WHITE PAPER

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ONCOLOGY

Phase 1 Trials: Strategies for Site Selection and Dose-Escalation

ABSTRACT

Well-designed, well-executed trials are essential for establishing meaningful safety and efficacy signals for investigative cancer drugs. Optimizing early-phase oncology trials through rigorous site selection strategies and a flexible yet statistically robust dose-escalation design increases the likelihood of advancing novel therapeutics to later stages of development.

By partnering with a contract research organization with deep experience in early-phase oncology trials, sponsors may be able to more easily navigate the unique regulatory environment to bring safe, effective therapies to cancer patients more quickly.

Introduction

Designing and executing an effective Phase 1 trial for a novel investigational oncology product can be challenging. Every facet of the process, from site selection and recruitment rate analysis to trial design and start-up, is interconnected. A nuanced approach is important, and early, careful planning is critical.

This white paper explores key considerations for site selection and dose-escalation design strategies in early-phase oncology trials. We provide insight into how to navigate regulatory and statistical challenges to keep these trials moving forward as quickly and safely as possible.

The role of medical informatics in site selection and clinical trial feasibility

Medical informatics plays a critical role in initial site identification and selection. This function involves analyzing where current active trials are being conducted to anticipate competition for a planned trial. It also involves evaluating similar trials that have been conducted recently to estimate recruitment rates by indication and identify opportunities to improve enrollment and condense trial timelines.

Various inputs are factored into a medical informatics analysis, including data gathered from published literature, publicly available databases, and even proprietary paid databases (see Figure 1). Depending on the specific trial requirements, additional factors such as next-generation sequencing (NGS) or cell therapy capabilities are also incorporated into the analysis. The analysis also considers sponsor preferences, including specific sites, key opinion leaders, and patient advocacy groups the sponsor would like to involve in the trial.

A key component of medical informatics is recruitment rate analysis performed using the indication, drug type, eligibility criteria, phase and size of the trial, and other customized search criteria. Figure 2 illustrates example enrollment projection models for a Phase 1/2 dose-escalation/dose-expansion trial, where benchmark rates are used to generate the enrollment projections and projected timelines.

The rate at which sites are onboarded to conduct the trial drives the enrollment projections. It is important to note that while this analysis provides a useful benchmark projection for enrollment, a critical next step is the validation of the expected enrollment rate on a site-by-site basis once the trial feasibility is initiated.

