A Precision for Medicine eBook

Cohort Management

Best Practices for Early Phase Oncology Clinical Trials

PRECISION for medicine®

The Art and Science of Cohort Management

Early phase oncology studies—including Phase 1, seamless Phase 1/2, and Phase 1 dose expansion—offer patients with cancer the opportunity to access novel investigational therapies, but they come along with many unknowns. As these studies seek to establish safe dosage levels for later phase trials, identify potential side effects, and gather preliminary data on efficacy signals, the right approach to cohort management is essential for ensuring patient safety, data integrity, and trial efficiency.

At Precision for Medicine, effective cohort management is as much an art as it is a science.

Effective cohort management requires a multidisciplinary team and a mix of scientific rigor, clinical expertise, and intuition. The right clinical research organization (CRO) partner brings more than technical knowledge, but also practical experience and the flexibility to adapt to the unpredictable nature of early phase oncology trials. Putting patients first, anticipating challenges, and making informed decisions in real time sets the stage for a successful program.

Within this eBook is a collection of insights into best practices for effective cohort management in early phase oncology clinical trials, from navigating the nuances of cohort planning to coordinating study execution.

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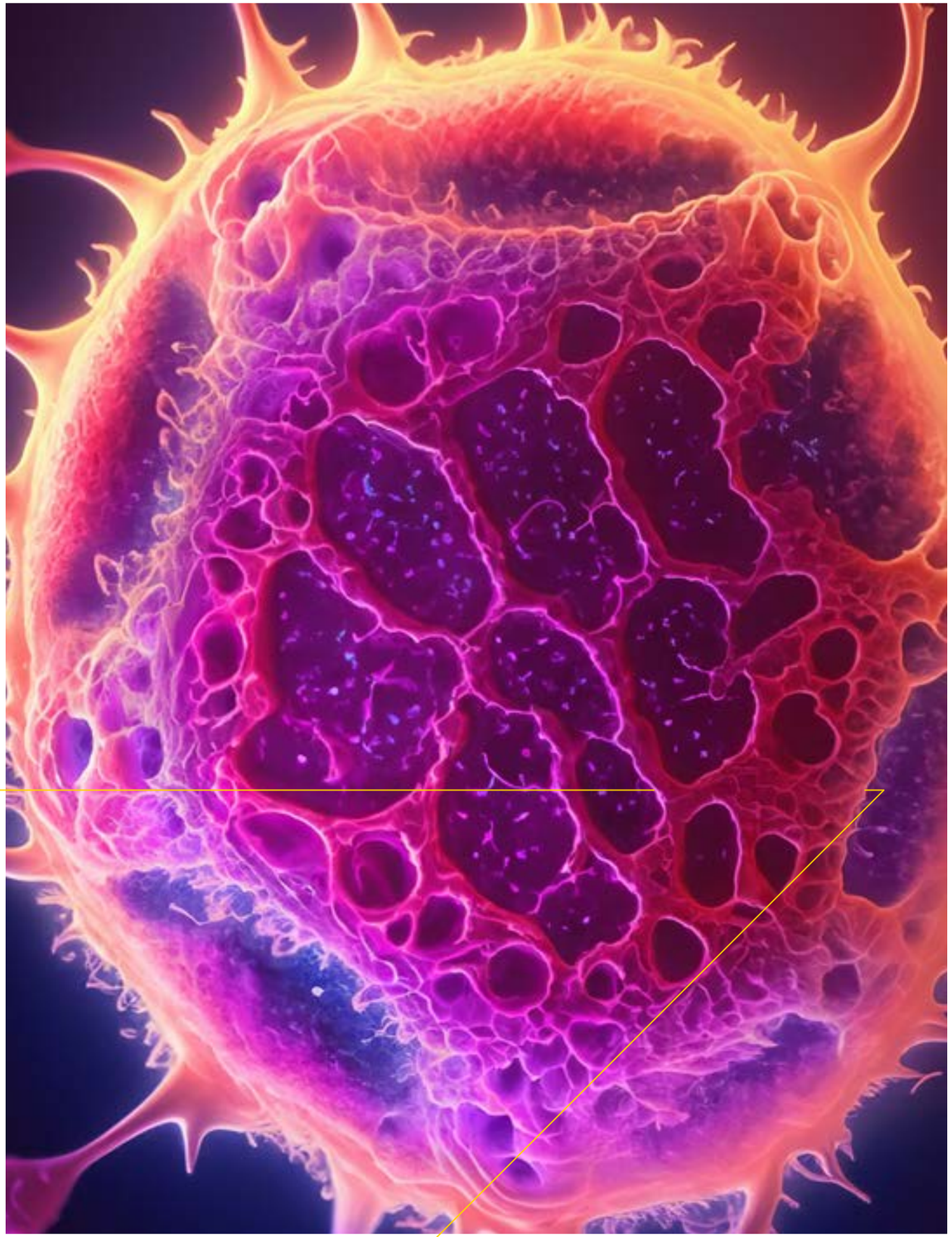


Chapter 1

Cohort Planning and Communication Strategies

Managing cohorts is a complex and highly nuanced process, requiring proactive planning and robust communication strategies. Since phase 1 trials often have short startup timelines and only recruit a few participants at a time, study coordinators are under pressure to identify and screen subjects quickly and to ensure that a slot is available before promising it to a patient. Tightly orchestrated cohort management strategies—together with robust clinical monitoring and protocol deviation plans—protect the safety of subjects and support the capture of quality data, particularly in dose escalation studies.

