

Challenges and approaches to implementing master/basket trials in oncology

Amy Burd,¹ Richard L. Schilsky,² John C. Byrd,^{1,3} Ross L. Levine,⁴ Vassiliki A. Papadimitrakopoulou,⁵ Roy S. Herbst,^{6,7} Mary W. Redman,⁸ Brian J. Druker,⁹ and David R. Gandara¹⁰

¹The Leukemia & Lymphoma Society, Rye Brook, NY; ²American Society of Clinical Oncology, Alexandria, VA; ³The Ohio State University Comprehensive Cancer Center, Columbus, OH; ⁴Memorial Sloan Kettering Cancer Center, New York, NY; ⁵The University of Texas MD Anderson Cancer Center, Houston, TX; ⁶Yale Cancer Center, New Haven, CT; ⁷Smilow Cancer Hospital, New Haven, CT; ⁸Fred Hutchinson Cancer Research Center, Seattle, WA; ⁹Knight Cancer Institute, Oregon Health and Science University, Portland, OR; and ¹⁰UC Davis Comprehensive Cancer Center, Sacramento, CA

Key Points

- Solid tumor/hematologic malignancy studies show that precision medicine trials with many treatment options can be nationally conducted.
- Recommended best practices show a common thread of fundamental principles to consider when creating and starting a master trial approach.

The appetite for cutting-edge cancer research, across medical institutions, scientific researchers, and health care providers, is increasing based on the promise of true breakthroughs and cures with new therapeutics available for investigation. At the same time, the barriers for advancing clinical research are impacting how quickly drug development efforts are conducted. For example, we know now that under a microscope, patients with the same type of cancer and histology might look the same; however, the reality is that most cancers are driven by genomic, transcriptional, and epigenetic changes that make each patient unique. Additionally, the immunologic reaction to different tumor types is distinct among patients. The challenge for researchers developing new therapies today is vastly different than it was in the era of cytotoxics. Today, we must identify a sufficient number of patients harboring a rare mutation or other characteristic and match this to the right therapeutic option. This summary provides a guide to help inform the scientific cancer community about the benefits and challenges of conducting umbrella or basket trials (master trials), and to create a roadmap to help make this new and evolving form of clinical trial design as effective as possible.

Introduction

New discoveries are driving the need for new approaches

Continued advances in our understanding of cancer biology have led to a new era of targeted and immune-based therapies based on mechanistic insight. The challenge for investigators focused on developing new therapies in the current era is vastly different from past eras. Today, the focus is “R³”: getting the right therapy to the right patient at the right time. In the current era of precision medicine and matching the best therapy to each patient, patients are grouped into subtypes based on specific mutations or other characteristics, often representing 10% or less of patients with any given type of cancer or of cancers more broadly. Innovation is driving us to look at cancer therapies in new ways, for example, using molecular aberrations rather than site of tumor origin as the basis for therapy selection. These advances, and our constantly expanding appreciation of the molecular basis of cancer, mandate innovative ways of evaluating efficacy in clinical trials. These must be accompanied by measurable outcomes, with a goal of delivering meaningful clinical benefit to patients rather than small incremental gains, and accelerating approval of drugs. This summary provides a guide to help inform the scientific cancer community about the benefits and challenges of conducting umbrella or basket trials (master trials), and to create a roadmap to help make this new and evolving form of clinical trial design as effective as possible.

New design models

This evolution of clinical trial design has resulted in multiple new trial concepts such as “umbrella or basket trials (master trials).”¹⁻⁹ In both cases, patients are assigned treatment based on a genetic mutation or other molecular, cellular, or immune marker. The concept of master trials is predicated on the notion that improving the efficiency of genomic screening will accelerate drug development and evaluation. This is achieved by providing the necessary infrastructure that allows for the flexibility to remove ineffective drugs or add new therapeutics based on efficacy or futility. The speed of clinical development is also enhanced by looking for “large effects” in a small patient population, thus providing the potential approval of new therapeutics in a defined molecular group more quickly than a traditional trial.¹⁻⁹ This acceleration in timelines is most evident with the signature trial, a phase 2 basket trial sponsored by Novartis that reported a median startup time of 3.6 weeks for a clinical site, compared with 10.4 months for a traditional trial. This rapid startup time led to accelerated accrual times that allowed 13 cohorts to reach target accrual for futility in 9.1 months.¹⁰

Beyond the efficiencies and acceleration of time, the real advantage of using a master trial design is the “funnel” effect of the screening approach, in which providing multiple treatment options can increase the number of patients able to participate in clinical trials and increase the “fit” between specific patients and proposed trial options.