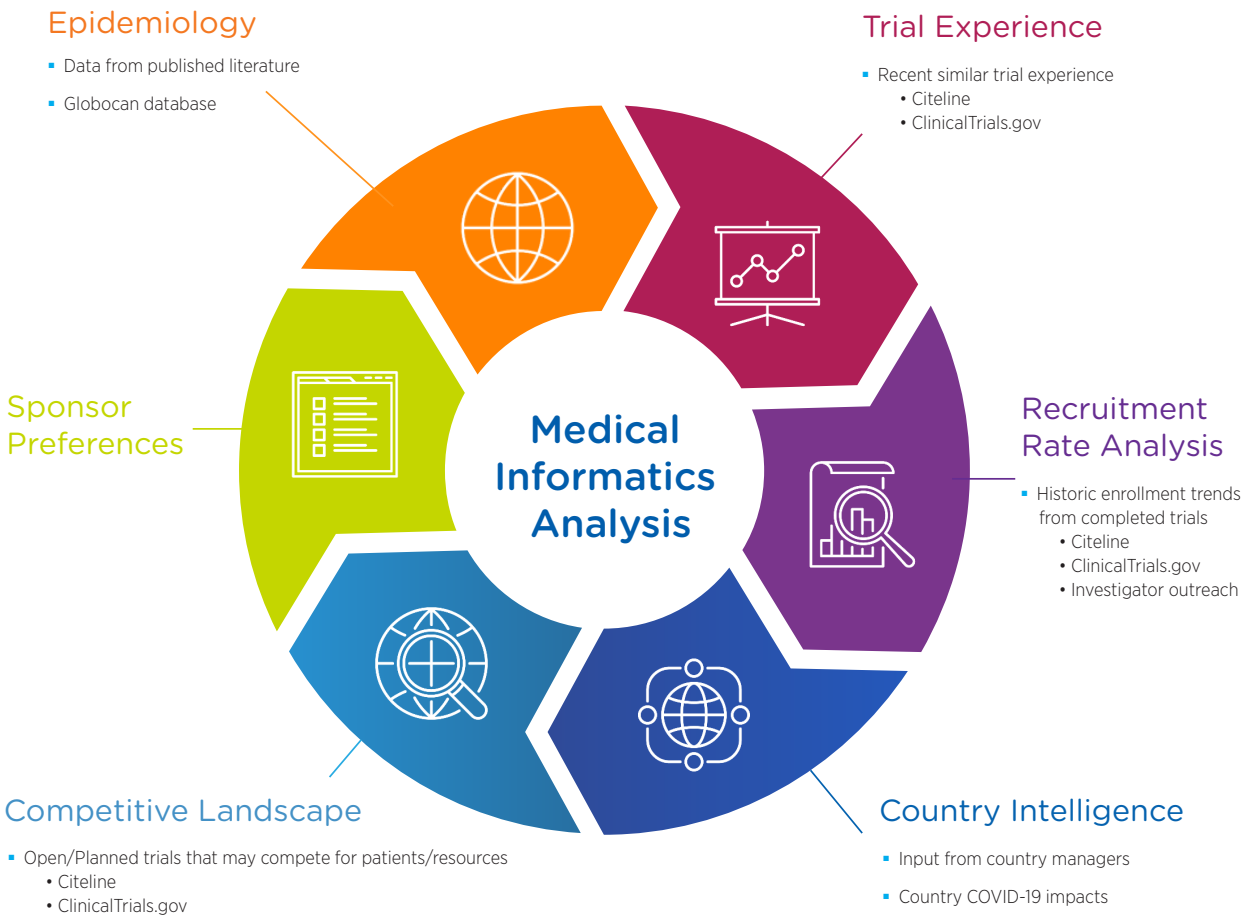
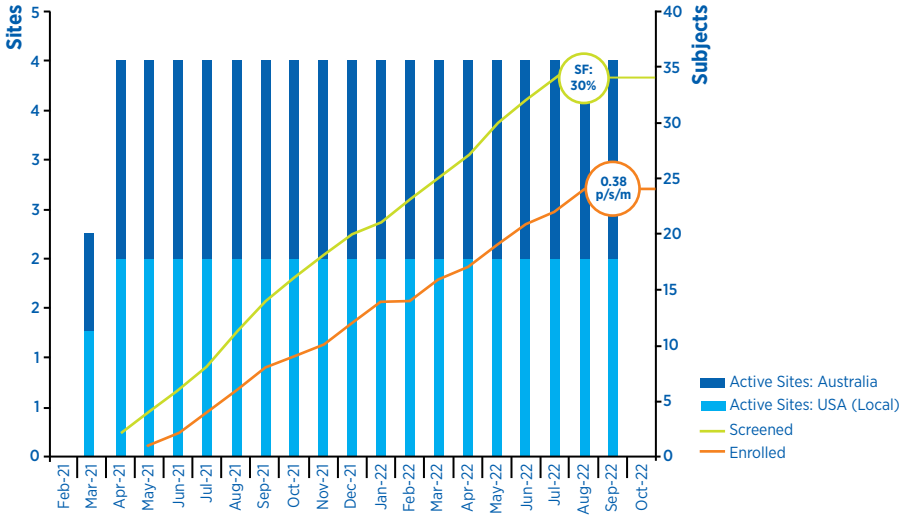