Creating a Cohort Management Plan

Developing a comprehensive cohort management plan early in the study is vital for aligning expectations among all stakeholders, including sponsors, sites, and clinical research teams. A well-crafted plan lays the groundwork for the trial's execution, setting clear guidelines on subject eligibility, slot allocation, and more. It also establishes a flow of communication that keeps all sites and study coordinators up-to-date on current enrollment.

BEST PRACTICE

Develop and disseminate a detailed cohort management plan early in the study to align expectations with sponsors and sites, ensuring a smooth and coordinated recruitment process.

Key Components of an Effective Cohort Management Plan

- **Slot Request Forms and approval.** When new slots in a cohort are opened, sites may request a slot using a Slot Request Form sent via email to a dedicated mailbox for slot allocation. The site should complete as much of the form as possible. Partially completed forms may lead to delay in slot assignment or assignment of the slot to another site.
- **Subject eligibility form.** Clearly define criteria to ensure consistent assessment by medical monitors across all sites.
- **Routing and review process.** Establish a streamlined process for reviewing and routing subject eligibility forms and Slot Request Forms, ideally using a general email distribution list to avoid delays caused by personnel absences.
- **Slot allocation strategy.** Create a transparent and fair method for assigning trial slots, including a process for managing waitlisted subjects. Patients not currently allotted a slot can be tracked on a pre-identification log or screened with forecasted enrollment data to minimize downtime and expedite enrollment of subsequent cohorts. By aligning study teams with biostats, any implications study design may have on slot allocation can be accounted for proactively.
- **Point of contact for enrollment decisions.** It is a common misconception that a site can pre-emptively hold a spot in a trial for a potential patient. Designate a central point of contact responsible for enrollment decisions, ensuring that no unauthorized promises are made to patients who have not yet met inclusion criteria.
- **Management of dose escalation and expansion.** The pace of dose escalation will be determined by dose-limiting toxicities (DLTs) observed in patients. Efficient cohort management will drive the speed of patient recruitment, supported by robust patient identification procedures and well-calibrated slot assignments based on current data. Maintaining up-to-date data is crucial for fast-paced decision-making. Additionally, it's important to be prepared to enroll extra patients to replace those who drop out or do not meet criteria. Comprehensive pre-screening and eligibility packets will help streamline the enrollment process.
- **Adaptive slot release.** Consider releasing slots during the DLT observation period to maintain momentum and a waiting list of pre-screened patients to quickly fill slots as they become available. This ensures sites are prepared and can minimize delays in slot allocation, keeping the trial on track and efficiently managing patient enrollment.
- **Data quality for safety oversight committee.** Ensure continuous and clear communication among Clinical Research Associates (CRAs), Medical Monitors (MMs), and the Precision Clinical Trial Management (CTM)/Project Management (PM) team. Implement efficient sample management and data reconciliation processes. Regularly clean and review data with input from Data Management (DM), Centralized Monitoring, and CRAs.
- **Determine triggers for data review meeting.** Establish clear criteria for triggering data review meetings and define the process for opening and closing cohorts. This includes setting specific milestones or events, such as reaching a certain number of enrolled patients, observing significant adverse events, or completing a predefined number of data collection points.

Proactive Site-Level Communication

Early phase dose escalation studies require an understanding of the patient journey from pre-screening to treatment and an awareness of slot availability, screen failures or dropouts, and safety events. A lack of awareness or understanding of these factors poses a risk to patient safety, data integrity, and study timelines. Effective communication at the site level is crucial for keeping all parties informed and engaged. This communication helps in monitoring individual patient pathways and maintaining transparency such that every site team has access to real-time data about the number of recruitment sites, the number of open slots in the current cohort, and the patients being considered for those slots.

- **Daily communication.** Use these conversations to discuss patient eligibility, slot assignments, and possible safety issues.
- **Weekly email updates.** Send regular updates to activated sites, providing information on open slots in the current cohort, anticipated completion dates, and guidance on requesting slots for upcoming cohorts.
- **Dashboards.** Use dashboards to give site teams a real-time view of cohort status and patient enrollment.
- **Relationship-building.** Be transparent with site teams and responsive to their needs to encourage ongoing engagement. Try setting expectations at the beginning of site activation on enrollments, monitoring visits, data entry, and query resolution timelines.
- **Identification of backup patients.** Proactively identify additional subjects to mitigate screen failure delays and prepare for safety-driven cohort expansions.
- **Two-way expectation management.** Maintain open communication with both sponsors and sites through regular calls with CRAs to discuss pre-screening activities, inclusion/exclusion criteria challenges, and other concerns.

