Clinical Cancer Research

Challenges with Novel Clinical Trial Designs: Master Protocols

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Abstract

The 2018 Accelerating Anticancer Agent Development (AAADV) Workshop assembled a panel of experts for an in-depth discussion session to present "Challenges with Novel Clinical Trial Designs." This panel offered assessments of the challenges faced by industry, the FDA, investigators, institutional review boards, and patients. The panel focused on master protocols, which include umbrella trials, platform trials, and basket trials. Umbrella trials and platform trials share many commonalities, whereas basket trials are more distinct. Umbrella and platform trials are generally designed with multiple arms where patients of the same histology or other unifying characteristics are enrolled into different arms and multiple investigational agents are evaluated in a single protocol. In contrast, basket studies generally enroll patients with different tumor types based on the presence of a specific mutation or biomarker regardless of histology; these trials may include expansion cohorts. These novel designs offer the promise of expedited drug assessment and approval, but they also place new challenges on all the stakeholders involved in the drug development process. Only by identifying the challenges of these complex, innovative clinical trial designs and highlighting challenges from each perspective can we begin to address these challenges. The 2018 AAADV Workshop convened a panel of experts from relevant disciplines to highlight the challenges that are created by master protocols, and, where appropriate, offer strategies to address these challenges.

Introduction

The goal of cancer drug development is to develop novel therapies that will improve patient outcomes though prolongation of survival and improvement in quality of life. All approved therapies follow a logical progression and regulatory approval process focused on safety and efficacy. More recently, acknowledgement of suboptimal development timelines, improved understanding of tumor biology (1), and innovative drug targets have led to the development of novel clinical trial designs, which may also be referred to as complex innovative designs. These trials include basket trials, platform trials, and umbrella trials, which have become useful tools for streamlining the modern drug development and approval process (2–5). Umbrella trials enroll study participants with the same type of cancer histology or organ involvement and assign them to different cohorts based on specific mutations (6). Platform trials randomize patients to different cohorts and take umbrella studies a step further by following algorithms to adapt and add new therapies or drop existing therapies from an ongoing study (6). Basket trials group study participants by mutation, regardless of histology or which organs are involved (7, 8). These innovative designs seek to evaluate multiple outcomes in a single clinical trial, which has historically required multiple separate trials. However, despite these characterizations, there is no uniform definition pursuant to each of these individual trial designs (9).

Although these trial designs aim to improve timelines, they also create new challenges driven by their increased complexity. These challenges affect the various stakeholders, including patients, investigators, regulatory agencies, and industry. As a result, continual reassessment and changes focusing on improvement in operational efficiencies are critical. There are multiple causes underlying this increasing trial complexity including our reliance on biomarkers, innovative biostatistical input, pressure from advocacy groups, regulatory requirements, appreciation of multiple unmet clinical needs in oncology, and the improved understanding of clinical research itself. Appropriate communication between the pharmaceutical industry, academia, regulatory agencies, and patients plays a major role in addressing many of these challenges.

The 15th Annual Accelerating Anticancer Agent Development and Validation (AAADV) Workshop held in 2018 was co-sponsored by the FDA, the American Association of Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), and Duke University. The workshop gathered a diverse team of experts to identify and address several of the challenges associated with novel clinical trial designs. This team included perspectives ranging from industry, regulatory agencies (FDA), clinical trial investigators, institutional/ethical review boards, and most importantly, the patients. Each stakeholder described challenges resulting

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Prior presentation: The results were presented in part at the 2018 Accelerating Anticancer Agent Development Workshop in Bethesda, Maryland.

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doi: 10.1158/1078-0432.CCR-18-3544

Translational Relevance

Master protocols, which include umbrella trials, platform trials, and basket trials, are changing the methodology of clinical drug development. These designs offer unprecedented opportunities to truly accelerate drug development; however, they are highly complex and their success requires a rigorous development process and conduct procedures. Improving the drug development process starts by properly identifying the challenges that these new trials create for all stakeholders involved in drug development. Appropriate upfront discussions between these stakeholders are the most effective way to mutually understand challenges that face all parties. It is only by properly identifying these challenges that effective strategies to address pitfalls can be implemented.

from clinical trial designs in their respective domain, and pivotal strategies to address them. Here we seek to summarize discussions and outline recommendations emanating from this discussion group to the broader oncology community and offer approaches to address these challenges.