With the promise of delivering therapies with meaningful clinical benefit for a defined molecular group and improving the overall efficiency of centralizing data collection, data analysis, and long-term follow up, in general, master trial protocols are more difficult to initiate. With many drugs moving in and out of master trials on an ongoing basis, the trials are never really complete, therefore, the trial platforms must be both flexible and enduring, with potential to add new treatments and approaches over time. Additionally, the modular structure is quite complex and both trial designs require unprecedented cooperation and participation of regulatory agencies, multiple pharmaceutical companies, genomic test providers, academic investigators, and clinical sites. In short, the infrastructure required to operationalize both umbrella and basket trials requires a willingness and an approach that can create a bridge across all of the multiple stakeholders of both solid tumor and hematologic malignancy trials.

Study design

Experience from ongoing genomic studies

There are several master protocols, including the Targeted Agent and Profiling Utilization Registration (TAPUR) Study,¹¹ Lung Cancer Master Protocol (Lung-MAP),^{12,13} National Cancer Institute Molecular Analysis for Therapy Choice (NCI MATCH),¹⁴ and Beat acute myeloid leukemia (AML; Beat AML),¹⁵ which demonstrated on a national scale that trials based on genomic profiling to make a treatment decision are feasible. From the operational success of the different studies, there are key early learning points that can aid future trials pursuing similar strategies. In some, but not all, of these studies, there is prioritization of dominant mutations (high variant allele frequency) that establishes a founder clone that is targetable with a specific therapeutic. When >1 targetable dominant clone is present, prioritization based upon curative potential would generally

be used. The science of such selection likely will be individualized to the specific study design. Integration of immune, cytogenetic, or biochemical markers would also be individually prioritized based upon the biology of the specific disease or target investigated.

NCI Match trial. The objective of the NCI Match Trial is to determine whether matching certain targeted therapeutic agents as monotherapy or in combination in adults whose tumors have specific mutational or gene abnormalities will effectively treat their cancer, regardless of the cancer type. This is a signal-finding trial where treatments that show promise can advance to larger, more definitive trials. As of November 2018, the trial had enrolled over 6000 patients from 1100 participating clinical sites with 40 treatment options. The challenge with any study of this type is that not all patients have a tumor with an abnormality that matches a drug on the study¹⁰ (www.ecog-acrin.org/nci-match-eay131). Patients not having a matching mutation are not allowed to participate in 1 of the treatment arms.

TAPUR trial. Sponsored by the American Society of Clinical Oncology (ASCO), the TAPUR study is a nonrandomized prospective study initiated in March 2016 to assess the antitumor activity and toxicity of commercially available, targeted anticancer drugs prescribed for treatment of patients with advanced solid tumors, B-cell non-Hodgkin lymphoma (NHL), or multiple myeloma, with a genomic variant known to be a drug target or to predict sensitivity to a drug. A secondary goal of the trial is to educate oncologists about implementation of precision medicine in clinical practice. As of August 2018, >1000 patients have enrolled in the study at >100 participating sites in 20 states. A total of 17 drugs yielding 15 different targeted treatment options are available from 7 pharmaceutical companies. A description of the rationale and design of the TAPUR study has been published⁷ and the status of completed or expanded cohorts can be found online (www.tapur.org).