BEST PRACTICE

Implement weekly email updates and ensure CRAs follow up with activated sites regularly to discuss pre-screening activities and address any issues promptly.

Site Management

Effective site management involves proactive strategies to ensure enrollment targets are met, site engagement is maintained, and all site staff are well-informed about the trial. Coordinating communication, tracking protocol deviations, and developing robust monitoring strategies are key components of this process.

Site Management Meetings

Ensure ongoing engagement, issue resolution, and best practice sharing among the sponsor, principal investigators (PIs), study coordinators, site staff, and the CRO. Key points to discuss in these meetings:

- Updates on the status of the current cohort and upcoming cohorts and treatment slots
- Discussion of protocol deviations or amendments that might affect cohort enrollment
- Consensus on best practices
- Review of patients currently on study
- Discussion about potential patients for pre-screening/screening
- Proactively develop recruitment strategies with sites (eg, site recruitment form)
- Sharing successes to maintain team engagement

The topics and takeaways discussed in these meetings should be reinforced with PIs through follow-up CRA site visits.

BEST PRACTICE

Conduct regular bi-weekly site management calls to maintain engagement and address any issues in a prompt manner. Be sure to include PIs on these calls, establishing a direct line of communication. Document these calls using site contact reports.

Safety Review Strategies

The conduct of dose escalation studies requires the establishment of a committee that reviews patient safety data and evaluates all data to make recommendations on dose escalation decisions. A robust safety review strategy is integral for identifying and managing DLTs and other adverse events (AEs). There should be weekly safety meetings during which all participating site PIs and SCs meet together to discuss ongoing active patients with the sponsor and CRO, as well as potential patients.

While data monitoring committees (DMCs) are commonly used to perform safety reviews in later phase studies, safety review committees (SRCs) are more efficient for early phase oncology trials. The SRC is typically composed of the medical monitor, PI, sponsor, and PM. Biostatisticians and centralized monitoring teams may also be involved, though they may not be present at every meeting.

The safety review committee is responsible for:

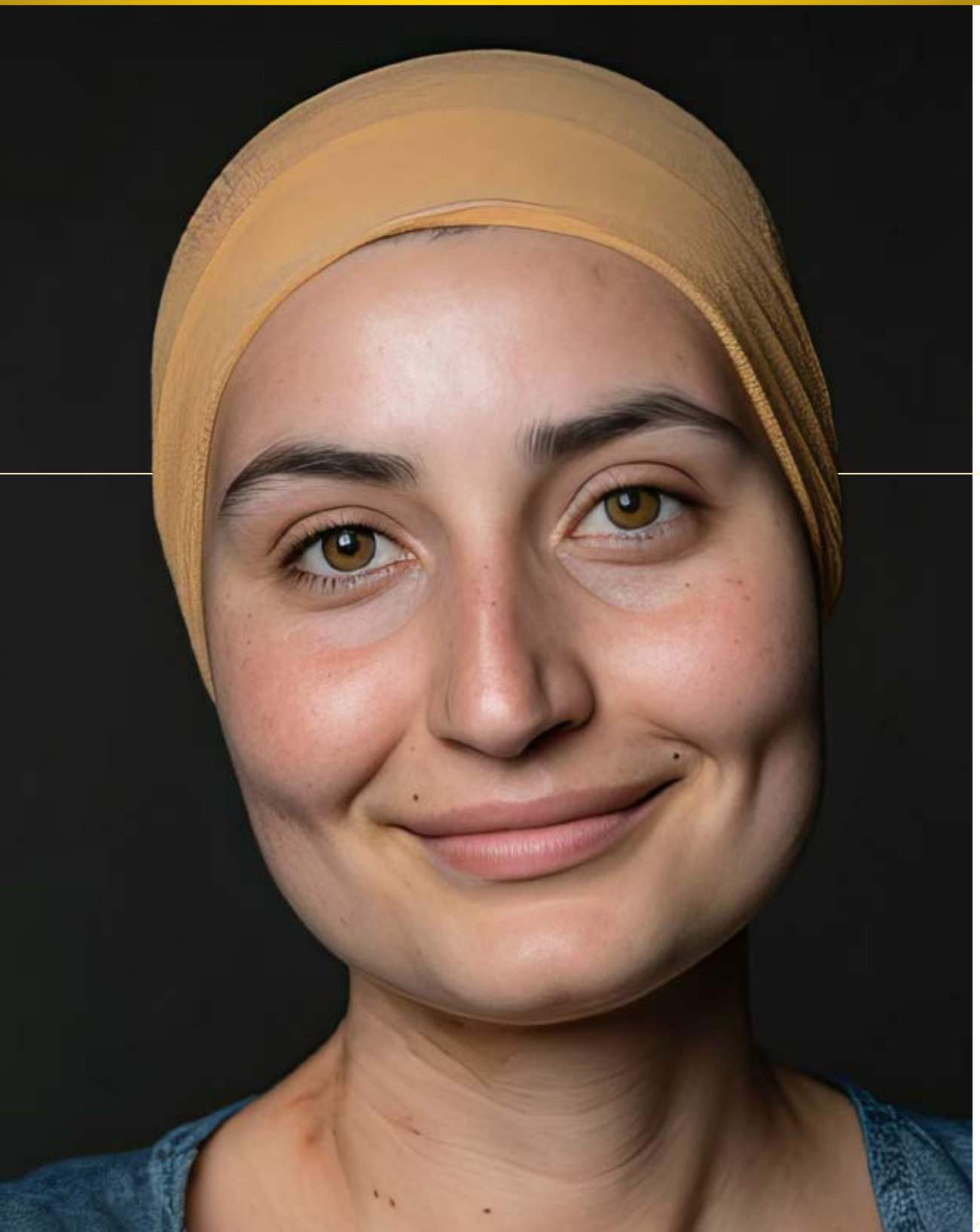
- **Developing a charte**r that outlines data that will be reviewed at the meeting if not handled by the Sponsor or biostatistician
- **Evaluating data** and establishing a review process for adverse events
- Discussing and examining AEs in the electronic data capture (EDC) and safety systems. The clinical data management and safety functions should continually reconcile the data between these two systems to maintain data integrity and accuracy throughout the trial
- **Making recommendations** on dose escalation/de-escalation after review and discussion of all data presented at the meeting
- **Managing consensus and dissent** and documenting agreement before making a recommendation for the next dose level