Novel Clinical Trials Designs

Master protocols, which include platform trials, umbrella trials, and basket trials (6), are overarching protocols with multiple objectives that involve coordinated efforts to evaluate one or more investigational products in one or more patient populations within the structure of a single clinical trial (10). In most instances regarding umbrella and platform studies, the recommended phase II dose (RP2D) has already been established for the investigational agent(s). This contrasts with first-in-human expansion cohorts in basket trials where investigators simultaneously confirm the safety of the RP2D and obtain signals of efficacy.

Umbrella trials and platform trials

Umbrella trials and platform trials generally involve a single tumor type with multiple experimental objectives (Fig. 1A; ref. 6). Often there is a shared control arm with multiple experimental arms. These studies can be either exploratory or they can have registration intent. Multiple treatments can be evaluated simultaneously for a single histology. These two designs share many similarities, and umbrella and platform studies are often lumped together. In both umbrella and platform trials, each arm is typically enriched with a biomarker and patients are enrolled and assigned to a cohort based on their biomarker status. Platform trials may be distinguished from umbrella studies in that they are thought to incorporate more adaptations—as responses are observed, patients are algorithmically allocated to specific treatment arms according to the best match between treatment effect and their tumor type. Experimental drugs drop out for lack of efficacy or they can "graduate" for efficacy testing depending on the observed response. Randomization is adapted such that the number of patients needed to determine efficacy across biomarker groups is minimized. Umbrella studies are also adaptive and can add and remove new therapies with improved efficiency, but for platform trials this process is much more automated by algorithms. Given the similarities between platform trials and umbrella trials, they face roughly the same challenges.

The goal of both umbrella and platform trials is to identify new drugs or drug combinations matched to biomarker derived subsets that then can be translated into a relatively small phase III trial with some assurance of success. A classic platform trial in breast cancer, which was done with exploratory intent, is I-SPY2 (11, 12). In this example, patients with early high-risk breast cancer are assigned a treatment arm according to standard-of-care diagnostic tests and treated with standard neoadjuvant chemotherapy plus a variety of investigational agents. Ultimately in this study, patients go on to surgery, and the primary endpoint is pathologic complete response. The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) is the model umbrella trial in non–small cell lung cancer (NSCLC). In BATTLE, patients with metastatic chemorefractory NSCLC were adaptively randomized to a specific arm based on the presence or absence of numerous biomarkers, and evaluated for the 8-week disease control rate as the primary endpoint (13). Both BATTLE and I-SPY2 have played leading roles in establishing umbrella

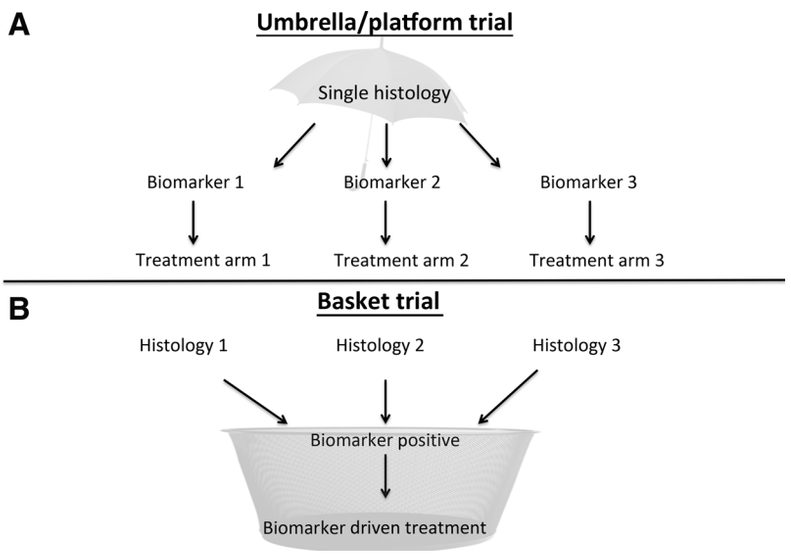

Figure 1.
A, Study schema for an umbrella or platform trial.
B, Study schema for a basket trial.

and platform trials as effective approaches to expedite drug development.