Lung-MAP trial. Lung-MAP is a public-private partnership of the NCI (with Southwest Oncology Group [SWOG] as the coordinating group for the National Clinical Trials Network [NCTN]), the Foundation for the National Institutes of Health (FNIH), and The Friends of Cancer Research (FOCR), working together with pharmaceutical and biomarker collaborators in a disease-specific master trial. The US Food and Drug Administration (FDA) is a counseling collaborator. Lung-MAP uses an umbrella-design master protocol using genomic testing by next-generation sequencing (NGS) to screen advanced non-small cell lung cancer (NSCLC) patients for specific molecular targets. Through a series of substudies, patients are then matched to investigational targeted therapies. Patients without a genotypic match are eligible for substudies investigating the efficacy of checkpoint immunotherapy. Since activation in 2014, Lung-MAP has undergone evolution in order to address ongoing rapid changes to the therapeutic landscape in lung cancer. Although originally designed for previously treated advanced squamous cell lung cancer, subsequent amendments allowed inclusion of all NSCLC histologies. A new “immunotherapy relapsed-refractory” component has been added, and a multifaceted statistical approach to achieving FDA approval of new agents has been initiated. As of June 2018, over 1700 patients have been accrued to the screening component. Nine substudies have activated; the original 5 are completed/closed and 4 are currently accruing. Completed studies evaluated tasisib for

phosphoinositide 3-kinase mutations, palbociclib for cell-cycle gene alterations, AZD4547 for fibroblast growth factor receptor alterations, rilotumumab and erlotinib for c-MET⁺ tumors, and durvalumab. The results to date demonstrate the feasibility of the Lung-MAP trial platform and the ability to simultaneously accrue and evaluate therapies in rare prevalence patient populations. Lung-MAP is a dynamic centralized platform that is well positioned to efficiently test novel therapeutics in advanced NSCLC. A series of new genotype-based and immunotherapeutic studies is under development under the auspices of this unique public-private partnership^{8,9} (<http://www.lung-map.org/>).

Beat AML master trial. The Beat AML master clinical trial, driven by a patient-focused voluntary health agency (The Leukemia & Lymphoma Society [LLS]), is a multiuniversity/disease organization collaborative clinical trial testing several novel targeted therapies for patients with AML, one of the deadliest blood cancers and the most commonly diagnosed form of leukemia in adults. AML is a heterogeneous disease with mutational heterogeneity and different genetic subtypes, making it difficult to develop treatments that work for AML patients regardless of genotype. The focus of new drug studies in AML, including in this trial, is in the development of new therapies for frontline treatment of AML. In AML patients with relapsed/progressive disease, there is extensive genetic and epigenetic evolution, making successful treatment more difficult and clinical trials less likely to demonstrate efficacy. Thus, treatment earlier in the disease course, when the disease is less biologically complex, when patients have not experienced side effects from intensive therapy, and when the AML patient's immune system is less compromised offers a chance for a better outcome. The study uses integrated analysis of metaphase cytogenetics and NGS to identify somatic alterations that contribute to AML pathogenesis and therapeutic response. Ultimately, this trial is patient-centric, as treatment decisions are focused on the best therapeutic option for the patient, even if that is outside of the Beat AML trial. Since launch in November 2016, >500 patients have been enrolled at 16 clinical sites to the overall study. The trial continues to expand with more clinical sites and substudies. The study is also planning to initiate novel-novel combination studies in specific genomic subtypes¹⁵ (<https://www.lls.org/beat-aml>).

Administrating and operating these new trial models

This new clinical trial paradigm requires new approaches to trial administration and oversight. Until recently, cancer clinical trials were designed to test 1 treatment of 1 type of cancer at a single or multiple institution(s). The governance and oversight with respect to scientific merit and protection of patients' rights has been the responsibility of local institutional review boards and scientific review committees. This approach is not optimal for master trials as it would result in administrative redundancies across multiple trial sites and arms and does not allow for allow rapid amendments to facilitate adaptive decisions. New cancer therapeutics with novel mechanisms of action challenge the traditional ways of running clinical trials, scientifically and clinically as well as operationally. Clinical and operational complexities are further magnified when trials are organized around "master" trial programs. More than ever before, such programs require operational nimbleness, access to data in near real time, and the ability to quickly evaluate patient responses.



Figure 1. Example of stakeholders required to conduct a master trial.

Roadmap for master trials

Master trials are complex trials that require multiple stakeholders to work together toward a common goal. From the 4 studies described earlier in this section, it has been demonstrated that a master trial can be done in an oncology disease setting on a national level. Collectively, from each study, there is a general "roadmap" with key elements that should be considered when establishing such a trial moving forward.

