WHITE PAPER

# **Innovative Designs in Early Phase Oncology Trials:** Leveraging CRM and Basket/Umbrella Designs to Improve Efficiency


**Jürgen Hummel**
Senior Director, Statistical Science, Biostatistics

**Rachael Song**
Associate Director, Project Management

**Dirk Reitsma, M.D.**
Vice President, Oncology, Global Product Development

**Kent Buhler**
Senior Director, Project Management

**Song Wang**
Statistical Science Director, Biostatistics

## Executive Summary

Applying innovative designs in early phase oncology trials can not only accelerate timelines and reduce costs, it can help focus development on the most promising agents at the right doses in the right indications for the right patients. In this white paper, we explore potential scientific and operational implications—along with approaches to address potential challenges—for two different innovative, yet well-established designs:

1. The continual reassessment method (CRM), an adaptive design that can be used to better identify the target dose
2. Basket and umbrella trial designs, types of master protocols that can efficiently address multiple research questions under the auspices of one protocol to identify target indications and patient populations

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## Advancing Early Phase Oncology Trials with Innovative Approaches

As the scientific community unlocks cancer codes—gaining newfound understanding of how, for example, therapies interact with biomarkers or how tumor and immune microenvironments interconnect—new and expanding treatments, indications and combinations are flooding the oncology pipeline. With more than 6,500 drugs in the R&D pipeline, cancer candidates now account for 37% of agents in clinical development, offering hope of much-needed advances.[1]

**The problem:** Of the oncology agents that enter Phase I trials, only 3% eventually receive U.S. Food and Drug Administration (FDA) approval.[2]

How can oncology clinical development teams facing increasingly complex scientific and operational challenges begin to turn the corner? The answer lies not just in shaking the trees, but in leveraging innovative new approaches to design more efficient studies that not only improve success rates but also fail faster with confidence to allow resources to be directed to more promising indications or assets.

**Traditional designs** contribute to high failure rates and escalating costs because each trial is designed to answer only one narrow scientific question at a time—a question that may or may not be the most important question—on a rigid sequential path. Moreover, answers to pivotal research questions are often obtained only at the end of the trial.

**Adaptive designs**, in contrast, potentially allow a trial to answer multiple questions at once, leveraging accumulating data so early findings can inform decisions in a flexible process. Adaptive designs allow for prospectively planned modifications to one or more aspects of the design based on accumulating data from patients in the trial. Modifying trials as they progress can accelerate timelines, reduce costs and generate more knowledge, thereby improving the overall quality and efficiency of decision-making.

*"In the traditional approach to clinical development, you begin with an assumption and then design and test against that one assumption throughout the study," said Rachael Song, associate director, project management, PPD. "But what if you could continuously update your hypothesis, building adaptations into the study design and using the data to help drive improved decisions? The result will usually be a better outcome. Other industries have been long moving toward iterative development methodologies for continual improvement. Agile is one prominent example. In many ways, biopharma is only catching up as we apply more flexible designs."*

## Bending the Cost and Time Curve of Drug Development

Perhaps nowhere can the application of innovative designs be more impactful than in the early phase when decisions are made that have far-reaching consequences. With thousands of potential drugs awaiting development—and with the vast majority of those unlikely to demonstrate efficacy—earlier, better information and decision-making is critical to identify the most valuable assets and improve success rates.

*"It's surprising that innovative designs are not used more often given that the methods are well-established, more efficient and that regulators encourage their use," said Dirk Reitsma, vice president, oncology, global product development, PPD. "The largest untapped opportunities are arguably in the early phases of clinical development where adoption of innovative designs may, in fact, help support an accelerated approval."*

## "The World Is Now Onboard"

Although adaptive design and master protocols can help make clinical trials more informative and efficient, the designs that emerged in the 2000s initially raised scientific and regulatory questions—and apprehensions—that slowed adoption.