The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) took the paradigm of umbrella studies a step beyond BATTLE and I-SPY2 by integrating multiple tumor types into a single umbrella study. As noted previously, umbrella studies are more commonly restricted to one tumor type. In addition, the scope of NCI-MATCH was unprecedented in both the number of treatment arms and overall size, with more than 1,000 participating sites ranging from tertiary centers to small community practices (14).

Both umbrella and platform trial designs have several key advantages over traditional clinical trials. One of these advantages includes the use of a shared control arm in some situations across multiple experimental treatments as opposed to the need for multiple two-arm studies. Perhaps even more valuable are the operational efficiencies of these designs to bring new drugs into the existing trial or remove drugs that are not showing promise, which in the past has required separate clinical trials. This potentially allows for streamlined enrollment, limited patient exposure to ineffective therapy, decreased cost, and less regulatory burden by adding in new arms through amendments as opposed to developing multiple new clinical trials.

Despite the advantages, there are instances where umbrella and platform designs are suboptimal. A critical instance would be when the appropriate infrastructure is lacking either with the sponsor or at too many sites to ensure patient safety. This limitation is especially pronounced in umbrella and platform studies given their increased operational challenges highlighted below. In addition, in circumstances where a tumor type lacks any biomarkers that would be used to assign patients to various treatment arms, the advantages of umbrella and platform trials are diminished. Similarly, the benefits of evaluating different experimental therapies based on biomarker status are lessened in tumors with homogenous molecular profiles, such as gastrointestinal stromal tumor, where targeting a single mutation predicts for response. Despite these limitations, the application for umbrella and platform trials is widespread, and their utility will expand as new biomarkers are developed in additional diseases.

Basket trials

Basket trials, in many ways, are orthogonal to umbrella and platform studies. Typically, there is a single experimental regimen and multiple cancer types are included (Fig. 1B; refs. 6, 8). Eligibility is more often, but not always, determined by a biomarker test that spans multiple tumor types. Statistically, outcomes may be shared across tumor types to account for random highs and lows. Similar to umbrella and platform studies, basket trials may be exploratory or with registration intent such as Keynote 158 (NCT02628067; ref. 15).

Keynote 158 evaluated pembrolizumab in microsatellite instability high (MSI-H) solid tumors (15). Tumors that are MSI-H are relatively uncommon; however, MSI-H tumors can be found at varying prevalence in virtually every cancer type (16). Data from a smaller investigator-initiated study suggested that pembrolizumab would be effective across multiple tumor types as long as they were MSI-H (16, 17). Therefore, Keynote 158 was designed as a basket trial and included a cohort (cohort K) for patients with any MSI-H solid tumor, with the exception of colorectal cancer, which was already being evaluated in this disease subtype as part of another trial (Keynote 164; ref. 15). Cohort K of Keynote 158 ultimately supported the FDA submission and approval of pembrolizumab for MSI-H solid tumors (18). However, other basket studies have shown that despite conserved molecular features across multiple histologies, treatment response may be dependent on tumor type. This was especially true in the vemurafenib basket trial by Hyman and colleagues where response of *V600E*-mutated cancers to vemurafenib was dependent on tumor type (19).

As with umbrella and platform trials, a major advantage of basket trials is the protocol executional efficiencies. As opposed to multiple separate studies, multiple tumor types can simultaneously be evaluated for drug efficacy within the context of one basket study. If emerging evidence suggests a tumor type should be added, the protocol can be amended to include the additional tumor type, rather than starting a new clinical trial. This is a more efficient way to explore tumor efficacy signals across multiple tumor types, which can subsequently guide registrational efforts. For drugs that are predicted to work across multiple tumor types, beginning with three to five tumor types as a first "wave" is a cost and time effective initial approach (20). Decisions to expand to a second "wave" in multiple other tumors can be made based on the initial findings. Histology-specific expansion cohorts may be preplanned on the basis of preclinical data or unplanned based on early efficacy signals. The response-adaptive Bayesian designs described by Ventz and colleagues provide appropriate biostatistical input into basket trials to identify tumor histologies that respond in a biomarker-positive group. Furthermore, ineffective cohorts can be dropped in response-adaptation designs, and expansion cohorts often have built in early stopping rules for futility in an effort to prevent exposure to ineffective therapy (21).