BEST PRACTICE

Use patient profiles prepared by the centralized monitoring team for efficient safety reviews. These profiles provide a comprehensive view of patient data and are often more effective than traditional statistical outputs in phase 1 studies.

Key Takeaway

Cohort planning and communication strategies are fundamental to the success of early phase oncology trials. By developing a comprehensive cohort management plan, maintaining proactive communication with site teams, conducting regular site management meetings, and implementing robust safety review strategies, trial teams can ensure that these complex studies are conducted efficiently and safely.



Chapter 2

Optimizing Enrollment in Early Phase Oncology Studies

The success of early phase oncology studies not only relies on careful site selection, efficient pre-screening, and effective recruitment of participants who meet the study's stringent inclusion and exclusion criteria; it also depends on study-wide visibility into slot availability.

Site Activation and FPI Strategy

The strategy for activating sites and achieving First Patient In (FPI) is critical to the overall success and timeline of a clinical trial. There are two primary approaches:

- **Performance-based activation.** Focused on activating sites based on metrics of historical performance, such as patient recruitment rates, data entry timeliness, and overall efficiency in conducting trials. The main advantage of this strategy is the potential to minimize study delays by relying on proven performers. However, focusing only on high-performing sites may limit geographic diversity and overlook newer sites or those with less trial experience but significant potential.
- **Key opinion leader (KOL)-centered activation.** Focused on activating sites led by oncology KOLs, particularly in competitive therapeutic areas or rare disease settings where patient populations are limited. While KOLs may lend credibility to the study, they do not always guarantee the fastest patient recruitment or data collection. This approach may also introduce biases if certain sites are chosen primarily for prestige or publication value rather than their performance capabilities.

BEST PRACTICE

Prioritize performance-based site activation to avoid potential study delays. However, be prepared to adapt to sponsor preferences, especially when dealing with high-priority sites.

Strategies for Slot Assignments

Slot assignment is a delicate process that requires balancing medical needs, site equity, and performance metrics. A well-crafted strategy ensures that the trial progresses smoothly without unnecessary delays or biases.

Key considerations when developing a slot assignment strategy include:

- **Prioritization based on medical need.** Depending on the degree of competition anticipated for the indication of interest, sponsors can choose to assign slots based on a first-come basis, medical need, or rotating site assignments. In our experience, patients with the most urgent medical needs should be prioritized in slot assignments, particularly in early phase oncology trials in which patients often have limited treatment options.
  - **Note:** In an escalation study, sponsors might select the site that can bring their patient to dose the earliest to help expedite the SRC process to determine the maximum tolerated dose (MTD).
- **Rotation among sites.** To ensure fairness and maintain site engagement, it is important to rotate slot assignments among participating sites. This approach prevents the concentration of enrollment at a few high-performing sites and encourages broader participation.
- **Balancing performance and preference.** While high-performing sites may naturally attract more slots, it is essential to balance this with the preferences of the sponsor and the unique circumstances of each site.