However, a growing body of evidence culminated in drafted guidance. In 2007, the European Medicines Agency (EMA) began introducing frameworks for adaptive designs and encouraged their use: "The option to modify the design of an ongoing clinical trial in the framework of an 'adaptive design' is intuitively appealing. The opportunity to correct misjudgments on the basis of data from a planned interim analysis is likely to increase the chance of the trial formally being a success."[4]

The FDA provided draft guidance in 2010, which was then refined and was finalized in 2019.[5,6] The FDA also drafted *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics* in 2018.[7] European Clinical Trial Facilitation Group (CTFG) perspectives on complex clinical trials with master protocols were presented in 2019.[8]

### Agile, an Iterative Development Methodology Seeing Rapid Adoption

Commonly applied in software development, agile advocates adaptive planning, early delivery, continual improvement and flexible responses to change. In 2011, less than 10% of major federal IT projects were described as "agile" or "iterative." By 2017, 80% of major federal IT projects were described as "agile" or "iterative."[3]

### FDA Adaptive Design Guidance (2019)

"Adaptive designs can provide a variety of advantages over non-adaptive designs. These advantages arise from the fundamental property of clinical trials with an adaptive design: they allow the trial to adjust to information that was not available when the trial began."[5]

*"Our experience in submitting protocols with adaptive designs in early stage oncology trials to U.S. and European regulators is that they not only accept these designs—if anything they actively encourage them. Investigators too have a growing understanding of the many benefits of these approaches. The world is now onboard," said Jürgen Hummel, senior director of statistical science, biostatistics, PPD.*

Innovative adaptive designs, though on the rise, continue to be underutilized. While adaptive designs are not relevant for every study, there is still substantial untapped opportunity to take advantage of these powerful innovations in oncology clinical research, particularly in the early phases. We will explore opportunities and case studies in this paper.

## SETTING THE STAGE FOR FLEXIBILITY

The adaptation process is typically prescribed in the trial protocol. Modifications may include dosage, sample size, patient selection criteria and "therapeutic cocktail" mix. In some master protocols, a trial becomes an ongoing process that regularly adds and drops therapies and patient groups as more information is gained. Importantly, the trial protocol is set before the trial begins; the protocol pre-specifies the adaptation schedule and processes.

## ADAPTIVE DESIGN IN CURRENT PRACTICE: DEFINING THE MAXIMUM TOLERATED DOSE (MTD)

Failure to define the optimal dose in clinical development is a common problem plaguing oncology research. Phase I trials have a correct MTD estimation rate of only about 40%,[9] which may result in patients being treated at subtherapeutic doses or doses that are too toxic, both of which disrupt the outcomes of all subsequent phases, and potentially—without a correction—may lead to the failure of the entire development program at a later stage.

The vast majority of trials continue to identify MTD using a rule-based method such as the 3+3 design, which offers simplicity, convenience and familiarity, but which may or may not produce an accurate MTD. The continual reassessment method (CRM), on the other hand, is an adaptive Bayesian model-based approach introduced in 1990 that is superior to the 3+3 design, both for determining the MTD and for treating more patients at the MTD in a trial.[10]

**Conventional 3+3 method.** Using the commonly applied 3+3 method, dose escalation steps are defined prior to the trial. A cohort of three patients receives drug at a starting dose based on preclinical data. If no toxicity is observed, another cohort of three patients is added and the dose is escalated to the next level. If one patient experiences a dose-limiting toxicity, another three-patient cohort is added at the same dose and dose escalation continues. However, if any additional toxicity is observed, the dose below is declared the MTD. The dose escalation steps are defined prior to the initiation of the trial and MTD determination is based only on data generated from the last dose level. When escalating one dose at a time, developers tend to select larger incremental "jumps" to observe toxicity more quickly in fewer steps. Lacking precision, this method often yields an over-estimation or underestimation of the true MTD, and, as such, we don't recommend its use.