Therefore, basket trials often expand from first-in-human to multiple expansion cohorts within the context of a single protocol. In many basket trials, an initial dose escalation phase is followed by three or more additional cohorts with cohort-specific objectives. These objectives are varied and may assess antitumor activity in specific cancer types, assessment of pediatric or elderly patients, patients with organ impairment, impact of food, drug–drug interactions, alternative doses or schedules, dose/schedule in combination with another drug, and/or evaluation of the predictive value of a potential biomarker. These expansion cohorts are often evaluated within the framework of basket trials.

Keynote 001 is an example of a first-in-human dose escalation basket trial with pembrolizumab, which evolved into a multicohort study with multiple amendments focused mainly on melanoma and NSCLC cancer following extraordinary clinical responses in these tumor types (22–27). The study evaluated different doses, schedules, biomarkers, subsets, test sets, and validation sets. It ultimately led to two accelerated approvals, one in advanced melanoma, and one in PD-L1–positive advanced NSCLC (23, 28, 29). As one of the largest phase I trials performed to date, the study ultimately enrolled over 1,200 patients.

Challenges with Novel Clinical Trials

Sponsor challenges

Umbrella trials, platform trials, and basket trials create challenges for industry, predicated on whether the trials are designed with registrational intent versus trials designed to assess surrogate markers of benefit (often exploratory intent). Registration trials, in contrast to exploratory intent, present challenges because of the potential for rapid changes in the standard-of-care arm. For

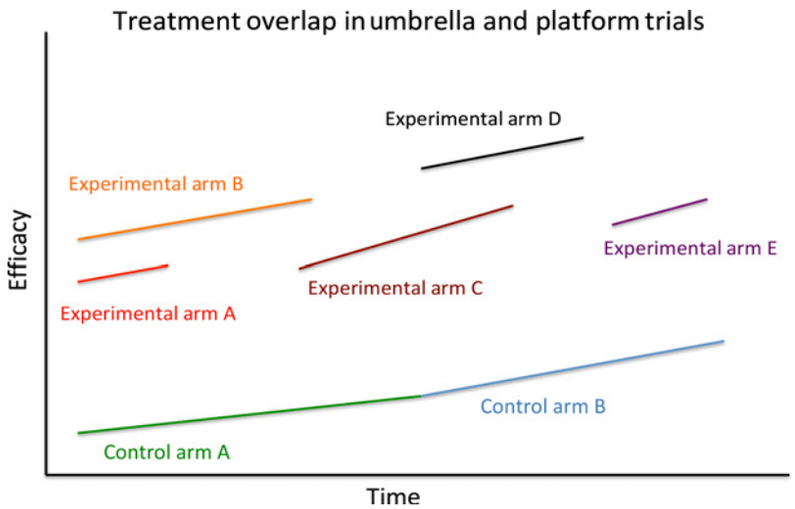

Figure 2.
The overlap of experimental arms varies with the control arm(s) because experimental arms start and can stop at different times in umbrella and platform studies.

example, the umbrella study, Lung-MAP, originally had chemotherapy standard-of-care control arms, but when immunotherapy was approved in this patient population, the study had to be revised to include a new standard-of-care control arm (30–33). Revisions may become necessary when control arms are no longer contemporaneous with a later arm in the study (due to adding and removing experimental arms at different time points in umbrella and platform trials; ref. 34). As a result, different experimental arms can vary in their temporal overlap with the control arms (Fig. 2). To maintain the integrity of the trial when a control arm is changed, the different experimental arms can be simultaneously compared to the control arms. This method allows for each arm to statistically support the other experimental arms (34). The use of existing treatment overlap of different experimental arms with the control arms is a sound strategy for approaching this challenge. Umbrella and platform trials are more likely to encounter issues with changes in the standard of care compared to traditional studies as new experimental arms may accrue after the control arm is closed. However, a change in the standard of care also presents a challenge for traditional studies. In traditional studies these changes also require an updated control arm and therefore additional enrollment. Compared with innovative designs, the limited number of treatment arms in traditional studies and simultaneous accrual to experimental and control arms simplify the statistical modeling needed to create estimates for the temporal changes by control-arm switching.

