REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

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Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

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N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

High-quality evidence is what we use to guide medical practice. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.[1-4] Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, each targeting a particular biomarker-defined population or disease subtype. Included under this broad definition of a master protocol are three distinct entities: umbrella, basket, and platform trials (Table 1 and Figs. 1 and 2). All constitute a collection of trials or substudies that share key design components and operational aspects to achieve better coordination than can be achieved in single trials designed and conducted independently.

A master protocol may involve direct comparisons of competing therapies or be structured to evaluate, in parallel, different therapies relative to their respective controls. Some take advantage of existing infrastructure to capitalize on similarities among trials, whereas others involve setting up a new trial network specific to the master protocol. All require intensive pretrial discussion among sponsors contributing therapies for evaluation and parties involved in the conduct and governance of the trials to ensure that issues surrounding data use, publication rights, and the timing of regulatory submissions are addressed and resolved before the start of the trial.

EXAMPLES

There have been more master protocols initiated for the study of cancer therapy than other therapeutic areas, owing to advances made in identifying tumor subtypes or mutations for targeting.[5] Table 2 summarizes selected master protocols in cancer and illustrates the variety of research objectives and trial designs used. The advantages of studying more than one therapy for a particular disease defined by both pathological and molecular criteria (an umbrella or platform trial) or studying more

than one disease for a particular therapy (a basket trial) are appealing because cancer research has advanced quite far in precision targeting of treatments. An example of a basket trial is the B2225 master protocol, in which a common biomarker–treatment combination is investigated in multiple disease cohorts, whereas the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) master protocol is an umbrella trial evaluating multiple genetic markers and associated targeted therapies for cancers of varying histologic features that carry the targeted mutation. We illustrate the concept using the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2) and the Lung Master Protocol (Lung-MAP).

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

I-SPY 2

I-SPY 2 is an exploratory-phase platform trial designed to investigate new treatments for biomarker-identified subtypes of early-stage breast cancer in the context of neoadjuvant therapy (i.e., treatment before surgery to reduce the tumor burden).[10-12] Various drugs are tested as neoadjuvant treatments, which allows the investigators to determine the primary outcome, a pathological complete response of the tumor at surgery, without having to wait for years. In addition, pathological complete response is considered reasonably likely to predict event-free survival, the typical outcome measure in confirmatory trials of neoadjuvant therapies.[16]

Innovative aspects of the I-SPY 2 trial design include response-adaptive randomization to assign patients to the most promising treatment or combination of treatments in their respective genetic breast-cancer subgroups (eight subgroups initially defined by three genetic markers) while maintaining a sufficient number of patients assigned to the standard of care, shared use of control patients across treatment comparisons, and Bayesian decision rules to determine whether or when therapies with low probabilities of success or side effects should be discontinued and therapies with high probabilities of future success (≥85% likelihood of success in a 300-person phase 3 trial) should advance for further study. A trial network and informatics infrastructure was established to enable the dynamic nature of the trial design.

As of March 2017, 12 therapies from 9 sponsors have been evaluated with the use of the I-SPY 2 protocol, 5 have advanced for further study (including 2 investigational products, veliparib–carboplatin and neratinib),[17,18] and others are queued for entry. Discussion is under way for an I-SPY 3 master protocol that would be designed to provide evidence of effectiveness for agents successfully completing I-SPY 2.[19]

Lung-MAP

Lung-MAP is a phase 2–3 master protocol involving rigorously defined advanced squamous non–small-cell lung cancer (NSCLC). Lung-MAP incorporates a common biomarker screening platform to classify patients into genetic subgroups and is designed to evaluate each targeted therapy independently of the others.[13-15] Patients qualifying for more than one subgroup are randomly assigned to subgroups in such a way that the groups for biomarkers with lower prevalence receive more patients (i.e., the probability of being assigned to a given subgroup is inversely proportional to biomarker prevalence). Patients whose biomarker signatures do not fall into any of the defined subgroups are assigned to the no-match subgroup, thus allowing more screened patients to participate. Four targeted therapies and one therapy for the no-match subgroup were identified for evaluation versus the standard of care in five independent substudies, each using a phase 2–3 seamless design with progression-free survival and overall survival, respectively, as end points.