**Other rule-based methods.** Several improved rule-based dose escalation designs have gained popularity in recent years, including the modified toxicity probability interval (mTPI) design and Bayesian optimal interval (BOIN) design. Decision rules are based on a pre-specified target toxicity level so they can identify the correct MTD with a higher accuracy than 3+3. These designs are also more flexible than 3+3 in terms of cohort size. All decision rules are pre-specified so they can be implemented without a statistician's help. However, like 3+3, decisions are made using data from the current cohort alone. Because they do not fully use all collected data, these methods have a lower accuracy than a model-based design like CRM. The difference in accuracy becomes more obvious as more dose levels are tested, therefore, we only recommend using mTPI or BOIN design if the number of dose levels to be tested is less than five.

**CRM design.** In most situations, the CRM adaptive design is the best choice for dose escalation studies. It improves MTD identification by efficiently evaluating more doses to estimate the MTD more precisely. While the 3+3 design bases the next allocation, and therefore the dose level eventually determined to be the MTD, on the last cohort of patients and ignores the data from the previous cohorts, a CRM models the probability of observing a dose-limiting toxicity as a function of dose and continuously refines it. All data are used to update the estimation of the MTD and to allocate the next patients, either in cohorts or continuously. The model is frequently updated and thus is improved with accruing data, allowing researchers to get more precise answers and make better, more efficient use of data from a smaller number of patients, which may serve as an advantage in many trials. The CRM provides an increased chance of treating study patients around the MTD and a decreased chance of exposing patients dosed at levels greater than MTD. It also often leads to cost savings and an accelerated timeline, while still achieving a more accurate recommended Phase II dose.

**Simulations.** Fixed designs rely on theoretical justification of trial behaviour. Adaptive designs, however, use simulations to understand trial behavior, risks and efficiencies as inputs to inform and optimize trial design. Regulators may require submission of simulation results in order to justify the scientific credibility of an adaptive trial. For exploratory studies, simulation results help regulators understand how safe the proposed design is, in particular regarding the potential of dosing patients at doses above the MTD. Simulations using CRM designs not only test scenarios for the dose toxicity most likely to happen, importantly, they also test scenarios for the dose toxicity less likely to happen. Although this approach is more complex, understanding how the design performs when unexpected events happen can help avoid costly mistakes.

*"As a best practice, we test as many scenarios as possible, so we can go into a study with a much better understanding of how the study is likely to pan out," said Song Wang, statistical science director, biostatistics, PPD.*

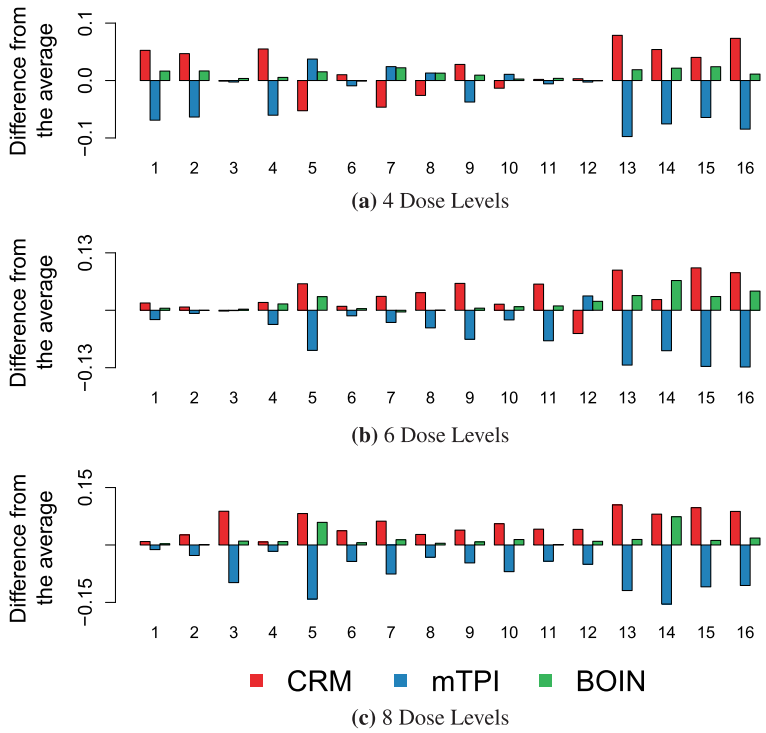
## FACTS: Fixed and Adaptive Clinical Trial Simulator

Widely regarded as the most powerful simulation software available to the industry, FACTS helps clinical teams optimize trial design. Its suite of programs enables simulation of many common dose escalation trials.