Figure 1. Inputs to a medical informatics analysis

Figure 2. Sample enrollment projection models

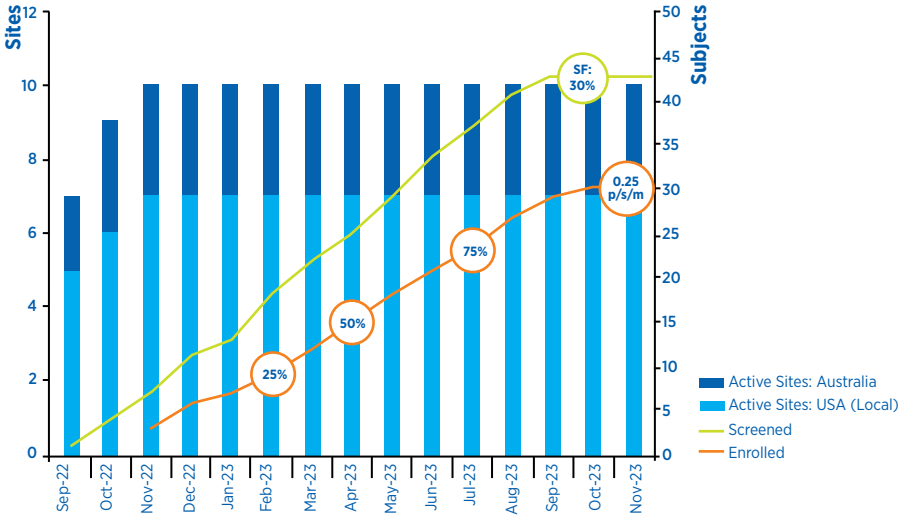
Dose Escalation Factors in generating enrollment projections and timelines include number of planned dose levels and statistical design of the study as well as benchmark rates

Overall Study Enrollment Rate 0.38 p/s/m					
Country	Enrollment Start	# Sites	Country-specific Enrollment Period (months)	# Patients Screened	# Patients Enrolled
USA	Mar-21	2	17.00	17	12
Australia	Apr-21	2	16.80	17	12
		4	17.00	34	24



Dose Expansion Dose expansion begins following identification of RP2D and after accounting for time needed to conduct interim analysis, etc.

Overall Study Enrollment Rate 0.25 p/s/m					
Country	Enrollment Start	# Sites	Country-specific Enrollment Period (months)	# Patients Screened	# Patients Enrolled
USA	Oct 22	7	12.00	30	21
Australia	Oct 22	3	12.00	13	9
		10	12.00	43	30



A closer look at investigator and site identification

During the site identification process, sponsors should look not only for experienced physicians but also experienced site staff. This step is even more critical if the investigational product (IP) is complex or if trial-specific requirements demand a great deal of coordination among functional areas. Sites should have the appropriate facilities and equipment to support the conduct of the trial. During the initial feasibility process, verification of projected activation timelines against the historical metrics of the site can help ensure that overall trial timelines are accurate.

Additionally, understanding the volume of research at the site provides insight into competition for site resources and potential constraints. It is also important to delve into the optimal recruitment strategy for each site and any anticipated challenges based on the protocol requirements. For example, is the length of the trial or the frequency of visits expected to be an obstacle to recruitment or retention? Are there key inclusion or exclusion criteria that will significantly reduce the pool of eligible patients at a site?

Obtaining feedback from key investigators early in the trial design process can be critical. This early engagement allows sponsors time to incorporate feedback into their final protocol, ensuring successful enrollment and trial compliance.

Perspectives and strategies for study start-up

Once sites have been identified, the next important step is study start-up. The start-up process is complex, and differences in the regulations and requirements in each country where the trial will be conducted may further complicate this step.

COVID-19 has also impacted many trial operational processes, including study start-up. As the evolving maze of new regulations intensifies the competing pressures for speed, efficiency, and safety, it is more important than ever for sponsors to consider patient needs at each step of the journey. Working with a partner with the expertise to navigate today's complex regulatory landscape can aid this process.

Site activation process

The start-up phase of a clinical trial is a multi-stakeholder, cross-functional effort. The activation pathway in the United States and Europe to allow initiation of enrollment breaks down into five key steps, some of which may overlap (see Figure 3):

1. **IND filing**. This step begins with engaging with regulatory agencies and other authorities for guidance and feedback on the protocol, ultimately leading to the submission of an investigational new drug (IND) application to the Food and Drug Administration (FDA) and a clinical trial application (CTA) in the European Union (EU).
2. **Site selection and qualification.** In addition to the medical informatics analyses discussed above, the site qualification process involves developing, reviewing, and distributing a site recruitment questionnaire. This questionnaire validates the medical informatics recruitment rate and assesses trial-specific requirements at a site level. Clinical research associates (CRAs) perform site qualification visits, either in person or over the phone.
3. **Submissions and site contract and budget negotiations.** Once sites have been selected, submissions and contract negotiations begin. Timelines and processes for submissions and site contracting vary greatly from country to country. For example, Belgium is one of the quickest countries for regulatory approval, while Romania is one of the slowest. As a result, it is important to develop an informed strategy before initiating submissions.