Governance and decision-making

Master trials require key stakeholders such as the FDA, pharmaceutical/biotechnology companies, genomic test providers, and a clinical research organization (CRO) or other group that manages day-to-day operations of the trial, clinical sites, and investigators to ensure all collaboratively work together (Figure 1). Although this is no small feat, the trial sponsor is usually a group such as a stable and well-established patient advocacy organization or a government-funded cooperative group that has the ability to align key stakeholders. Examples include FOCCR working closely with SWOG for the Lung-MAP study or the LLS coordinating the Beat AML master clinical trial.

As with any clinical trial, there are multiple decisions that must be made at essentially every level. In general, the decisions can be broken down into 2 categories: general oversight for the entire trial and treatment decisions for individual patients and/or treatment arms within a trial. In either case, a governance and decision-making group that can provide the general oversight required to conduct a trial needs to be established. There are several ways to ensure appropriate governance of a master trial. For example, in the Lung-MAP study, the trial is conducted as a SWOG study and adheres to their decision-making system. This includes a well-demarcated written approach of how patients will be assigned centrally with multiple committees providing necessary oversight. The principal investigator of the study or his or her proxy addresses questions related to initial enrollment, and once a patient is assigned to a particular trial, the subinvestigator assumes responsibility for subsequent events postenrollment.

In contrast, for the TAPUR study, there is a governance group convened by ASCO that manages study operations. A molecular tumor board was developed that can be solicited for advice on treatment decisions. Ultimately, treatment decisions are at the discretion of the physician but within the context of protocol-specified procedures and data collection requirements.

The Beat AML study has a senior advisory group of principals who work with the LLS to provide overarching guidance on the study. All treatment decisions are made centrally after receipt of pathology reports, genomic testing, and cytogenetic results. For this study, the disease treatment assignment depends on the presence or absence of a treatable translocation or mutation, variant allele frequency of specific mutation(s), and priority of the target. In some treatment arms, there is an option to receive standard chemotherapy with a targeted agent, whereas those patients who are not appropriate for chemotherapy receive targeted therapy alone. The LLS study and the Lung-MAP study also include a “marker negative” arm so that all patients can receive therapy if they enroll in the trial regardless of whether there is a genotype-specific therapy available.

Protocol design

Protocols are usually designed not only with the key objective of either signal finding (measured as response to therapy as a surrogate end point of benefit) or drug registration, but also with flexibility and adaptation to changes in the therapeutic landscape. The master protocol infrastructure and autonomy of each substudy facilitates the opening and closing of new substudies quickly and makes them self-sustaining. Additionally, offering both a marker-directed and marker-negative substudy is attractive to both physicians and patients such that every patient, regardless of genotype can be provided with a therapeutic option. In all cases, careful consideration must be given to designing and analyzing the various cohorts with an eye toward making rapid decisions about the utility of specific agents in each substudy. Newer statistical designs for these protocols are emerging to use the statistical efficiency of having a common control arm across multiple studies; however, this may compromise implementation, particularly if equipoise is not sustained when early evidence of efficacy of a specific targeted drug emerges during the course of the study. Although randomization provides the most definitive comparison, the requirement of large numbers of patients is limiting for rare diseases. An alternative option is to use historical data for comparison, with care to match patient study characteristics

including clinical and molecular parameters. Significant guidance on randomized design for master trials has come forth from several teams that can be considered for larger patient groups or where therapy available has efficacy that would be difficult to distinguish from a control population without a randomized design. Additionally, sites opening specific trials over a varied period of time have the potential to bias enrollment to a general population and may require statistical assessment to assure outcome and/or toxicity is not specific to sites with different early or late trial activation.

Design, specificity of end points, and eligibility

Disease- or target-specific master trials generally will have designs that are not only unique but also in common. In most, the end point will be a surrogate one such as response, although randomized trials in diseases with poor outcome can also include progression-free survival or survival. These end points may also be applicable to therapeutic targets whose inhibition mediate disease stabilization over time as well. Most trials with precision medicine-directed therapies look for big differences in response over what is expected for standard therapy and hence have small sample sizes that leave for possibility of missing an active therapeutic that could be beneficial. To enable completion in a realistic time, this has to occur for uncommon cancers, whereas for common solid tumors, larger sample sizes can be included to avoid false-positive and -negative results. To assure optimal access of patients enrolling in master trials, eligibility criteria should follow FDA guidelines to better approximate the real-world patient who will receive the treatment. Although exclusion criteria may be required for specific agents in substudies, these should generally be minimized if possible and alternative options or registries should be available for patients not going on such trials to assure lack of bias in the patient enrollment population.