Combination studies in umbrella and platform trials also create challenges in instances of multiple database logs frequently needed for registration studies, which can significantly add to trial complexity. If the trial is primarily exploratory, an appendix to the trial can be used to introduce new therapies into the treatment armamentarium. Such an approach has been successful in the I-SPY2 trial. Combinations involving products from different sponsors can pose significant contracting challenges.

The multiagent nature of platform and umbrella studies creates opportunities for novel combinations through collaboration between multiple companies. Collaborative efforts between two companies in a single study have been undertaken in multiple traditional studies and are not a challenge that is unique to umbrella and platform studies. However, the scope of these collaborative efforts is broader in platform and umbrella studies, with the potential for the involvement of many companies given the multitude of treatment arms. In addition, the pace of amendments, which may introduce new drugs and therefore new companies into ongoing studies, creates challenges not typically seen in traditional studies. Platform and umbrella studies require a thoughtful upfront assessment by sponsors to address conflicts of interest and competing interests among companies. Additional questions must be addressed, such as how best to fund the control arm, especially in instances where experimental arms are added after the control arm has finished accrual, or how best to divide the costs of data storage and ensuring all companies have standardized data interpretation and reporting. Master contracts between companies require an upfront investment in time and resources, but ultimately help support the unique opportunity for rapid evaluation of novel agents from multiple companies in the same study.

For basket trials designed with registrational intent, it should be determined a priori if the trial is designed to demonstrate benefit based on a specific biomarker, and have tissue agnostic efficacy, or designed to demonstrate benefit for a specific tumor type. If tissue agnostic, it is important to predetermine if specific tumor types will be included and what biological evidence will be required to support the drug efficacy regardless of tumor type. Tissue agnostic trials introduce the concept of reclassification of cancer based on genetic criteria rather than histology. Rare, but highly predictive biomarkers such as tropomyosin receptor kinase (TRK) fusions that are highly predictive of response to larotrectinib (35) have helped support this reclassification.

If trial sponsors hope to demonstrate efficacy to support a regulatory submission for individual tumor types within the context of a basket trial, programming challenges must be identified to isolate data from individual cohorts that are required for submission. In addition, if a basket trial includes multiple exploratory arms, a statistical quandary arises in identification of the correct number of patients within the individual baskets (tumor types) that can be enrolled into each "exploratory" basket without the need for new protocols. The FDA recommendations currently suggest that nonrandomized cohorts should use a Simon-2 stage design to limit exposure of additional patients to ineffective drug (36). It is becoming more common that both registrational and exploratory basket studies may require independent data monitoring committees to assure that large numbers of patients are not exposed to potentially ineffective treatments. Finally, the

tissue agnostic principle of basket studies creates real-world challenges for partnering with cancer centers, which are generally organized by tumor type. This leads to the dilemma of who should be a site principal investigator (PI), and ultimately creates challenges for recruitment, publication, and authorship.

FDA challenges

The FDA has been instrumental in encouraging and promoting innovations in clinical trial design. The Critical Path Initiative in 2004 by the FDA was an important initial step, and the 21st Century Cures Act further highlighted the agency's desire for more efficient treatment advances. More recently, the FDA has developed a number of guidelines for industry to help address challenges with contemporary oncology drug development. One recent guideline is focused on master protocols (37), whereas another focuses on expansion cohorts in first-in-human clinical trials (36). At this time both of these guidelines are in their draft form. The FDA has made it a priority to produce informative guidelines in a timely fashion to support the efficient development of effective new therapies, and to help sponsors navigate through the approval process.

These novel trial designs pose many challenges from a regulatory standpoint. A major challenge is timely dissemination of new safety information to investigators, the institutional review board (IRB), and regulators due to the rapid changes seen in these studies. Challenges with the dissemination of information create the risk of a failure to provide adequate informed consent. With the increase in size and operational complexity, it becomes challenging to update patients on safety risks that emerge. Therefore, a predetermined plan is recommended to update investigators and patients as toxicities arise. There are also concerns regarding trial size and the prospect of exposing large numbers of patients across multiple simultaneous cohorts to potentially suboptimal or toxic doses of investigational therapies.