Drawing from lessons learned from previous studies, Precision for Medicine recommends planning to prioritize patient medical need whenever possible.

BEST PRACTICE

Conduct regular biweekly site management calls to maintain engagement and address any issues in a prompt manner. Be sure to include PIs on these calls, establishing a direct line of communication. Document these calls using site contact reports.

Site-Specific Recruitment Plans

Translating feasibility estimates into actionable recruitment plans is vital for meeting enrollment targets. Each site should have a tailored recruitment plan based on its unique patient population and compliance needs.

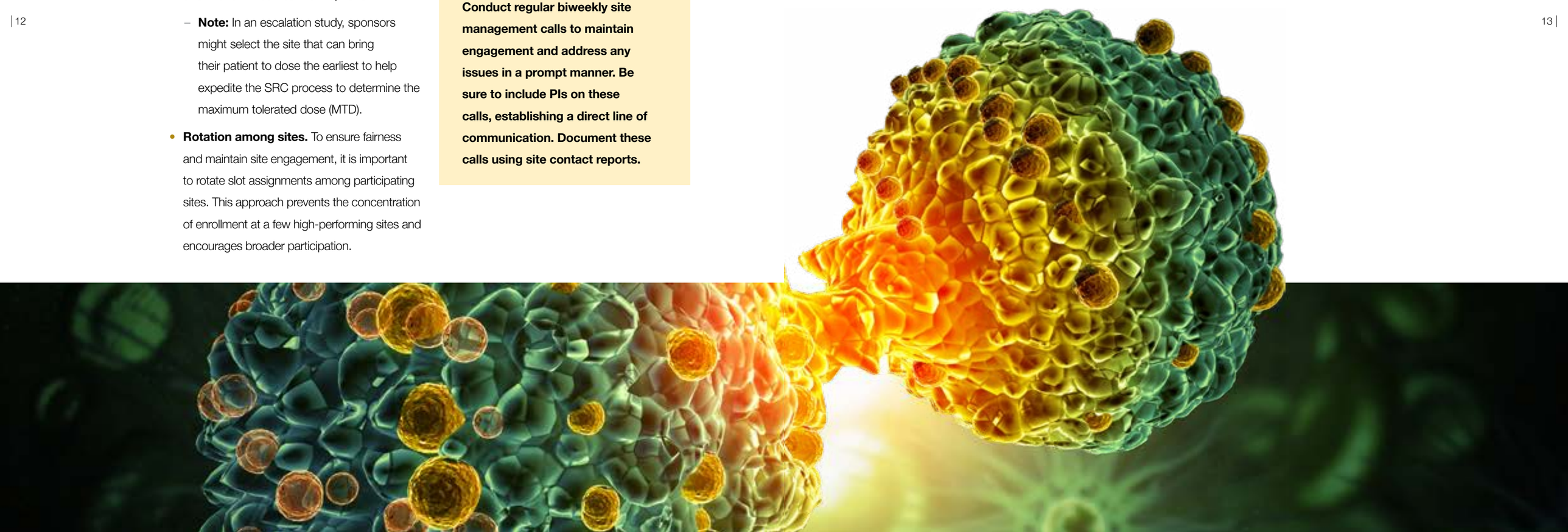
The components of this plan include:

- Use of recruitment materials, such as flyers and Dear Doctor letters, to facilitate physician and patient outreach
- Site-specific outreach strategies that are customized to the site's patient demographics, geographic location, and advertising resources
- Consideration of country-specific regulatory requirements, which may impact enrollment targets and timelines

Before implementing these plans, it is crucial to obtain agreement and sign-off from the sponsor.

BEST PRACTICE

Develop and implement site-specific recruitment plans early in the feasibility stage to ensure alignment with sponsors and commitment from sites. Regularly review these plans to make adjustments as needed.



Checkpointed Enrollment Pathway

A checkpointed enrollment pathway ensures that all eligibility criteria are met before a patient is assigned a slot in the study. This site-facing pathway makes the process of slot assignment transparent for both the site and the patient so they can make informed decisions about the potential timing of study treatment and the need for bridging therapies while awaiting enrollment. To implement such a pathway:

- Develop a comprehensive checklist of all eligibility criteria
- Establish a clear approval process for enrollment decisions
- Double check that all patients enrolled meet the eligibility criteria to help avoid protocol deviations and the need to replace patients who do not meet all criteria, which can waste resources and increase risk to patients

BEST PRACTICE

Implement a checkpointed enrollment pathway that includes a rigorous eligibility confirmation checklist and a well-defined approval process. This helps to enforce eligibility criteria and ensures the integrity of the trial data.

Real-Time Trial Availability Tracking

Keeping track of open slots in real time is essential for optimizing patient enrollment. Dashboards that provide a clear view of up-to-date slot availability can help sites manage their recruitment efforts more effectively. As the trial progresses, consider additional sites to accommodate expansion cohorts, ensuring that the trial can scale up smoothly without delays.