   It is also important to consider any protocol or investigational product-related nuances that may impact the submission pathway. For instance, if a trial requires radiation treatments that are not part of the in-country standard of care, the sponsor may need additional approval depending on the country. Additional submissions and approvals often impact activation timelines and, ultimately, enrollment.
4. **Site preparation**. Following approvals, contract execution, and essential document review, CRAs train the sites on the protocol and procedures. The monitoring team also ensures that each site receives the necessary equipment and supplies.
5. **Site activation**. Once the drug release form has been signed, all training has been conducted, accesses have been granted, and IP/supplies have been received, the site is officially activated for screening.

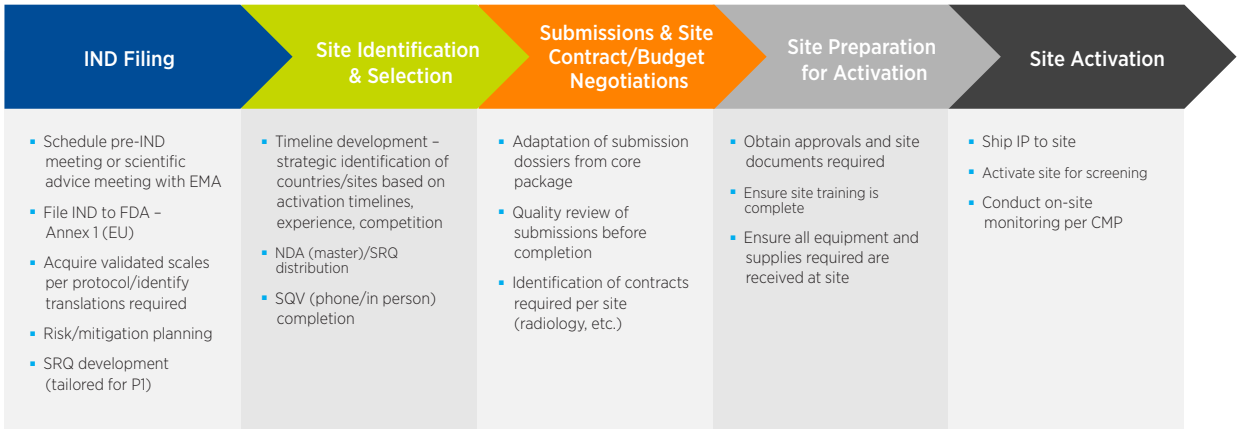


Figure 3. High-level workflow for site activation

The terms "dose escalation" and "dose finding" are sometimes wrongly used interchangeably. Empirically, there is an important difference between the two. The goal of dose escalation is to determine an optimally safe and well-tolerated dose in humans, which can be defined as a maximum tolerated dose (MTD) or maximum effective dose (MED).

On the other hand, the empirical goal of dose finding is to identify a specific dose (or doses) within a dose range, up to and including the MTD/MED, that demonstrates evidence of a possible efficacy signal.

Study start-up timelines

The timelines for study start-up will depend on the regulatory nuances of each country. While central Institutional Review Board (IRB) sites in the U.S. are typically activated quickly, most Phase 1 oncology trials are conducted at academic centers requiring a local IRB agreement. Local IRB timelines vary by institution, so examining the process and historical metrics on a site-by-site basis to refine and validate expected activation timelines is important.

While many academic centers can defer review to a central IRB to compress the review timeline, the overall contracting timeline generally remains the same. Additionally, review by the local IRB before or after submission to the central IRB is often still required. Some sites in the U.S. require a fully executed contract or agreed-upon budget before submission, which can further extend the activation timeline.