After Food and Drug Administration (FDA) approval of nivolumab, several changes were made to Lung-MAP. First, the substudies were redesigned as single-group (phase 2) investigations with a primary end point of overall response rate. A targeted therapy in any of the substudies is considered successful if an overall response rate of 15% or less is ruled out with sufficient confidence in

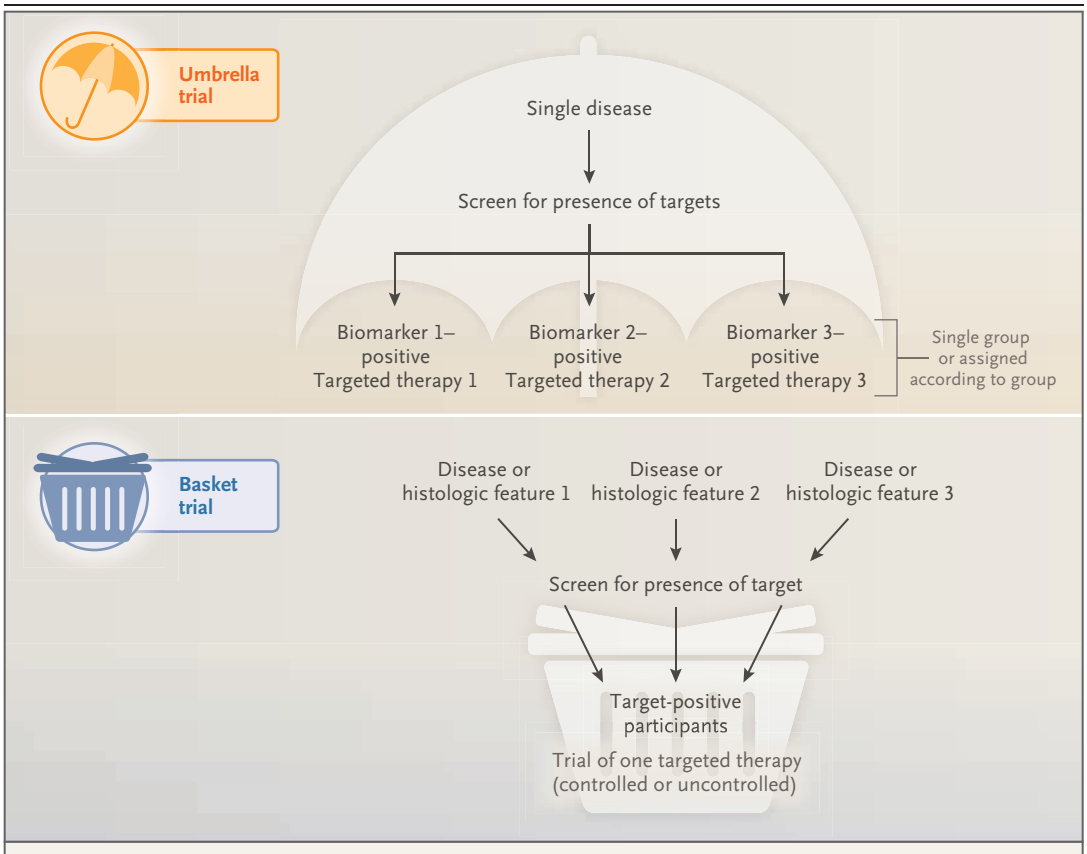

Figure 1. Umbrella Trial and Basket Trial.

An umbrella trial (top) evaluates various (often biomarker-defined) subgroups within a conventionally defined disease. Patients with the disease are screened for the presence of a biomarker or other characteristic and then assigned to a stratum on the basis of the results. Multiple drugs are studied in the various strata, and the design may be randomized or use external controls depending on the disease. A basket trial (bottom) involves multiple diseases or histologic features (i.e., in cancer). After participants are screened for the presence of a target, target-positive participants are entered into the trial; as a result, the trial may involve many different diseases or histologic features. A master protocol for a basket trial could contain multiple strata that test various biomarker–drug pairs. Statistical approaches are not depicted in this figure.

phase 2. If the success criteria are met and projected enrollment is feasible (i.e., expected duration of ≤3 years), a phase 3 investigation will be planned, with the standard of care for the control group to be determined at that time. Second, the no-match substudy, which was originally designed to investigate MED14736, now compares nivolumab with nivolumab plus ipilimumab. Lung-MAP shares some aspects of perpetual platform trials with I-SPY 2, in that new drugs can be added and ineffective drugs discontinued in a perpetual manner, but most of the adaptive design features of I-SPY 2 are absent. As of March 2017, MED14736 and one of the biomarker-matched therapies (rilotumumab) have been discontinued, and three remain (taselisib, palbociclib, and AZD4547).