Simulations also can incorporate information on neighbouring doses, different populations, similar compounds, preclinical modelling, genetic targeting and historical data to inform the design of the current trial.

**Pinpointing the correct dose.** CRM has been shown to assign more study patients at or close to the MTD compared with rule-based designs. A recent study comparing the CRM method with mTPI and BOIN, found that CRM most often outperformed both mTPI and BOIN in terms of accuracy.[11] Figure 1 shows the accuracy index for dose selection as found in 16 simulations in which scenarios were independently created for each set of dose level curves at four-dose, six-dose and eight-dose levels. As the number of dose levels increased, the accuracy levels of each method became increasingly differentiated. In the set of scenarios with eight-dose levels, CRM achieved the highest accuracy index values, followed by BOIN and mTPI.

**Figure 1.** Accuracy Index of Dose Selections: Comparing CRM, mTPI and BOIN[11]




Source: Horton BJ, Wages NA, Conaway MR. Performance of toxicity probability interval-based designs in contrast to the continual reassessment method. *Statistics in Medicine*. 2017;36(2):291-300.

Another study, comparing CRM to 3+3, similarly found that in simulations, in the majority of cases, CRM yields a better estimation of the MTD.[12] The CRM design performed better than the 3+3 method at identifying the correct dose level in nine of 10 scenarios presented.

*"Even if you make a non-perfect decision somewhere along the way, when you collect enough data, CRM still converges to the correct dose," said Wang. "With 3+3, if you make a mistake, the model cannot forgive it and will ultimately produce the wrong dose."*

**Flexibility.** CRM also provides much more flexibility than a rule-based model—both scientifically and operationally. For one, it allows teams to design a study that meets their own unique requirements. If accuracy is deemed to be the most important priority, for example, a study could plan for a higher level of investment in the dose escalation phase to arrive at an extremely precise MTD. A team facing budget or timeline constraints, on the other hand, might be willing to sacrifice a few degrees of precision to achieve a faster, lower-cost study. Or, if there is uncertainty about the toxicity profile, and consequently many dose levels that must be tested, the CRM may require a much smaller sample size as compared to rule-based methodology, potentially leading to significant cost savings.

Because of its flexibility, adaptive designs can overcome inherent limitations in the fixed structure of traditional designs. In a fixed structure, pivotal decisions must be made based on limited information available in only a fixed window of time. At the end of a fixed trial, it is common for researchers to regret decisions based on assumptions regarding the dose that were used in the study. An adaptive design, in contrast, uses accruing information to provide more relevant data to guide critical decisions—with speed—throughout the development process.

Late toxicities are an example of the type of data that the CRM design can uniquely accommodate.

*"We conducted one study in which a bone-density toxicity had emerged only after the four-week observation period for dose-limiting toxicities had been reached," said Hummel. "If we had conducted the study using 3+3, we would have been unable to adjust the MTD based on this newly emerging safety data. But because we used a CRM design, we had the flexibility to go back and update the MTD as the information became available."*

**Combination trials.** Dose escalation studies in combination trials, which have the potential for many more possible escalations/de-escalations of one or both drugs, are clearly more complex than single-agent trials. Moreover, a multitude of MTDs may exist.[13] An adaptive design offers significant advantages over a rule-based design in combination trials:

- Often, rich historic information is available on the dose-toxicity response from previous monotherapy studies. All the knowledge that was gained in these studies can be applied in a CRM design. A rule-based design, in contrast, cannot take advantage of borrowing of information.
- When a study is prescribed to proceed step by step, as in a 3+3 design, it becomes necessary to test every possible dose combination, which is a formidable task. Because CRM borrows previous knowledge, it can generate predictions and directional guidance that can steer determination of the number of doses to investigate, as well as what those doses might be.