BEST PRACTICE

Utilize dashboards to provide sites with up-to-date information on available slots, helping them to prioritize and schedule patient enrollments efficiently.

Site Performance Monitoring

Ongoing monitoring of site performance is critical for ensuring follow-through after site activation and addressing common issues. This involves continual assessment of key metrics, such as:

- **Data entry.** Timely and accurate data entry is essential for the real-time monitoring of trial progress. Sites should be evaluated on their ability to enter data promptly after patient visits.
- **Patient recruitment.** Regularly track the number of patients recruited by each site to identify underperforming sites early and address any issues that may be hindering recruitment.
- **Source data verification (SDV).** SDV is crucial for maintaining the integrity of the trial data. Regularly check that sites are strictly following SDV protocols and address any discrepancies immediately.

BEST PRACTICE

Present site data entry and SDV metrics weekly during internal calls to track performance. Use these data to inform slot allocation decisions and address any emerging issues. It is critical to discuss weekly metrics with CRAs and share the metrics with sites individually to keep them on track and guide them to ensure queries are resolved, data is entered in timely manner, and AEs/SAEs are reported for review.

Key Takeaway

By developing a comprehensive cohort management plan, maintaining proactive communication with site teams, conducting regular site management meetings, and implementing robust safety review strategies, trial teams can ensure that these complex studies are conducted efficiently and safely.

Chapter 3

Data Monitoring Strategies

Data monitoring is a cornerstone of early phase oncology clinical trials, where the need for timely, accurate data is paramount for making dosing decisions and protecting patient safety.

Centralized Monitoring

Centralized monitoring allows for the continuous oversight of data from various sites and ensures that critical information is captured and assessed in real time.

A key aspect of centralized monitoring is the prioritization of form monitoring, with a particular focus on critical fields on case report forms (CRFs) that are directly linked to the generation of tables, listings, and figures (TLFs) outputs. These fields are crucial for interim analyses and safety reviews, making their accurate and timely completion a top priority.

To be effective, centralized monitoring requires close coordination among data management, biostatistics, centralized monitoring, and clinical teams. This collaboration ensures that data reconciliation, particularly with vendor data transfers and safety systems, is conducted in a timely manner, optimizing the quality and usability of the data for TLF outputs.

BEST PRACTICE

Align monitoring priorities with the needs of interim analyses and safety review meetings. Clearly communicate which fields on the CRF are required for specific outputs, ensuring that all team members are aware of these priorities.

Accelerated Clinical Data Cleaning

Data cleaning is the continuous process of reviewing clinical data, detecting missing information and discrepancies, and issuing queries to clinical site staff. It is essential to accelerate this process to inform decision-making.

Early and timely programming of safety specifications ensures that any potential safety issues are identified and addressed promptly. This involves creating automated processes that can detect and flag inconsistencies or missing data as soon as they are entered into the system.

The query and resolution process between the data management and clinical teams should be streamlined to facilitate quick responses to any data issues. This requires clear communication channels and a shared understanding of the data quality standards of the study.

The centralized monitoring should perform proactive data review, including:

- Daily reviews of EDC data
- Query generation for inconsistencies or missing data
- Holistic review of all patient data in the clinical database, including its diverse data sources, to identify patterns or connections—for example, the association between concomitant medications and AEs

BEST PRACTICE:

Enhance the overall quality of study data by leveraging collaboration among centralized monitoring, data management, and clinical operations teams. This proactive approach facilitates ongoing data review and query generation, enabling quick identification and resolution of issues.

Key Takeaway

Data monitoring strategies in early phase oncology studies are fundamental to the success of these trials. By implementing centralized monitoring, accelerating clinical data cleaning, conducting ongoing data reviews, and ensuring robust documentation and communication, trial teams can maintain the integrity of their data and make timely, informed decisions.

Ongoing Data Reviews

Regular and systematic data reviews help identify trends, signals, and potential issues early in the trial process. Early and ongoing collaboration among centralized monitoring, data management, and biostatistics teams allows for the identification of trends and signals that may indicate underlying issues or areas of interest.

A collaborative approach ensures that data are analyzed from both clinical and logic check perspectives, providing a more comprehensive analysis.

Regular review of patient profiles offers a detailed view of patient data across the trial. These profiles are invaluable for identifying potential issues with patient safety, data integrity, or protocol adherence.

BEST PRACTICE:

Foster early collaboration among centralized monitoring, data management, and biostatistics teams on input and specification documents to ensure the quality of the EDC system.

Documentation and Dissemination

Effective documentation and communication are crucial for ensuring that data monitoring insights are accurately captured and shared with relevant stakeholders.