COMPARING I-SPY 2 AND LUNG-MAP

Comparing these two case studies illustrates the range of research questions that a master protocol can address. Lung-MAP can be viewed as a collection of separate substudies corresponding to genetic subgroups, conducted under a single master protocol and intended to eventually provide evidence of safety and effectiveness for biomarker-matched therapies. I-SPY 2, in contrast, takes a more integrated and adaptive approach to trial design and conduct, an approach that is consistent with its exploratory objectives. Both I-SPY 2 and Lung-MAP are registered at ClinicalTrials.gov as single protocols, consistent with the coordination and collaborative research effort each represents, but the Lung-MAP substudies are also

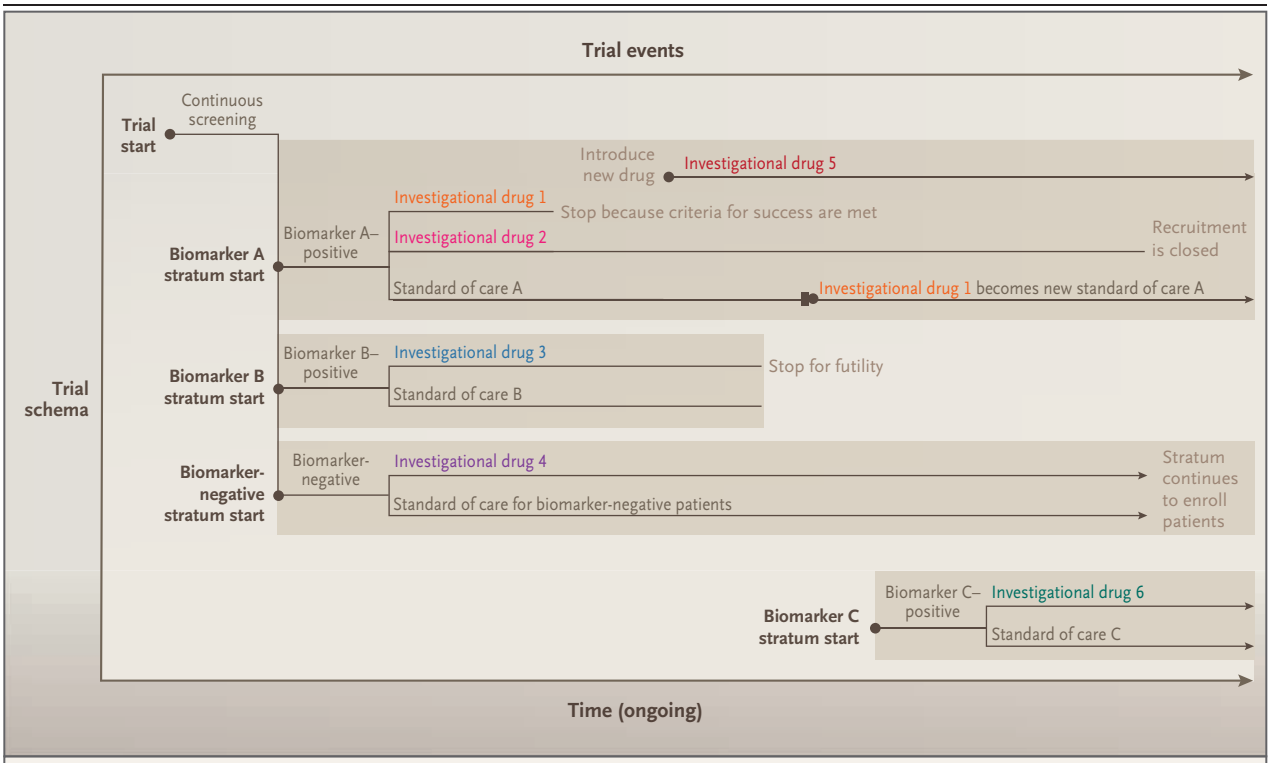

Figure 2. Potential Design of a Platform Trial Involving a Single Disease.