Screening platform

Although the majority of trials have used a NGS approach as the primary platform to screen for multiple genes and stratify patients, the concept can be broadly applied to any biomarker assay including epigenomic tests, gene-expression profiles, and/or proteomic signatures. Regardless of the technology, the aim is to screen a large number of patients in a consistent, expedient manner that allows rapid treatment assignment. Once the profiling strategy has been determined, there are 2 challenges. The first is to ensure the quality, timeliness, and agility of the technology platform. Investigational device exemption determination is based on a risk-stratification approach. A sponsor must be prepared to demonstrate that the risks to human subjects in the proposed protocol are outweighed by the anticipated benefits, that there is potential knowledge to be gained, and whether the investigation is scientifically sound. The investigational device exemption submission will be dependent on the patient population, study design, and the risks, for example, the clinical ramifications of a “false-positive” or a “false-negative” result for therapy selection and patient outcome. This is particularly challenging for targeted agents that have little to no activity in patients who do not have the drug-sensitizing biomarker (eg, kinase inhibitor for patients without the intended mutational target). In this case, assignment of a patient to a specific targeted therapy could result in patient harm if the assay results in a false-positive for a drug-sensitizing lesion. The type and level of risk would need to be determined in consultation with the

institutional review board (IRB) of jurisdiction and the FDA to accurately define the risk potential.

The second challenge is creating the guidelines that govern the treatment decisions. These guidelines should be data driven and must be established at the beginning of the study with revisions based only on new trial arms opening and/or new data emerging relating to efficacy of specific agents. Because master trials are often self-sustaining, the guidelines need to be reviewed on a regular basis. An example would be the identification of RAS pathway mutations (NRAS, KRAS, PTPN11, NF1, etc) that may promote resistance to specific agents, for example, isocitrate dehydrogenase–targeted therapies in AML. Determining whether there are sufficient data to support modifying treatment guidelines to exclude these patients from specific treatment arms or to direct them to different treatment assignments is challenging. Ultimately, careful consideration should be given to the long-term goal of developing an accompanying companion diagnostic assay. This will allow dissemination of the specific targeted therapy at the time of regulatory approval. For master studies, consideration of this step needs to begin as soon as a strong signal of activity is observed.

Clinical trial operations

Although some of the earlier master trials depend on conventional clinical trial systems and legacy monitoring approaches, these practices are not well suited to conducting dynamic, early-stage, parallel studies. Items to consider when developing a master trial are included in the following sections.

Regulatory perspective. The regulatory strategy for a clinical trial starts with the objectives of the study and protocol. For some studies, such as the TAPUR study, which evaluates FDA-approved drugs, an investigational new drug application may not be required, whereas in other studies, such as the Beat AML study, which evaluates investigational drugs, an investigational new drug specific to the patient population is required. The regulatory approach and strategy will thus vary depending on the overall intent of the clinical trial, the agents being evaluated, and the patient population being studied.

Scientific review boards. Many clinical sites that participate in master studies will either be NCI-designated cancer centers or affiliates of one. NCI guidelines require all protocols to be peer reviewed by a cancer center scientific review committee for feasibility and scientific integrity. NCI peer-reviewed protocols are exceptions to the rule and only receive an administrative review. For studies such as the LLS Beat AML master trial that are not sponsored by the NCI, individual site scientific review was initially required. This had the potential to greatly lengthen the timeline of study opening and accruing patients. Collaborative discussion between the NCI and LLS Beat AML study team resulted in modification of these guidelines to allow 1 comprehensive cancer center to assume responsibility for scientific review and the remaining sites to accept this review. These guidelines have greatly expedited the approval process and timelines of this non-NCI-sponsored trial.

IRB. The role of the IRB is to protect the rights and welfare of patients involved in clinical trials. The IRB is responsible for providing guidance and oversight and helping to maintain compliance with applicable laws, regulations, and policies. Although every academic center has a local IRB, the majority of master trials

use a centralized IRB. By using a centralized IRB, 1 committee provides the necessary oversight of the trial rather than a host of individual committees. This allows for streamlined oversight of the trial.