**Subsequent trials.** Another "borrowing of information" advantage in Bayesian design is the potential to improve decision-making in different populations in subsequent trials. For example, if you run a dose escalation study on adults and you want to now arrive at a pediatric dose or if you have completed a study in the United States and you now need to run that same study in Japan, you can use the dose-toxicity information you have previously collected to help make informed predictions that will result in smaller and more efficient subsequent trials—at substantial cost savings.

**Adaptive designs may address multiple research questions simultaneously.** For example, the CRM design offers the potential to model for both toxicity and efficacy, producing not only the MTD but also the minimum effective dose level using the bivariate CRM dose escalation model.

*"This is a powerful—and surprisingly underutilized—advantage," said Reitsma. "It works particularly well for drugs that have both high activity and high toxicity because then you have something to adapt to. I predict we will see a rise in adoption of these more sophisticated studies in coming years, particularly for immuno-oncology agents."*

**How to implement CRM designs operationally.** Although the scientific methodology can be more difficult to understand, in large part, operational considerations for a CRM design are similar to that of a 3+3 design.

*"A common misconception is the notion that, operationally, CRM is a whole new world," said Wang. "Unfortunately, this lack of familiarity with the model deters adoption. In fact, operationally, CRM is not very different from 3+3, and we have a great deal of experience developing the workstream and documents to guide implementation of CRM to minimize difficulty. As well, the user-friendly simulation software we employ ensures the design is optimized. Another misconception is that updating the CRM design with new data takes a lot of time, which is incorrect. We typically update CRM designs with new data within one working day."*

**The case for early engagement.** Early engagement—that is, beginning a collaboration with the synopsis still in draft form—allows for the development of a protocol that incorporates a CRM design without introducing delays. On the other hand, when engaging a CRO with a written protocol and a timeline with targets for achieving first patient in (FPI), on the face of it, revising a protocol for the introduction of a CRM design vs. 3+3 may appear to introduce a six- to eight-week start of timeline startup delay to incorporate time for simulations.

Another implementation barrier can be a fear that recommendations from a model-based design cannot be overridden by clinicians.[10] "It's important to bear in mind that the CRM only provides a recommendation that can be overruled by a dose escalation committee," said Reitsma.

While a CRM design does, in fact, require more time on the front end, as evidenced in the following case study, it also may shave significant time off a timeline *overall* by requiring fewer patients and by allowing for more rapid progression through early dosing levels depending on the operating characteristics and rules that are established in the design. In general, the most benefit can be obtained by engaging early with a CRO to partner on statistical design decisions, protocol writing and investigator engagement to not only achieve the optimal dose, but to accelerate the timeline and thus maximize cost savings.

*"Bigger picture, from a cost perspective, a CRM design carries a much lower risk of over- or underestimating the MTD," said Hummel. "In fact, when you consider the potential costs of taking a suboptimal dose into the next phase, it becomes clear identifying the right MTD in the dose escalation phase could arguably generate the greatest cost savings—and advantage—that a program could gain."*

## CASE STUDY: Faster, cheaper, more accurate MTD

**Background**

PPD recommended the use of a CRM design rather than a conventional 3+3 design to establish the MTD in solid tumors, due to its potential to:

- Establish MTD accurately
- Achieve MTD faster and with fewer patients
- Allow for quick analysis of data and updates to the model
- Incorporate changes to the dosing levels if required

**Results**

Exceeded the client's expectations:

- MTD was established after six out of eight planned dose levels
- 15 patients were dosed vs. a range of 21 to 39 patients required in a 3+3 design
- MTD was established after 11 months vs. 20+ months required in a 3+3 design
- Three additional dose levels were included mid-study in response to emerging information without undermining the chances of identifying MTD
- Cost savings: At least $850,000 from reducing patient numbers and at least $830,000 from a reduced timeline

## MASTER PROTOCOLS: EFFICIENT AND ACCELERATED DEVELOPMENT THAT CAN IMPROVE THE ODDS OF SUCCESS

The right dose is, of course, only a part of the equation. The right treatment also must be used in the right indication for the right patient.