The figure depicts the trial schema over time, not the flow of individual patients. The platform trial is ongoing over time, with no fixed stopping date, and is governed by a master protocol that envisions adding and dropping strata. At trial start, entering patients undergo screening for biomarkers A and B and are assigned to one of three strata on the basis of the results. Biomarker A–positive patients are randomly assigned to one of three groups, testing two investigational drugs against a common standard of care. When investigational drug 1 meets the criteria for success, that group of the stratum is stopped, and after further testing, drug 1 ultimately replaces the previous standard of care as the control. Randomization to an investigational drug 5 group is initiated in the biomarker A stratum when that drug becomes available, sharing the common control group for patients with similar biomarker profiles. The investigational drug 2 group completes planned enrollment and stops. Entry of patients into the biomarker B stratum is stopped when investigational drug 3 appears unlikely to provide benefit. At that point, new biomarker B–positive patients are assigned to the biomarker-negative stratum. A biomarker C stratum is opened when both a biomarker assay and an investigational targeted drug become available to the trial. At this time in the trial, patients are screened for biomarkers A and C and then assigned to the appropriate stratum. Only one possible platform-trial schema is depicted in this figure. The statistical methods shown here involve randomized treatment assignment, sharing of common control patients, and sequential analyses with the possibility of stopping early for success or failure. Other types of adaptive designs are possible, including adaptive randomization, as are the use of other criteria for early stopping. For example, if a biomarker stratum includes only a single treatment group without randomized assignment, then stopping early after exceeding a specified threshold for the response rate might be used.

registered separately. I-SPY 2 and Lung-MAP are each being conducted under a single investigational new drug application at the FDA.

EXAMPLES BEYOND CANCER

Interest in master protocols in the non-oncology sector is growing.[20] The Antibiotic Resistance Leadership Group is undertaking the evaluation of therapies targeted to resistant pathogens at multiple body sites of infection under a single master protocol (ADAPT) with the use of adaptive methods and technology similar to those in I-SPY 2.[21,22] The Partnership for Research on Ebola Virus in Liberia II (PREVAIL II) clinical trial to evaluate multiple therapies for Ebola virus disease under a single protocol incorporated a flexible Bayesian adaptive design with the potential to add new therapies and update the standard of care as experimental therapies became available for testing.[23] The trial was stopped early, when enrollment decreased owing to the subsiding of the epidemic, with only one treatment evaluated.[24] The Dominantly Inherited Alzheimer Network Trial (DIAN-TU) is a study of potential disease-