Although often a primary goal of novel trials is to treat the minimum number of patients to achieve the study objectives, there are examples of phase I studies where sample size estimation of expansion cohorts are not specified in the statistical plan. This creates the concern that more patients may be exposed to investigational therapies than appropriate and the trial's type I error rate may be greatly inflated. There are rare examples of suboptimal drug development based on over-interpretation of study findings. This includes suboptimal selection of dose regimens, or inappropriate or misleading conclusions about differential biomarker subsets that may benefit based on *ad hoc* cohort comparisons.

A pre-Investigational New Drug (IND) meeting with the FDA is strongly encouraged to receive adequate scientific advice from the FDA. Master protocols should be submitted as a new IND, and major FDA considerations regarding safety, biomarkers, and statistics are highlighted in Table 1. For protocol amendments, the FDA requests 48 hours of advanced notice prior to the planned activation of a substantial amendment to allow for safety review. However, urgent safety issues requiring immediate attention should be addressed immediately. It is recommended that the master protocol be the only study conducted under the IND and be submitted to the appropriate review division. There may be examples, such as a tissue agnostic basket trial, where the study crosses FDA review divisions, and the sponsors should ensure that the appropriate clinical division is notified. In addition, the FDA also needs to ensure good communication across clinical divisions.

Table 1. Major FDA considerations when reviewing master protocols

FDA considerations	FDA recommendations
Safety	• Early plan for regular submissions of accumulative safety summaries more frequent than an annual report. • Reference safety reports in protocol amendments. • Maintain medical monitors with cancer treatment experience. • Establish an independent data monitoring committee. • Central IRB use.
Biomarker development	• Analytically validate *in vitro* diagnostic assays. • Clear descriptions of procedures for sampling, acquisition handling, testing, and analysis. • Study-risk determination for investigational device exemption (IDE; ref. 48). • Early contact of FDA to obtain risk assessment (simultaneous with 30-day IND submission).
Statistical	• Limit exposure for nonrandomized studies with a primary endpoint of response rate. • Utilize two-stage design. • Vigorous data collection for registrational intent studies. • Use of a common control arm for randomized studies (i.e., umbrella studies). • Avoid cross-experimental drug comparisons. • Include futility analysis and sample size modification.

Good clinical practice

Adherence to the good clinical practice (GCP) quality standards is a very important issue in the protection of the rights, safety, and welfare of study participants in novel clinical trials (38–40). For registration trials, the FDA conducts clinical inspection for GCP when deemed necessary. The most common GCP challenges identified during clinical investigator inspections are failure to follow the protocol, which accounts for approximately half of the inspection deficiencies internally assessed by the FDA. This is followed by problems related to inaccurate and inadequate records. The propensity for these novel clinical trials to evolve throughout the study, which may include new amendments, creates risks to GCP. Examples of the failure to follow the investigational plan demonstrate the need to proactively and systematically include quality controls in these studies. It is equally important to identify the risks that play a major role in impacting reliability and integrity upfront. Addressing these challenges requires the sponsors to engage all stakeholders early in clinical planning.

A major challenge that is particularly problematic in adaptive clinical studies are issues related to un-blinding, which can introduce bias to the patient, clinical investigators, and sponsors. It is therefore critical for sponsors to have a validated system to capture data and ensure that only authorized individuals have access.

Investigator challenges

Increased trial complexity has created significant challenges for investigators including numerous sample collections, multiple required committee approvals, more intensive patient monitoring, complex drug administration, and multiple protocol amendments. The end result of this increase in complexity is a considerable increase in the operational challenges imparted on site staff.

Cost. The appropriate reimbursement for study staff time is a critical issue for investigators, site staff, and institutions. This is made even more difficult by varied complexities among studies, which may require justification to a sponsor regarding why staff time may be more expensive for one study versus another.

Amendments. The increased number of treatment arms utilized in novel clinical trials has led to a higher number of amendments compared with the historical norms for early phase studies. These amendments increase the complexity of all clinical trials, generate excess paperwork, and greatly increase the financial considerations for studies. The investigator and staff time dedicated to regulatory approval, training, and education on amendments is considerable. Although required with each amendment, the retraining for a single consent change is often irrelevant for virtually every involved party. Similarly the re-consenting required with amendments is often frustrating for patients and investigators. The need to manage multiple amendments in real time and keep track of the specific status of amendments has led sites to develop their own electronic monitoring systems as well as hire additional site staff, which both increase study costs. To the extent possible, protocol updates should be consolidated to minimize amendments.