Master protocols employed in the early stages of a trial can create trials that help answer multiple questions simultaneously using a single infrastructure, design and protocol—not only adding speed and efficiencies but enabling rapid learning and data-driven improved decision-making. Study teams can become more nimble, flexing midstream to add or remove indication cohorts, drug combinations, and conduct other investigations in response to early findings without having to go back to the drawing board to write a new protocol and set up additional studies. Recent advances in analytics have further accelerated the benefits of master protocols in various therapeutic areas, including oncology, neurology, immunology and infectious disease.

*"Master protocols are not only advantageous scientifically, but, from an operational perspective, they can allow you to allocate your resources more efficiently and potentially reduce costs and development timelines," said Song.*

A master protocol may be used for exploratory purposes or to support a marketing application. It can incorporate a fixed or an adaptive design with the intent to modify the protocol to add or terminate individual substudies within the master protocol. Several innovations can be applied within a master protocol to improve trial efficiency. In an umbrella trial, which seeks to test the activity of a different targeted drug/combination within one indication, a common control arm can be used to reduce sample size. In a basket trial, where one drug is evaluated in multiple patient populations, a Bayesian hierarchical model would allow for information borrowing across patient cohorts and detect signals earlier with high efficiency. In both umbrella and basket trials, investigators may be able to save resources and treat more patients with more promising drugs by adding or stopping indication cohorts and/or treatment arms. Or they may adjust randomization ratio among treatment arms based on interim analysis results. Bayesian decision rules based on posterior probability of meaningful treatment effect or success in future trials would provide flexibility in interim data monitoring and decision-making, making it easier to detect efficacy signals earlier and hence reduce sample size. Many designs can be made adaptive, making it both more efficient and better able to answer questions accurately.

**Core benefits.** Leveraging master protocols in the early stages of a trial can be particularly impactful to develop, amend and answer hypotheses. Master protocols potentially can provide multiple benefits:

- Increase speed and quality of decisions: De-risk by accelerating successful investigations and failing faster

### FDA Master Protocol Guidance in Oncology Trials, 2018

"In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, master protocols use a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple substudies, **allowing for efficient and accelerated drug development**."[7]

**Figure 2.**
Deloitte Cost-Savings Assumptions for Master Protocols (2018 analysis)[14]

| Cost Component | Estimated reductin in cost (percent)* |
|---|---|
| Source data verification costs | 10-20% |
| Site recruitment costs | 20-25% |
| Administrative costs | 20-25% |
| Shared cost of control arms | 30-35% |
| Overhead costs | 30-35% |
| Aggregate savings across entire trial | 12%-15% |

*Calculated by applying cost-savings ranges to absolute dollar values as provided per Eastern Research Group benchmarks.[15]

Source: Deloitte Center for Health Solutions analysis

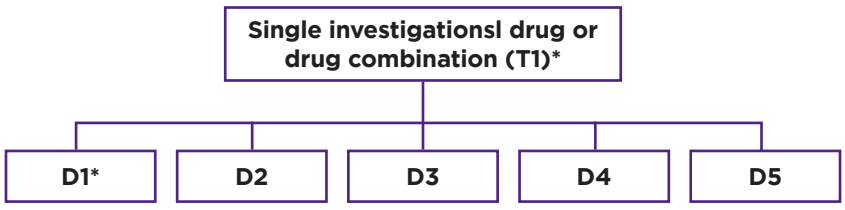
- Reduced costs: Shared trial infrastructure, design and protocol deliver cost efficiencies
- Shortened timeline: Efficiencies accelerate effective therapies to market. Deloitte estimates master protocols reduce timelines by 13-18 percent[14]

*"Master protocol trials offer very practical operational benefits," said Reitsma. "For example, because of the common protocol, you gain the ability to roll out amendments quickly and have IRBs review and approve them quickly as well. Other efficiencies include site contract and budget negotiations, streamlined site communications, and increased enrollment momentum. In balance, our experiences show the efficiencies and benefits far outweigh the complexities."*