Table 2. Examples of Master Protocols in Cancer.*

Trial	Description	Design	Drug or Drugs	Disease and Target	Study Population	End Points
B2225[6]	Basket trial to determine cancers responsive to imatinib	Phase 2, multicenter, open-label, noncomparative trial	Single: imatinib (400 or 800 mg per day)	40 cancers (solid tumors and hematologic cancers) with activation of imatinib target kinases	186 patients ≥15 yr of age	Tumor response (SWOG criteria and investigator's assessment)
BRAF V600[7]	Basket trial to evaluate the efficacy of vemurafenib in nonmelanoma cancers	Early phase 2, multicenter, open-label, noncomparative, adaptive trial using Simon's two-stage design	Vemurafenib monotherapy or (in some patients with colorectal cancer) vemurafenib plus cetuximab	Multiple nonmelanoma cancers with *BRAF* V600 mutations; eight tumor-specific cohorts plus an "all others" cohort	122 adults (≥18 yr of age)	Response rate (assessed by investigators according to RECIST or IMWG criteria) at wk 8
NCI-Match[8]	Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective	Exploratory, multicenter, noncomparative trial	Multiple: 30 treatments (as of May 2016), both FDA-approved and investigational, that target gene abnormalities	Advanced solid tumor, lymphoma, or myeloma; DNA sequencing for actionable mutations	35 adults planned per substudy; pediatric study to begin in 2017	Tumor response (primary) and progression-free survival
BATTLE-1[9]	Umbrella trial to evaluate targeted therapies in chemotherapy-refractory NSCLC	Phase 2, single-center, comparative, adaptive randomization trial	Multiple: three monotherapies (erlotinib, vandetanib, and sorafenib) and one combination (erlotinib plus bexarotene)	Advanced NSCLC; targets included *EGFR* mutation, *KRAS/BRAF* mutation, VEGF expression, and RXRs/CyclinD1 expression	255 adults in whom ≥1 chemotherapy regimen had failed	Complete or partial response or stable disease according to RECIST criteria at wk 8 (primary), progression-free survival, overall survival, and toxicity
I-SPY 2[10-12]	Adaptive platform trial to identify treatment regimens for locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures	Phase 2, multicenter, comparative, adaptive randomization trial	Multiple: standard chemotherapy and five new drugs (initially) as add-on to chemotherapy; 12 treatments tested to date, with latest (patritumab) added October 2016	Early, high-risk breast cancer; three biomarkers (hormone-receptor status, HER2 status, and MammaPrint risk score) define eight genetic subgroups	1920 women (estimated) with invasive tumor ≥2.5 cm in diameter	Pathological complete response
Lung-MAP[13-15]	Master protocol to evaluate biomarker-matched therapies in rare squamous-cell subsets of NSCLC	Phase 2–3 comparative trial	Multiple: four investigational drugs plus one therapy for no-match control group (initially); three investigational drugs remain	Squamous-cell NSCLC; multiple targets (four molecular targets initially; three remain)	100–170 patients planned for phase 2 (40 are now enrolled); 300–400 planned for phase 3	Objective response rate, progression-free survival, and overall survival

* BATTLE-1 denotes Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination 1, IMWG International Myeloma Working Group, I-SPY 2 Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2, Lung-MAP Lung Master Protocol, NCI-MATCH National Cancer Institute Molecular Analysis for Therapy Choice, NSCLC non–small-cell lung cancer, RECIST Response Evaluation Criteria in Solid Tumors, and SWOG Southwest Oncology Group.

modifying treatments in persons at risk for or with a type of early-onset Alzheimer's disease caused by a genetic mutation. Two therapies are currently under study, with additional therapies planned.[25,26] Older clinical-trial networks, such as those funded by the National Institutes of Health (NIH) in the 1990s (e.g., the National Heart, Lung, and Blood Institute–sponsored Asthma Clinical Research Network[27]), laid much of the groundwork for modern master protocols through centralization of trial systems and governance. The National Institute of Mental Health–sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) comparing multiple atypical antipsychotic agents with standard therapy for schizophrenia represent another early NIH example.[28,29]

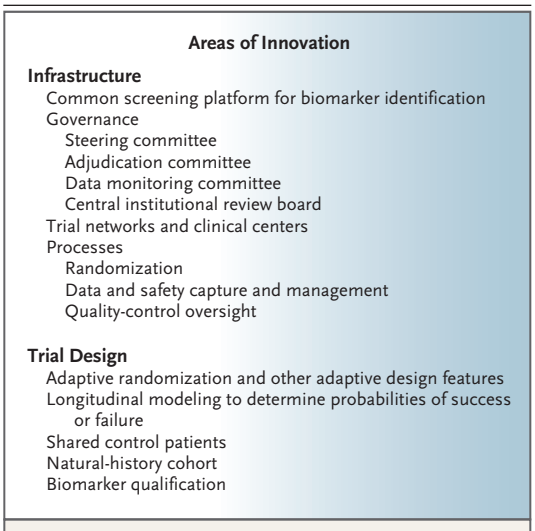

Figure 3. Areas of Innovation in Master Protocols.

TRIAL INNOVATIONS

Two types of innovation are hallmarks of master protocols: the use of a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing; and the use of a common protocol that incorporates innovative statistical approaches to study design and data analysis, enabling a broader set of objectives to be met more effectively than would be possible in independent trials (Fig. 3).[30,31] Since medicine is taught by example, we outline a few innovations below.