A deeper dive into submissions and contract negotiations

As mentioned earlier, average approval and contracting timelines can vary among countries. Depending upon the country or even the site, there are also variations in the type and number of reviews and contracts required. Examples include:

- Both central and local ethics committees must review submissions in Italy; in addition, the Ministry of Health and the competent authority must review Phase 1 trials
- In Australia, only a subset of ethics committees can review early-phase clinical trials
- Early phase oncology trials in the U.S. often require a scientific committee or other pre-review board before sending the protocol to the IRB
- Russia requires export licenses for biological samples
- Germany and the U.K. have radiology review boards

This variability underscores the importance of developing a start-up strategy based on a robust medical informatics assessment and other analyses to accurately project activation timelines across all the sites involved in a trial.

Other key considerations for trial start-up

Other factors might need consideration in the course of trial start-up planning. For instance, the type of IP can impact the overall timeline. For example, when working with a genetically modified organism or radiopharmaceutical product, additional review boards may be required before site activation. Additionally, for Phase 1 trials, certain EU sites require Phase 1 certification.

Ensuring streamlined enrollment and protocol compliance requires organization and strong communication among the sponsor, contract research organization, sites, and other involved parties.

Design considerations for dose-escalation trials

A quick clarification of terms

The terms "dose escalation" and "dose-finding" are sometimes wrongly used interchangeably. Empirically, there is an important difference between the two. The goal of dose escalation is to determine an optimally safe and well-tolerated dose in humans, which can be defined as a maximum tolerated dose (MTD) or maximum effective dose (MED), for example. Dose escalation is typically conducted in Phase 1 trials, where the primary

endpoint follows a pre-specified definition of toxicity or another critical safety criterion. The resulting maximally safe dose (MTD/MED) is termed the recommended Phase 2 dose.

On the other hand, the empirical goal of dose finding is to identify a specific dose (or doses) within a dose range, up to and including the MTD/MED, that demonstrates evidence of a possible efficacy signal. This evidence then triggers a further investigation of the identified dose(s) for confirmation of efficacy in a Phase 3 trial. Dose finding is usually conducted in Phase 2.

Dose-escalation design strategies

The past two decades have seen several improvements to the traditional 3+3 design, with more advanced dose-escalation paradigms introduced in Phase 1 clinical trial research. This trend is especially true in oncology, where there is heightened clinical concern to limit the number of patients receiving ineffective doses and rapidly identify a dose that can be moved into Phase 2. A key consideration for a dose-escalation design is speeding up time to determine the maximally safe dose while limiting the number of patients treated at sub-therapeutic doses.

Dose escalation design strategies fall into two broad classes: rules-based designs and model-based designs. Figure 4 provides a high-level summary of key differences between these design classes.

With **rules-based designs**, dose-escalation or de-escalation decisions are based solely on a pre-specified set of clinical decision rules about the occurrence of dose-limiting toxicities (DLTs). Examples of rules-based designs include the traditional 3+3 design and the rolling 6 design. An enhancement of both these designs is the accelerated 3+3 and the accelerated rolling 6.

Rules-based Designs (3+3 or Rolling 6)	Model-based Designs (CRM; TITE-CRM; BOIN; mTPI; BLRM; etc.)
Requires fixed cohort size during trial	May allow adaptive changes to cohort size during trial (e.g., BOIN)
MTD is the dose directly below the dose with ≥2 DLTs – ignores totality of patient data observed at a dose level	MTD determined using isotonic regression – pools information across dose levels to obtain efficient statistical estimate of MTD (unique statistical property)
Escalation/de-escalation decisions restricted to information from specified number of evaluable patients in a cohort	Accounts for information from patient whose observation period has not ended (e.g., TITE-CRM) Escalation/de-escalation decisions based on cumulative number of evaluable patients at any dose level Allows escalation/de-escalation decisions with any number of evaluable patients – can be less than cohort size (e.g., BOIN)
Starting dose is the lowest dose	Starting dose may be any dose level
Unreliable estimate of true DLT rate because: ▪ Actual sample size is random since trial stops when ≥2 DLTs are observed ▪ MTD decision based on cohort DLT information only	Scientifically robust estimate of DTL rate because: ▪ Set sample size has higher probability of correctly estimating and selecting the MTD ▪ MTD decision based on cumulative DLT information

Figure 4. Comparison of rules-based and model-based designs

There is no one-size-fits-all approach to designing a dose-escalation trial. Involving an experienced biostatistician in the planning process can help sponsors select and implement the most appropriate design.