Master protocol design can also help shift the drug development approach from trial- and compound-centric to disease- and patient-centric by building an integrated research platform. This approach can provide benefits to patients by better allocating patients to the most promising treatments, enabling the efficient study of asset combinations across companies/organizations, and increasing site performance and operational efficiency through standardization and decreased phase transition time. Patients also need to go through the screening process only once, potentially gaining increased access to multiple targeted therapy trials. For example, trials that use NextGen sequencing, (i.e., screen for a multitude of genetic variations, mutations, etc.) may allow patients and their providers to gain faster access to alternate treatments if their current treatments fail.

**Basket trial designs** can enroll patients based not only on the type or location of the cancer, but on whether tumors have molecular alterations that can be targeted by approved or investigational therapies. Basket trials are useful for finding signals related to the functionality of the aberration and treatment response irrespective of histology. For example, the FDA approval of pembrolizumab for cancers that share mismatch repair deficiency (MMR), a genetic abnormality, represents the first time a drug has been approved on the basis of a specific genetic profile rather than where the cancer originated. The basket trial enrolled patients with a dozen different cancer types. Results demonstrated that the potential for a response to immunotherapy was not unique to MMR-deficient colorectal cancer but held true for all the MMR-deficient cancers, regardless of tissue of origin.

**Figure 3.** Schematic Representation of a Master Protocol with Basket Trial Design[7]




*T = Investigational Drug; D = Protocol defined subpopulation in mulitple disease subtypes.

Source: FDA master protocol guidance, 2018

## CASE STUDY: Leveraging a basket design to realize cost efficiencies

**Background**

A client planned to run a Phase II cohort expansion study to assess the efficacy of a new treatment on one indication using Simon's two-stage design. However, the FDA requested the treatment be tested in at least four indications. Using a conventional design would have led to a sample size that exceeded the client's resources.

**Solution**

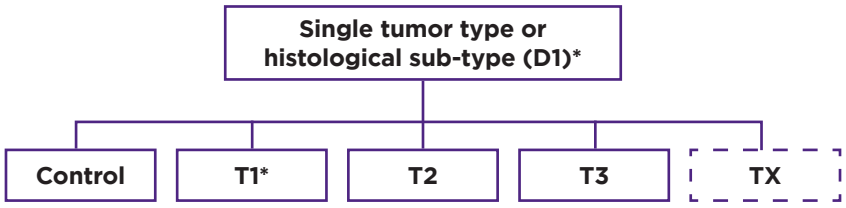
PPD recommended a basket trial design with Bayesian decision rules to allow for continuous evaluation of the efficacy results leading to a reduced mean sample size. This is a more intuitive approach to align decision rule (stop the cohort when adequate confidence is gained in the size of the overall response rate improvement) and the sponsor's goal (to identify the most promising indication as quickly as possible). Comprehensive trial simulations further helped evaluate the performance of different design choices under various scenarios to optimize the trial design.

## MANAGING OPERATIONAL CONSIDERATIONS: LESSONS LEARNED

Trials that address many questions simultaneously using a master protocol can be operationally complicated. However, as illustrated in the following umbrella case study, these complexities can be managed, even in global studies used to support a marketing application.

*"Operational activity will not be linear, but instead is happening concurrently on parallel tracks," said Kent Buhler, senior director, project management, PPD. "Study teams must be poised to manage near-constant change, but with proper diligence and operational excellence, great advantages can be realized with these innovative designs."*

**Figure 4.** Schematic Representation of a Master Protocol with Umbrella Trial Design[7]




*T = Investigational Drug; D= Protocol defined subpopulation in mulitple disease subtypes; TX = dotted boarder depicts future treatment arm.