TRIAL NETWORK AND INFRASTRUCTURE

Common Screening Platform

Under the paradigm of conducting independent trials for each therapy, patients may be recruited and screened for one protocol, not meet the inclusion criteria, and either get screened for another trial or miss the opportunity to participate altogether. For each separate trial, the process of data collection and testing is repeated, with overlapping information gathered for multiple trials but not shared among them. The master-protocol counterpart is the use of a common screening platform to identify all trials for which a patient is eligible. This coordinated screening is at the heart of a master protocol and represents one of its chief advantages — more efficient use of patients and resources. Sponsors and research investigators benefit from a streamlined recruitment process, often of higher quality and yielding fewer screening failures and shorter recruitment times. Patients benefit through more opportunities to participate in investigational research and earlier access to potentially beneficial therapies.

Centralization and Shared Governance

The use of centralized shared governance for all trials that are conducted under the master protocol represents another major advantage. Single governing bodies such as the steering committee, institutional review board, and data monitoring committee can be established and assigned oversight for all trials or substudies in a master protocol. In addition to using fewer resources, centralized governance enables uniform decisions to be made about various aspects of all the trials being conducted under the protocol. Decisions about discontinuing or adding therapies in both of our examples depend on such centralization. Central laboratories, reading centers (e.g., imaging center and spirometry center), adjudication committees, and other central facilities enhance data quality through coordinated training efforts and quality-control oversight. Quality improvements that are identified for one trial are applied to all.

Study Sites and Systems

The use of a common trial network and associated infrastructure affords considerable advantages in both efficiency and quality. Having a network of experienced clinical centers to serve as study sites for multiple trials under a master protocol makes sense as compared with establishing study centers one trial at a time. The use

of a single system for clinical data management will enable shorter start-up times as the protocol is expanded to incorporate new investigations. The use of a single central randomization system facilitates the addition of new therapies with minimal disruption. Real-time access to the genomic, proteomic, pathological, and imaging data streams is requisite for the adaptive features of I-SPY 2.

COMMON PROTOCOL AND DESIGN ELEMENTS

Protocol Elements

Trials that are conducted under a master protocol have similar study designs and protocol elements, with differences dictated only by peculiarities of the individual therapies under investigation. The schedule of visits, clinical examination components, measurement procedures, outcome definitions, and ascertainment procedures are shared across trials, allowing for reuse of study materials. Even though Lung-MAP consists of individual substudies for each biomarker–therapy combination, protocol elements such as visit schedules and imaging protocols are shared as much as possible.

Innovative Designs

With multiple questions to address under a single protocol, usually in an area of unmet need, and an extensive infrastructure in place to handle data flow, master protocols are a natural environment for considering innovative trial designs.[32-35] The flexibility to allow promising new therapies to enter and poor-performing therapies to discontinue usually requires some form of adaptive design, but the level of complexity of those adaptations can vary according to the objectives of the master protocol. For example, I-SPY 2 incorporates both Bayesian adaptation algorithms for basing trial decisions on estimated posterior probabilities that are computed at frequent interim-analysis points and response-adaptive randomization. Although the use of response-adaptive randomization (i.e., purposefully assigning patients to more promising treatments on the basis of accruing data) has been the subject of much discussion in single-purpose clinical trials,[36] the I-SPY 2 investigators argue that its use is consistent with the objectives of the trial on statistical, ethical, scientific, economic, and logistic grounds.[37] In contrast, the individual substudies of Lung-MAP, which are designed to evaluate biomarker-matched therapies in parallel and independently of each other, do not involve any trial adaptations, beyond the ability to start and stop the substudies themselves.

One innovative design feature unique to the master-protocol setting is the shared use of control patients among trials of the same biomarker or disease. In a simple case, a trial of two therapies that target the same biomarker signature can share control patients, even if the drugs enter and exit the master protocol at different times, under the assumption that there have not been substantial ecologic changes in care that could alter the outcome in the control group. Comparative analyses of each drug versus control take advantage of shared control patients, reducing the overall sample size, and correlations between the analyses are not an issue, provided the test drugs are not compared with each other. If the recruitment periods overlap but are not identical, the randomization algorithm can switch between a two-group and three-group scheme. In this case, shared control patients may be limited to those assigned concurrently to each drug (i.e., in the overlapping recruitment period) or expanded to include nonconcurrent control patients, provided the potential for ecologic changes to confound treatment effects is addressed. In Lung-MAP, for example, only a single treatment is being investigated for each biomarker profile to date, but if a second treatment is identified, the potential to share control patients with the same biomarker profile is available.