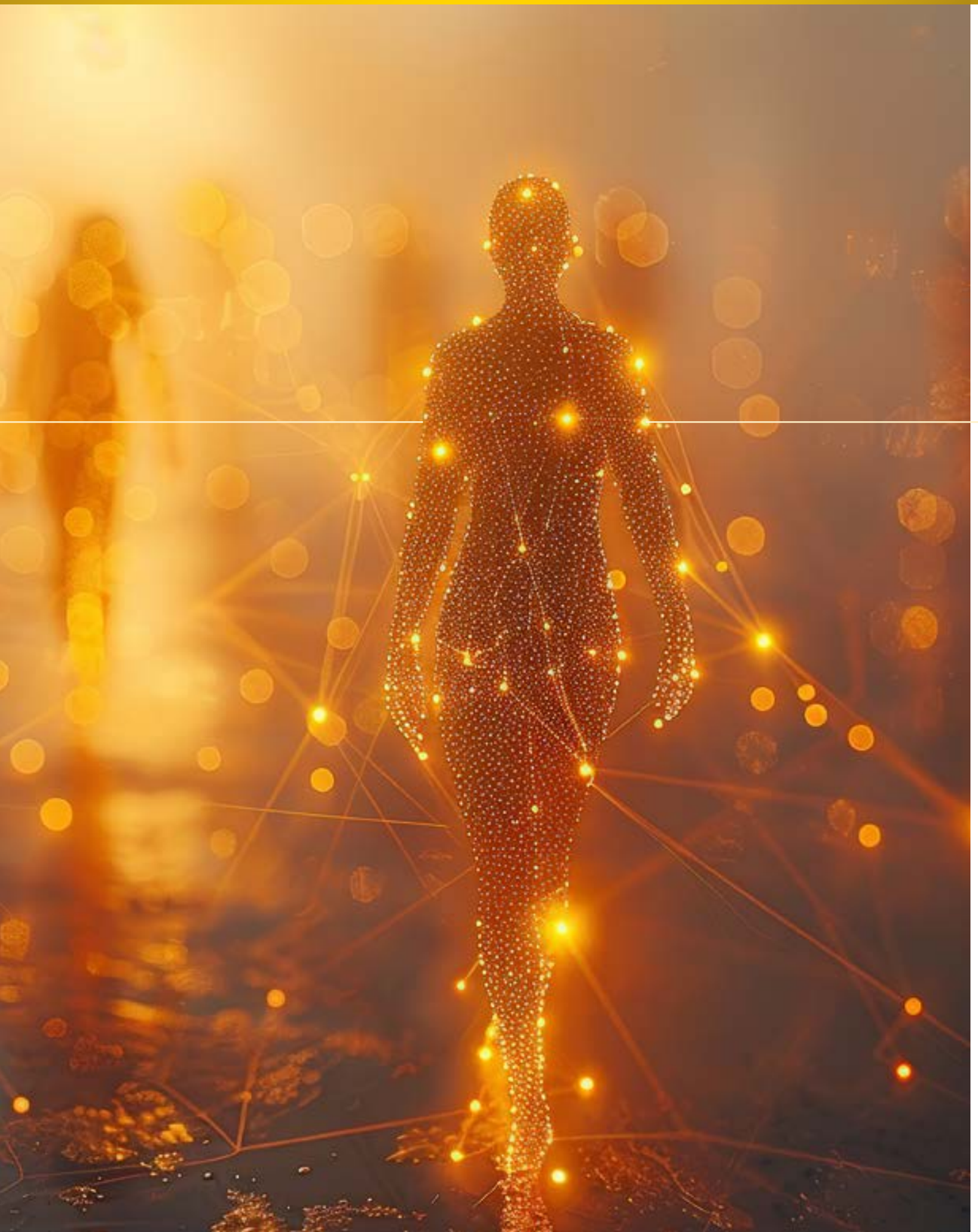
Utilize standardized templates for metrics on status along with meeting minutes to ensure consistent documentation across all data-monitoring activities. These templates should include key discussion points, decisions made, and any action items.

Key findings from data monitoring activities should be communicated to relevant stakeholders, including sponsors, site teams, and regulatory authorities. All outputs—including reports and data summaries—should be version-controlled to maintain a clear audit trail of changes and updates.

This practice is essential for maintaining data integrity and ensuring that all stakeholders are working with the most current information.

BEST PRACTICE:

Internal and focused collaboration between sponsors and study teams on input and specification documents is crucial to the quality of all deliverables. Consistent and clear communication throughout the trial helps maintain data integrity and supports informed decision-making.



Chapter 4

Statistical Considerations in Cohort Management

Managing cohorts in early phase oncology trials requires careful statistical planning and analysis. These trials, often characterized by small patient populations and innovative therapies, depend heavily on the statistical team to uphold the integrity of the study, ensure the accuracy of trial data, and ultimately drive the project's success.

Early Planning for Interim Analyses

Interim analyses provide periodic insights into safety and efficacy, and are often used to inform decisions on dose escalation, cohort expansion, or even trial continuation.