Source: FDA master protocol guidance, 2018

# CASE STUDY: Pivot to address evolving opportunities within an umbrella trial

**Background**

With the expectation that combination strategies hold more potential than monotherapy, in many cases, sponsors are setting up combination trials as early as possible in clinical development. As a result, immuno-oncology combination studies are often large, complex, multi-national, resource-intensive, competitive and highly specialized. This PD-1 first-in-human (FIH) study encompassed all these factors—and more. It was designed to study PD-1 as monotherapy and in combination with other anti-cancer therapies in patients with advanced malignances. An umbrella design was selected in order to explore four different treatment and treatment combinations at various dose levels across multiple indications simultaneously within a single master protocol. The intent was to use findings to support a marketing application.

**High-level considerations.** This study managed challenges on many fronts, including:

- Dynamic cohort: Originally, six Phase I cohorts were planned. This was expanded to 25 cohorts across four different treatments and treatment combinations at various dose levels
- Rapid cohort enrollment and competition for patients
- Study required to be "audit ready" as study data would be used for marketing purposes
- Global footprint across North America, Europe and Asia-Pacific added complexity in regulatory, IRB and ethics committee submissions and reviews
- Continuous protocol amendments and database modifications: Eight substantial protocol amendments and 25 database modifications
- Rapid enrollment and frequent interim data reviews drove high demand for resources

**Results**

- Original final protocol December 2014
- First Site Activation target achieved January 2015
- First Subject First Visit target achieved February 2015
- Successful regulatory inspection led to marketing approval

*"What had started as a six-cohort study expanded into a 25-cohort study as signals were seen as the study expanded into Phase II cohorts," said Buhler. "This program accomplished under one umbrella what may have taken 10 to 15 traditional studies."*

Cohort expansion, in turn, required activation of 50 sites in North America, Europe and Asia-Pacific. In the dose escalation enrollment phase, 60 patients enrolled, and in dose expansion submission and startup, conducted in parallel, 338 patients enrolled.

To help minimize change management, protocol amendments were strategically grouped together and released over time. In total, the study team managed eight protocol amendments. A portfolio of tools—including a cohort management plan, tracking and projection of cohort status, enrollment status, visit and patient data and investigator payment—was implemented. Tools helped streamline and align work activities across different functions and participating organizations, laying the groundwork for the successful trial implementation and data deliverable.

*"It's important to guard against site fatigue in the face of so much change," said Song. "Particular care must be taken with the planning of key aspects of the trial. Effective communication and clear, simplified processes also are critical. The smallest details, for example, accurately labelling a lab kit to differentiate it from different protocol versions, can add up to a significant impact."*

## Regulatory Support and Buy-in

Many sponsors worry about diverging from traditional regulatory pathways, but our experience is that regulatory agencies not only encourage these models, they welcome dialogue with sponsors pursuing these models. Early engagement with regulatory agencies is key. FDA, for example, strongly encourages sponsors to discuss plans to develop drugs under a master protocol with the clinical review division early in the program to obtain feedback.

## CONCLUSION

Similar to other industries moving toward more flexible methodologies that foster continual improvement and operational efficiencies, many companies performing clinical development also are moving toward the adoption of adaptive designs and master protocols, innovations that are encouraged by regulatory agencies.

Clinical trial designs in oncology are evolving—and will continue to do so. We focused this paper on early phase opportunities where there is substantial untapped potential to design more efficient studies that not only improve success rates, but also fail faster to allow resources to be directed to more promising indications or assets.

All the advantages of adaptive designs and master protocols—flexible decision-making, accelerated timelines and cost efficiencies—also are well established in later stages. For example, a trial might include adaptive approaches to allow early stopping for futility and/or efficacy as well as blinded or unblinded sample size re-estimations. The groundbreaking I-SPY 2 trial of neoadjuvant treatment for locally advanced breast cancer established a new benchmark for efficiency of Phase II clinical trials.[16] I-SPY 2 was one of the first, and is now the longest-running "platform" trial, a type of master protocol. The trial contains adaptive design elements, such as an adaptive randomization. Its success continues to inspire and influence the development of next-generation trial designs in oncology and, more recently, other therapeutic areas. These advances and other opportunities to speed progress and eliminate waste through adaptive designs and master protocols will be explored in more detail in a future white paper.

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