Sites that do not allow the use of a central IRB can cause a challenge on how to navigate the local site rules for IRB review. In some cases, a hybrid approach can be considered for sites that do not allow the use of a centralized IRB, using both a centralized board and local IRB. This can prove to be challenging for trials of this complexity, as the local IRB process and associated committees can significantly prolong the time to trial activation. In our opinion, a central IRB is the best way to ensure efficient implementation of these studies.

Training/communication. From the outset, all stakeholders should realize there are numerous parallel activities when managing and conducting as many as 10 to 15 simultaneous protocols across different pharmaceutical companies, vendors, sites, and laboratories. This is further complicated when factoring in the early-phase nature of these studies, where exploration and frequent study amendments are the norm.

Communication is key among all participants in a master protocol and requires collaboration tools that link the entire trial ecosystem. The solution should be intuitive, user-friendly, and out of the box, taking no more than a few hours to set up and to be readily accessed from any user device. A single point of communication is a must for study teams, whether vendors, sites, laboratories, or pharmaceutical companies.

Trial management. As with any clinical trial, there are day-to-day operations that must occur that span everything from making sure laboratory kits are available at sites, safety reporting to the IRB and FDA, as well as site monitoring and oversight. High-quality trial oversight can be done by establishing internal infrastructure or by hiring a CRO. In either case, there are challenges in managing a trial with a patient “funnel.” The initial period, where patients are consented to the master trial and confirmation of the suspected diagnosis occurs, functions as a stand-alone feasibility study. Once this initial phase is completed, the patient is assigned to the next stage where the new protocol begins (with another consenting process) or to a predetermined treatment course.

Results and discussion

Recommendations for best practices

All trials come in various sizes and forms, but master trials take more coordination, planning, and tremendous effort to meet the needs of all parties involved. For example, the TAPUR, Lung-MAP, NCI Match, and Beat AML studies have proven that there is no magic formula for how master trials should be conducted. Rather, collectively, these studies have shown that a variety of approaches can be used depending on the objectives of the trial, the agents, and patient populations being studied. The recommended best practices listed in Figure 2 illustrate the common thread of the fundamental principles that should be considered when designing and implementing a master trial approach.

Several studies have now demonstrated that precision medicine trials with multiple treatment options can be conducted successfully on a national scale, however, it is too early to determine whether the trials will meet all of their objectives. Additionally, given the