Support for Other Research

By taking advantage of coordinated data collection across multiple trials, master protocols can enhance other research initiatives. For example, having a master protocol in place for a rare disease can facilitate the collection of case histories of patients seen in the participating clinical practices, providing a data source for future externally controlled trials that may be more relevant than other historical data sources.

Similarly, activities that are needed to evaluate the performance of new biomarkers that are not linked to a target therapy can be conducted within a master protocol. Typically, extensive studies relating biomarker results to clinical outcomes are needed to understand biomarker performance characteristics and set cutoff values. These data are difficult to gather and may come from retrospective samples with incom-

plete or inadequate outcome data. Ongoing master protocols constitute an ideal means of collecting such information.

CONSIDERATIONS FOR USE

INCREASED PLANNING AND COORDINATION

The advantages that are associated with the use of a master protocol come at a price — namely, the cost in time and resources to establish the needed trial infrastructure and the increased up-front planning and coordination to bring a larger number of parties into agreement on trial design, operations, and governance than a stand-alone trial requires. I-SPY 2, for example, is the result of collaboration among academic investigators, the NCI, multiple pharmaceutical sponsors, and the FDA, under the auspices of QuantumLeap Healthcare Collaborative. For Lung-MAP, the Friends of Cancer Research served as the catalyst for building the consortium, which also includes the FDA, the NCI, SWOG Cancer Research, multiple pharmaceutical companies, and the Foundation for the National Institutes of Health.

Additional up-front planning is also usually required owing to the more complex trial designs and real-time decision making on which master protocols tend to rely. A framework for making and implementing decisions about which treatments to study, which to discontinue, and which to advance for further study or for regulatory submission typically involves the development of statistical models and algorithms as well as procedures to ensure the rapid flow of information among the involved parties (e.g., steering committee, sponsors, and data monitoring committee).

Whenever multiple questions are being addressed under a single protocol, questions of multiplicity come into play, and master protocols are no different.[38] Exploratory protocols such as I-SPY 2 may identify therapies for further study, whereas master protocols such as Lung-MAP may be evaluating therapies in parallel — neither requiring multiplicity adjustment from a regulatory standpoint. But this may not always be the case, and as precision medicine focuses on smaller and smaller disease subtypes, traditional methods for multiplicity adjustment become impractical. During the planning stage, analysis methods should be aligned with the research objectives, and the chances of coming to an erroneous conclusion carefully considered, as with any research endeavor.

Taken together, stakeholder coordination, infrastructure requirements, and complex trial-design elements can extend the start-up time for a master protocol considerably, as compared with that for a single-purpose trial.

CHANGES IN THE MARKETPLACE

As new drugs are approved for marketing, the standard of care in clinical practice can change, possibly affecting a long-running master protocol. This occurred in Lung-MAP when nivolumab was shown to have superiority over docetaxel, the standard of care selected for the biomarker-matched substudies. In I-SPY 2, the approval of pertuzumab, which had been included as a test treatment, resulted in its substitution for trastuzumab as the standard of care for HER2-positive breast cancer. In both cases, the master protocol allowed for a coordinated response to the changing marketplace in terms of redesign, which can be an advantage as compared with single, stand-alone trials. However, marketplace changes can negatively affect master protocols in other ways — for example, the need for a temporary halt in recruitment while design changes are worked out, the need to modify statistical analysis plans to accommodate changing comparators, or the ability to attract new therapies when a more effective standard of care becomes the comparator.

SUMMARY

Master protocols come in different sizes and shapes but share many commonalities. All require increased planning efforts and coordination to satisfy the objectives of different stakeholders. Innovative design elements help ensure that maximum information is obtained from the research effort, and the infrastructure required for implementation increases data quality and trial efficiencies, as compared with those in stand-alone trials. If designed correctly, master protocols can last many years, even decades, with innovations from the laboratory translating quickly to clinical evaluation. As the targets for new drugs become more and more precise, there is no alternative but to move forward with these coordinated research efforts.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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