In both 3+3 and rolling 6 designs, the decision to escalate to a higher dose level is based solely on the number of evaluable patients in the current dose cohort. Here, an evaluable patient is one who has either completed the treatment cycle without a DLT or has experienced a DLT during the treatment cycle. This eligibility requirement for deciding to escalate can be a significant limitation. Having even one unevaluable patient in the current cohort will prevent a dose-escalation decision and prompt the need to extend patient accrual to replace the ineligible patient in that cohort.

A rolling 6 design that requires a minimum of six patients per cohort offers more opportunities to escalate since escalation can occur when three of three, four of four, five of five, or more than five of six patients in a cohort have no DLTs. With both the 3+3 and rolling 6 designs, dose de-escalation may occur when two or more DLTs are detected in a cohort. The resulting lower dose may then be considered the MTD.

In **model-based designs**, dose-escalation or de-escalation decisions are based on the output of a pre-specified DLT probability model instead of basic clinical decision rules as with the 3+3. Model-based designs are more robust than rules-based designs since they incorporate the totality of data across all previous dose cohorts in making an escalation or de-escalation decision. Unlike the rules-based designs, most model-based designs are not constrained by the patient eligibility requirement to complete the treatment cycle. Therefore, they provide added flexibility and can accelerate the process of getting to the MTD. Both the FDA and the European Medicines Agency (EMA) recognize the advantages of model-based designs and have encouraged their use.

There is a wide array of model-based dose-escalation designs. Perhaps the most commonly used is the continual reassessment method (CRM). This design begins by defining a model based on a pre-specified set of Bayesian priors of the toxicity probability for each dose level. As patients enroll and data accrues, the CRM model is updated every time a cohort has completed the treatment cycle using the totality of available accrued data, yielding posterior estimates of the probability of toxicity at each dose. The next cohort of patients is then assigned to the dose showing the highest predicted probability that is less than the target DLT rate. The CRM design operates similarly to the 3+3 in setting the eligibility constraint.

Other more flexible model-based designs that are not constrained by the eligibility criterion of the 3+3 and CRM designs include the Bayesian Optimal INterval model (BOIN), the modified Total Probability Interval model (mTPI), and the Bayesian Logistic Regression Model (BLRM). CRM, BOIN, and mTPI are all single-parameter logistical regression models in which the probability of toxicity is estimated using a single parameter. The BOIN design combines the 3+3, rolling 6, and accelerated titration designs. It differs from CRM in that it includes pre-specified upper and lower toxicity boundaries, which simplify escalation and de-escalation decisions. The mTPI design is similar to BOIN but includes three separate toxicity probability intervals. BLRM is more complex as it is based on two parameters but adds flexibility and robustness in that it allows for overdose control. Figure 5 provides a high-level summary of the important aspects of each of the aforementioned model-based designs.

Model-Based Design Type	Key Elements of Design
CRM	Based on single-parameter logit toxicity model Uses Bayesian priori, ß, to define initial function for the probability of dose toxicity, p With new patient, estimate of ß is updated to get new predicted probability of toxicity Assign new patient to highest dose having predicted probability less than target DLT rate
BOIN	Based on single-parameter logit toxicity model Generalization of the 3+3; rolling 6; Accelerated Titration Design (ATD) Trades larger cohort and sample size for fast trial completion Compares DLT rate at current dose with pre-specified toxicity boundaries $\{L_e, U_d\}$
mTPI	Based on single-parameter logit toxicity model Dose selection is based on toxicity probability intervals **{under-dosing interval}** **{equivalence interval}** **{over-dosing interval}** **Escalate** **Stay** **De-escalate**
BLRM	Based on two-parameter logit toxicity model Flexible cohort sizes Enrolls next patient to highest dose having predicted probability less than target DLT rate Allows for overdose control

Figure 5. Comparison of model-based designs

Planning a dose-escalation clinical trial design

When planning a dose-escalation trial, several components should be defined upfront to ensure the trial is robust. First, it is critical to develop a clear clinical definition of what constitutes a DLT. The next step is to determine the target DLT rate, which will be used to define the MTD. Acceptable DLT rates vary by disease indication but are typically about 33 percent for most oncology indications. It is also important to define the length of the treatment cycle in which to observe patients for toxicities and define the dose levels to be administered and the rules of dose escalation, dose de-escalation, or trial stoppage.