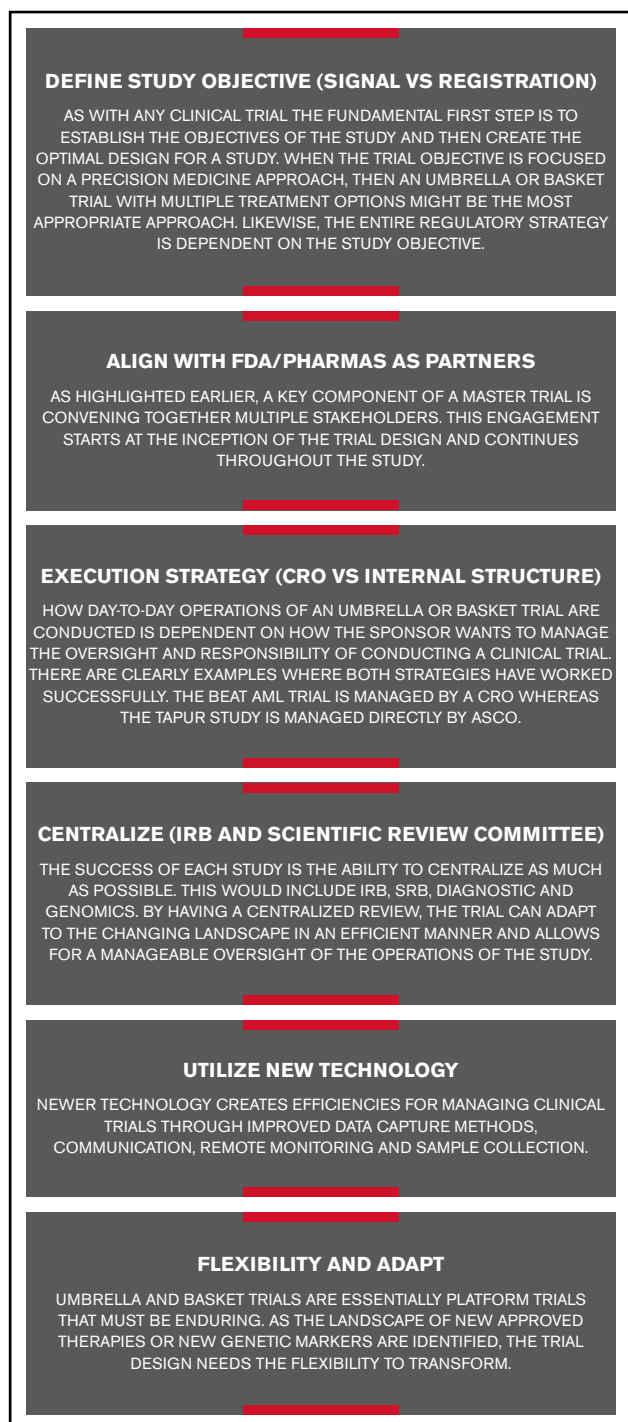


Figure 2. Recommended general best practices.

molecular complexity of cancer at large, both on an inpatient and outpatient basis, it is not likely that there is an ideal targeted agent or combination for every cancer patient. Although the master trial, precision medicine approach has limitations, the time for changing the way we conduct clinical trials is upon us. Our goal is to leverage biologic insights into clinical translation as rapidly as possible, in order to bring maximal benefit to cancer patients as expeditiously as can be achieved.

The paradigm for conducting clinical trials will continue to evolve with future models using a precision medicine approach to explore and credential novel-novel combination studies. The next collective challenge in this ever-shifting trial landscape is how to design combination studies that allow for truly personalized treatment options that can further improve patient outcomes.

Acknowledgment

This work was supported in part by National Institutes of Health, National Cancer Institute grant R35 CA197734 (J.C.B.).

Authorship

Contribution: All authors contributed to the manuscript via face-to-face meetings and teleconferences, and reviewed and approved the manuscript.

Conflict-of-interest disclosure: B.J.D. participates in scientific advisory boards for Aileron Therapeutics, ALLCRON, Cepheid, Vivid Biosciences, Celgene, and RUNX1 Research Program; participated in scientific advisory boards for Gilead, Baxalta, MonoJUL, GRAIL, and CTI Biopharma; participates and holds stock in Aptose Biosciences, Blueprint Medicines, Beta Cat, and Third Coast Therapeutics; is a scientific founder of and holds stock in MolecularMD; is on the board of directors for and holds stock in Amgen; is on the board of directors for Burroughs Wellcome Fund and CureOne; is on the joint steering committee for Beat AML of The Leukemia & Lymphoma Society; received clinical trial funding from Novartis, Bristol-Myers Squibb, and Pfizer; and receives royalties from patent 6958335 (Novartis exclusive license) and Oregon Health and Science University and Dana-Farber Cancer Institute (1 Merck exclusive license). J.C.B. receives funding from Acerta, Genentech, Janssen, and Pharmacyclics. R.L.L. participates on the supervisory board of Qiagen and is a scientific advisor to Loxo, Imago, C4 Therapeutics, and Isoplexis (each of which include an equity interest); receives research support from and consulted for Celgene and Roche; has received research support from Prelude Therapeutics; has consulted for Incyte, Novartis, Morphosys, and Janssen; and has received honoraria from Lilly and Amgen (for invited lectures) and Gilead (for grant reviews). R.L.S. receives research funding on behalf of the ASCO in support of the TAPUR trial from the following companies: AstraZeneca, Bayer, Bristol-Myers Squibb, Genentech, Eli Lilly, Merck, and Pfizer. A.B. receives funding on behalf of The Leukemia & Lymphoma Society from the following companies: AbbVie, Agios Pharmaceutical, Inc, Alexion Pharmaceuticals, Amgen, Astellas, Inc, AstraZeneca, Boehringer Ingelheim International GmbH, Boston Biomedical, Inc, Bristol-Myers Squibb, Celgene Corporation, Genentech, Gilead Sciences, Inc, Immunogen, Jazz, Johnson & Johnson, Novartis, Pfizer, and Pharmacyclics. D.R.G. has been a consultant to AstraZeneca, Celgene, CellMax Life, Genentech/Roche, Guardant Health, Lilly, Liquid Genomics, and NantHealth; and received research grants (institutional) from AstraZeneca/Medi and Genentech/Roche. R.S.H. provided consulting services to AbbVie Pharmaceuticals, AstraZeneca, Biodesix, Bristol-Myers Squibb, Eli Lilly and Company, EMD Serrano, Genentech/Roche, Heat Biologics, Jun Shi Pharmaceuticals, Loxo Oncology, Merck and Company, Nektar, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, and Tesaro; provided research support to AstraZeneca, Eli Lilly and Company, and Merck and Company; and participated on