Serial biopsies and integral biomarkers. The NCI Investigational Drug Steering Committee defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to therapeutic intervention" (41, 42). Integral biomarkers are used for preselection of patient treatment as part of eligibility criteria. If fresh tissue is required, the patient may require a pretreatment biopsy only to find out that the biomarker required for protocol recruitment is negative and hence the patient is ineligible. Another aspect that limits patient eligibility is the absence of disease amenable to biopsy such as a patient with prostate cancer and bone-only metastasis.

The number of biopsies, sequential biopsies, and needle passes per biopsy has greatly increased. There are also increasing complexities around the exact site of biopsy acquisition, with extreme demands such as requiring tumor tissue from areas of prior direct intratumoral therapy injections or repeat serial biopsies in the same tumor location. The evolving biopsy requirements demand significant infrastructure. This also requires investigators to have close relationships with specific providers in specialties able to perform the biopsies, such as interventional radiology, surgery, and pulmonary. These increasingly complex biopsy requirements create real barriers for many sites, even major academic centers, which may not be able to meet these specific trial demands.

Consents. Informed consent documents used in novel clinical trials are often overly cumbersome and confusing for both patients and investigators in large part because the trials themselves are so complicated and difficult to explain. Early review by patients, patient advocates, and potential enrolling sites is recommended to clarify and simplify consent language and the consent process. Multiple components of the clinical trial need to be discussed in a single consent. With master protocols, when the consent is originally drafted it is not known which expansion arm a patient is going to end up in, and the aligned risks or potential benefits of the research are not necessarily understood and may change as the study evolves. Some studies utilize a second consent form specific to the study arm a patient is enrolled in, as a way to properly account for risk. Across all oncology clinical trials, the average consent form is 20 pages long (43) and even expert investigators and research staff reviewing a consent form may not be aware of how much of the content the patient comprehends. Shorter and simplified consent forms are more likely to engender participant comprehension; this can be aided by early involvement with patient advocacy groups.

Adding to the complexity is the need to reconsent participants when changes are made that impact the risk–benefit ratio or the willingness of participants to continue in the research. Significant resources are needed to track which patients need re-consenting, and these staff requirements should be budgeted with the sponsor when possible.

Table 2. Major investigator challenges with first-in-human expansion cohorts

Investigator challenges for expansion cohorts	Investigator strategies
Early line of therapy expansion cohorts	• Advocate with referring physicians for timely referrals. • Understand competition from standard-of-care therapy.
Ability to provide disease management expertise	• Identify specific investigators with disease expertise within the phase I unit. • Clear roles for various investigators in the phase I unit.
Genomic (pan-histology)–driven expansion cohorts	• Identify the appropriate PI. • Identify ideal referral pattern based on expected incidence. • Optimize timing for genomic testing of referrals.
Infrastructure for large expansion cohorts	• Early identification of appropriate studies to move outside phase I units in expansion. • Ensure appropriate oversight and data management for studies that move out of phase I units.

Expansion cohorts. Expansion cohorts provide additional unique challenges for investigators (Table 2), and are increasingly moving into earlier lines of therapy, making it challenging to identify appropriate patients. In addition, given the complex interdisciplinary care, it is increasingly important to have disease management expertise, which can be further complicated for expansion of a cohort characterized by a specific genomic aberration. Finally, there are practical considerations, such as allowing patients eligible for the expansion cohorts to be seen by physicians in the disease specific clinics of an academic center rather than creating a bottleneck in the specialized phase I unit. To transition these studies into the disease-specific units or community-based settings requires appropriate infrastructure and efficiency. Approaches to address these challenges are further highlighted in Table 2.