Model-based designs require additional pre-planning. With these designs, prior assumptions (or initial estimates) of the DLT probability of each dose level must be set. The initial DLT probabilities at each dose are termed Bayesian priors, and these are refined (or updated) during the trial using data accrued with each dose cohort. The refined values represent the estimate of the updated probability of toxicity for each dose level. Other upfront considerations for model-based designs include selecting a starting dose level to assign to the first patient and choosing the size of each dose cohort. Of note, when deciding the dose range to be investigated, it is important to ensure that the target toxicity rate falls within the range of Bayesian prior probabilities for the doses being investigated. Importantly, no studied dose levels need to have an initial DLT probability exactly equal to the target DLT rate.

There is no one-size-fits-all approach to designing a dose-escalation trial. Involving an experienced biostatistician in the planning process can help sponsors select and implement the most appropriate design.

Conclusion

Selecting appropriate sites and choosing an adequate dose-escalation design for early-phase oncology trials can help sponsors adhere to projected timelines, limit the number of patients exposed to ineffective doses, and accelerate the process of identifying a Phase 2 dose. By partnering with a contract research organization with deep experience in early-phase oncology trials, sponsors may be able to more easily navigate the unique regulatory environment to bring safe, effective therapies to cancer patients more quickly.

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Abie Ekangaki, Ph.D. | Vice President, Statistical Consulting

Dr. Ekangaki brings his expertise in biostatistics in providing strategic guidance on trial design and analysis techniques, as well as trial planning and execution for both sponsor clinical trials and standalone consultative services. He supports the Premier Research business development and customer engagement services in advising on efficient trial design for clinical trial programs and applying specific statistical, drug development, and operational knowledge. Dr. Ekangaki received his Ph.D. in statistics from the University of Southampton, U.K.

Ashley Herrick, Ph.D. | Executive Director, Oncology Program Strategy

Dr. Herrick provides strategic planning, coordination, knowledge, and expertise for oncology projects. She has more than 13 years of experience in oncology clinical trial oversight and drug development. Dr. Herrick has familiarity with all phases of clinical trials and a keen interest and deep knowledge of early-phase and first-in-man trials. Dr. Herrick holds a doctorate in molecular and cellular biology with a focus on acute myeloid leukemia from Baylor College of Medicine. She is CCRP-certified and is a member of the American Association for Cancer Research and the American Society of Clinical Oncology.

Federica Vinciati, Ph.D. | Senior Regulatory Start-Up Manager, Study Start-Up

Dr. Vinciati is a senior regulatory start-up manager responsible for leading first-in-human and Phase 1-4 trials in the EU, North America, and Asia Pacific regions. She is responsible for the global regulatory start-up strategy for each given project for products or medical devices in psychiatry, rare disease, cardiology, rheumatology, and oncology indications. Dr. Vinciati is a neuroscientist by training with a publication record in neurodegenerative disorders.

Meghan Shea | Manager and Solutions Lead, Study Start-Up

Ms. Shea is a manager and solutions lead, overseeing staff and driving the regulatory/start up strategy for Phase 1-4 global trials. She has overseen clinical trial submissions in over 30 countries. Her key therapeutic experiences are within oncology, dermatology, endocrinology, pediatrics, and rare diseases. Prior to joining Premier Research, Ms. Shea worked as a global regulatory lead at a CRO and contributed to preclinical laboratory research for a biotechnology company focused on novel therapies for treating diabetic nephropathy.

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North America: +1 919 627 9100 | Europe: +44 118 936 4000 | info@premier-research.com | premier-research.com