scientific advisory boards for Neon Therapeutics, Infinity Pharmaceuticals, and NextCure. V.A.P. participated on advisory boards for Nektar Therapeutics, Bristol-Myers Squibb, AstraZeneca, Novartis, Merck, Arrys, LOXO Oncology, F. Hoffman–La Roche, Janssen Research Foundation, Clovis Oncology, Eli Lilly, Takeda, AbbVie, Tesaro, Exelixis, and Gritstone; received speaker fees from F. Hoffman–La Roche; and provided research support (institutional) to Eli Lilly, Novartis, Merck, Nektar, Astra Zeneca, F. Hoffman–La Roche, Janssen, Checkmate,

Incyte, and Bristol-Myers Squibb. M.W.R. declares no competing financial interests.

ORCID profiles: J.C.B., 0000-0001-8331-8206; D.R.G., 0000-0003-1784-048X.

Correspondence: Amy Burd, The Leukemia & Lymphoma Society, 3 International Dr, Suite 200, Rye Brook, NY 10573; e-mail: amy.burd@lls.org.

References

1. American Society of Clinical Oncology (ASCO). Clinical trial designs for studying targeted therapies. ASCO Daily News (<https://dailynews.ascopubs.org/>). 31 May 2015. Accessed 1 November 2018.
2. Berry DA. The brave new world of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research. *Mol Oncol*. 2015;9(5):951-959.
3. Catenacci DV. Next-generation clinical trials: novel strategies to address the challenge of tumor molecular heterogeneity. *Mol Oncol*. 2015;9(5):967-996.
4. Redig AJ, Jänne PA. Basket trials and the evolution of clinical trial design in an era of genomic medicine. *J Clin Oncol*. 2015;33(9):975-977.
5. Fridlyand J, Simon RM, Walrath JC, et al. Considerations for the successful co-development of targeted cancer therapies and companion diagnostics. *Nat Rev Drug Discov*. 2013;12(10):743-755.
6. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med*. 2017;377(1):62-70.
7. Redman MW, Allegra CJ. The master protocol concept. *Semin Oncol*. 2015;42(5):724-730.
8. Joffe E, Iasonos A, Younes A. Clinical trials in the genomic era. *J Clin Oncol*. 2017;35(9):1011-1017.
9. Saville BR, Berry SM. Efficiencies of platform clinical trials: a vision of the future. *Clin Trials*. 2016;13(3):358-366.
10. Slosberg ED, Kang BP, Peguero J, et al. Signature program: a platform of basket trials. *Oncotarget*. 2018;9(30):21383-21395.
11. Mangat PK, Halabi S, Bruinooge SS, et al. Rationale and design of the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *JCO Precis Oncol*. 2018;2018:1-14.
12. Herbst RS, Gandara DR, Hirsch FR, et al. Lung Master Protocol (Lung-MAP)—biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res*. 2015;21(7):1514-1524.
13. Steuer CE, Papadimitrakopoulou V, Herbst RS, et al. Innovative clinical trials: the LUNG-MAP study. *Clin Pharmacol Ther*. 2015;97(5):488-491.
14. National Cancer Institute. NCI-MATCH Trial (Molecular Analysis for Therapy Choice). <http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>. Accessed 1 November 2018.
15. Leukemia & Lymphoma Society. The Beat AML Master Trial. <https://www.lls.org/beat-aml>. Accessed 1 November 2018.