Analysis/publications/presentations. Investigator acceptance and endorsement for a study is critical, and it is important to keep sites engaged. Enthusiasm is significantly diminished when eligible patients cannot be enrolled on a routine basis, or when only patients with an uncommon mutation are sought, and many patients are ineligible. In addition, scholarly recognition is a high priority for career advancement of academic investigators, and

Table 3. Challenges faced by the IRB when evaluating novel clinical trials

IRB topics	IRB-specific challenges
Adaptive protocols	• Planned modifications impact informed consent as risks evolve throughout the study. • How often to require consent revisions. • Difficulties ensuring patient risks are minimized.
Toxicities	• Difficulty weighing severe toxicities that are expected (e.g., CAR-T cytokine release).
Expectations of phase I, II, and III trials	• Whether to allow efficacy objectives in phase I. • Appropriateness of randomized phase II vs. phase III to achieve stated objectives.
Genomic-driven inclusion criteria	• Assessment of investigator qualifications. • Ensure investigator communication with other disease experts and oversight.

Abbreviation: CAR, chimeric antigen receptor.

novel clinical trials create new challenges for authorship. For example, phase I investigators that are integrally involved in the first several patients treated with an agent are sometimes not recognized as authors if accrual activity within expansion cohorts is used to prioritize authorship contributions. Therefore, the leadership and extra effort required for early investigator involvement should be recognized when determining authorship of reports of the study.

IRB challenges

The IRB, whose primary mission is to ensure the protection of human subjects in research, faces unique challenges with novel clinical trial designs. Several important topics that drive many of the challenges faced by the IRB are highlighted in Table 3. The adaptive nature and changing design of many master protocols creates issues related to the adequacy and accuracy of the descriptions in the informed consent. Toxicities experienced during trials create challenges for the multidisciplinary IRB that may not have adequate expertise to understand the unique toxicities and safety issues arising from new therapies such as immunotherapies. The expectations of trials are evolving, and the IRB follows FDA guidance to ensure appropriate objectives are measured. Finally, expansion of a cohort characterized by a specific genomic aberration creates some of the same problems for the IRB as noted for investigators. Sponsors should thoroughly address these issues prior to IRB submission to assure a proper and timely IRB assessment.

The patient advocate

Patient advocates are welcome partners in the development and execution of novel trial designs and in recommending endpoints that are important to patients and clinicians. They can provide important advice on issues ranging from specimen collection to simplifying informed consent and reducing out of pocket cost burden. Improved patient understanding allows for shared decision making, which is critical for enrollment and retention. Several shared treatment decision-making tools have been validated to reduce patient distress, anxiety, and improve patient–physician communication (44, 45). These abilities have demonstrated that advocates can be key players in the development of novel trials (10, 30, 44–47).

As this article describes, novel clinical trials are complex for the clinician to explain and for patients to comprehend, therefore it is critical for enrolling clinicians to invite patients to consider their preferences, challenges, and personal goals prior to enrollment. In the long run, this can aid adherence and improve the overall patient experience.

Conclusions

The 2018 AAADV Workshop highlighted the major challenges of developing and implementing novel trial designs including umbrella trials, platform trials, and basket trials. The goal of these designs is to deliver new therapies to patients safely and more quickly and efficiently than in the past. However, these complex designs require thoughtful planning and implementation. The diverse panel of experts that participated in this workshop each described their respective challenges. Also included are preliminary strategies to help address many of these challenges, although there are undoubtedly alternatives to overcome some of these challenges. These novel trial designs provide unique opportunities to expedite drug development, but sponsors, investigators, the FDA, IRBs, and patients must collaborate to address the unique challenges that result. This partnership requires extraordinary rigor from all stakeholders. The AAADV Workshop continues to provide an annual forum for sponsors, investigators, regulatory agencies, and patients to come together and discuss the challenges with the drug development and approval process. Promising drugs are being developed at an extraordinary rate, and delays in the approval process of exciting new agents can be directly translated into life lost for patients. Through continued collaboration among all parties we can continually improve this process and truly accelerate anticancer agent development.

Disclosure of Potential Conflicts of Interest

P.M. LoRusso is a consultant/advisory board member for Agios, Genmab, Pfizer, Roche/Genentech, Genentech, Agenus, Cybrexa, CytomX, and SOTIO. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

This article reflects the perspectives of the individual authors in an evolving area of regulatory science and health care policy. The article should not be construed to represent official views or policies of the FDA, AACR, or ASCO.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Cecchini, S. Boerner, P.M. LoRusso
Study supervision: M. Cecchini, E.H. Rubin

Received November 9, 2018; revised January 7, 2019; accepted January 25, 2019; published first January 29, 2019.

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