have been limited by variability of terminology and lack of standardized nomenclatures and indexing of master protocols in the medical databases. However, we believe this was offset by our rigorous approach of database that was complemented by our strong supplemental searching strategy. We first reviewed the key papers on master protocols to gain an overview of the existing literature [3-6, 15] before coming up with our search strategy (we recommend the readers of this manuscript to review these key publications). Then developed search terms were complemented by hand-searches of bibliographies of 52 published reviews that we found before and during the screening process (Appendix Table 5) and international trial registries.

We have identified several directions for future research. An improved approach to standardized nomenclature and database indexing is essential to improve the identification and retrieval of these study designs. Moreover, efforts are needed to improve the awareness and technical expertise [3-6, 15] in master protocols to investigators in fields outside of oncology and in geographic regions outside of high-income countries (e.g. United States). Platform trials are, by nature, potentially
perpetual, and permit research questions to evolve over time in the context of new information [11, 12]. Basket trials and umbrella trials have had considerable emphasis and dependencies on the accuracy of genomic biomarkers used to characterize cancers, in addition to their histology and location [5], but it is important to point out that other baseline patient characteristics may be used to determine the intervention strategies. Thus, an emphasis on the study of how genomic screening tests impact the operational characteristics of these biomarker trials is warranted. Comparing different nomenclatures used in published trials and reviews may also be warranted in order to come up with a consensus on master protocols.

Conclusion

This is the first systematic review-based bibliometric analysis of master protocols. The number of master protocols, especially in the last five years, has increased dramatically and we anticipate that this trend will continue over the coming years. Master protocols, particularly platform trials, have the potential to improve both the efficiency across the broad spectrum of clinical trial research. This study has been done at an opportunistic time, as the United States FDA recently released draft guidance on master protocols in September 2018 [15]. We anticipate that this landscape analysis may be useful for regulatory agencies as well as clinical investigators and readers who are looking to broaden their expertise into this emerging field.

List of Abbreviations

FDA: Food and Drug Administration
Declarations

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and material**

All data generated or analysed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests

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This study was not funded.

**Authors’ contributions**

JJHP conceptualised and designed the study. JJHP, ES, MJZ, and LD acquired the data. JJHP, ES, MJZ, LD, OH, JS, RTL, KT and EJM analyzed and interpreted the data. JJHP, ES, MJZ, LD, and OH drafted the manuscript. All authors critically revised the manuscript for important intellectual content. KT and EJM obtained funding. JS, RTL, KT, and EJM provided administrative, technical, or material support. JS, RTL, KT, and EJM supervised the study. All authors read and approved the final manuscript.

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Table 1. PICOS criteria

| Category     | Inclusion criteria                                                                                       |
|--------------|---------------------------------------------------------------------------------------------------------|
| Population   | Humans                                                                                                  |
| Interventions| No restrictions                                                                                        |
| Comparator   | No restrictions                                                                                        |
| Outcomes     | No restrictions                                                                                        |
| Study design | Master protocols defined as a comprehensive single protocol that allows for evaluation of multiple hypotheses, with the goal of improving efficiency and/or establishing standardization of research study procedures. They included but were not limited to: - Basket trials - Umbrella trials - Platform trials |
| Other        | Peer-reviewed publications and conference abstracts with results or published protocols in the English language |

‘Basket trials’ were defined as any prospective clinical trials that tested the utility (e.g. effectiveness, dosage, safety) of intervention(s) in a study population of multiple diseases with common predictive biomarkers and/or other common predictive patient characteristics that can be used to predict whether a patient will respond to a specific intervention as the unifying eligibility criteria.

‘Umbrella trials’ were defined as any prospective clinical trials that tested the utility of targeted interventions based on predictive biomarkers and/or other patient characteristics; in umbrella trials, the single disease study population is stratified into multiple subgroups on predictive biomarkers and/or other characteristics.

‘Platform trials’ were defined as any clinical trials that allowed for the intervention arm(s) to be dropped and the flexibility of introducing new intervention(s) during
the trial. Platform trials are sometimes referred to as multi-arm, multi-stage (MAMS) designs, but the MAMS designs that do not allow for flexibility of adding new arms during the trial are not truly platform trials.

Additional Files

Additional file 1
File name: BMC Trials - Appendix – v2.0.docx
Title of data: Supplementary Appendix
Description of data: Supplementary to “Systematic review of basket trials, umbrella trials, and platform trials: A landscape analysis of master protocols”

Additional file 2
File name: BMC Trials – EQUATOR checklist – v2.0.docx
Title of data: EQUATOR Checklist
Description of data: EQUATOR Checklist for “Systematic review of basket trials, umbrella trials, and platform trials: A landscape analysis of master protocols”

Figures
Figure 1

Graphical representation of basket trials, umbrella trials, and platform trials. This
Figure 2

Trends of master protocols over time. This figure illustrates the accumulating number of basket (white), umbrella (grey), and platform (black) trials over time.
Figure 3

Sample size distribution of master protocols Acronym: IQR – interquartile range T
Geographical representation of master protocols. This figure illustrates the accumulating number of basket (white), umbrella (grey), and platform (black) trials over time.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

Master protocol SLR - EQUATOR checklist - v2.0.pdf
Master protocol SLR - Appendix - v2.0.pdf