To ensure that interim analyses serve their intended purpose, it is essential to identify the required statistical outputs as early as possible in the trial planning process. This involves achieving alignment among all stakeholders, including sponsors and investigators, on which metrics and data points will be critical for on-study decision-making.

If the sponsor plans to include Clinical Data Interchange Standards Consortium (CDISC) standards in early phase oncology studies, the Analysis Data Model (ADaM) datasets are pivotal for generating the statistical outputs needed for interim analyses submitted to the FDA. However, interim analyses can also be conducted using analysis datasets that do not meet CDISC standards. Regardless, the development of these analysis datasets requires time, so it is crucial to factor in programming time when setting deadlines. Delays in dataset preparation can lead to bottlenecks in the interim analysis process, potentially impacting the overall trial timeline.

BEST PRACTICE:

Engage with sponsors early in the trial planning process to discuss and agree on the necessary interim analysis outputs. Educate them on the time required for statistical programming and the importance of timely decisions to avoid delays.

Tailored Statistical Outputs for Safety Review Meetings

Safety review meetings are a critical component of early phase oncology trials, where decisions about patient safety and dose adjustments are made based on the data collected.

One effective strategy is to develop mock TLFs for sponsor review early in the study. These mock outputs can serve as a template for how the final outputs will look, helping to align sponsor expectations and ensure that the necessary data are being captured appropriately.

Tailoring the statistical outputs to the specific needs of the study and sponsor's preferences is essential. This customization might involve focusing on particular safety signals or efficacy markers that are of interest in the context of the novel oncology treatment being tested.

Close collaboration among function leads—including clinical, data management, and biostatistics—is vital for developing a comprehensive perspective on study requirements. These cross-functional discussions help ensure that the statistical analyses are appropriately designed to address the unique challenges and objectives of the trial.

BEST PRACTICE:

Prepare and share mock TLFs with sponsors early in the study to align expectations and facilitate productive discussions on the required outputs for safety review meetings.

Key Takeaway

Statistical considerations are integral to the successful management of cohorts in early phase oncology trials. By engaging in early planning for interim analyses, tailoring statistical outputs for safety reviews, choosing optimal trial designs, and carefully considering sample size, trial teams can ensure that their studies are both scientifically rigorous and practically feasible.

Optimal Trial Designs for Early Phase Oncology

The choice of trial design can make or break an early phase oncology study. To identify a recommended dose for expansion, the design must balance patient safety, efficiency, transparency, and simplicity.

Several trial designs are commonly used in early phase oncology, each with its own advantages and limitations. The traditional 3+3 design is straightforward, but has been shown to be less efficient in identifying the maximum tolerated dose. Modern designs, such as the modified Toxicity Probability Interval (mTPI-2), Bayesian Optimal Interval (BOIN), and Backfill i3+3 (Bi3+3), offer greater flexibility and efficiency in dose-finding.

- **mTPI-2** builds on the original mTPI design by simplifying the decision rules and improving computational efficiency while retaining accuracy. This model-based approach relies on predefined intervals of toxicity probabilities to guide dose escalation or de-escalation
- **BOIN** focuses on optimizing the interval for dose escalation and de-escalation decisions based on the probability of observed DLTs, with the goal of providing a balance between patient safety and efficient identification of the MTD
- **Bi3+3** incorporates Bayesian principles to assess the probability of DLTs at each dose level, providing more flexible and robust decision-making compared to the fixed rules of the traditional 3+3 design

The choice of trial design should be guided by the specific goals of the study, the characteristics of the patient population, and the nature of the therapy being tested. Factors such as the expected toxicity profile, the need for dose escalation flexibility, and the desired balance between patient safety and trial efficiency should all be considered.

BEST PRACTICE:

Select the trial design that best aligns with the study's objectives, patient population, and therapeutic context. Engage with biostatisticians early in the design process to ensure that the selected design is sufficiently robust and appropriate for the needs of the study.

Oncology Success Starts With Precision

Addressing the inherent complexities of early phase oncology trials takes a concerted effort to manage patient safety, data integrity, and study timelines. Precision for Medicine approaches cohort management with rigorous planning, detailed coordination among clinical teams, and the continuous, active management of all trial components.

Leveraging well-choreographed communication strategies, vital information flows seamlessly among teams, streamlining and accelerating data collection and analysis. Centralized monitoring further enhances this process, allowing for a more comprehensive view of trial progress and facilitating more rapid identification of issues or outliers. These practices help in anticipating challenges and addressing them proactively so that the trial stays on track and that patient safety is protected.

For early-phase oncology trials, successful cohort management hinges on seamlessly blending scientific precision with practical experience.

Position your program for success with Precision.

Precision for Medicine integrates deep oncology expertise with an integrated suite of clinical, translational, and manufacturing solutions.

FROM PROMISING MOLECULE TO NEXT-GENERATION THERAPY

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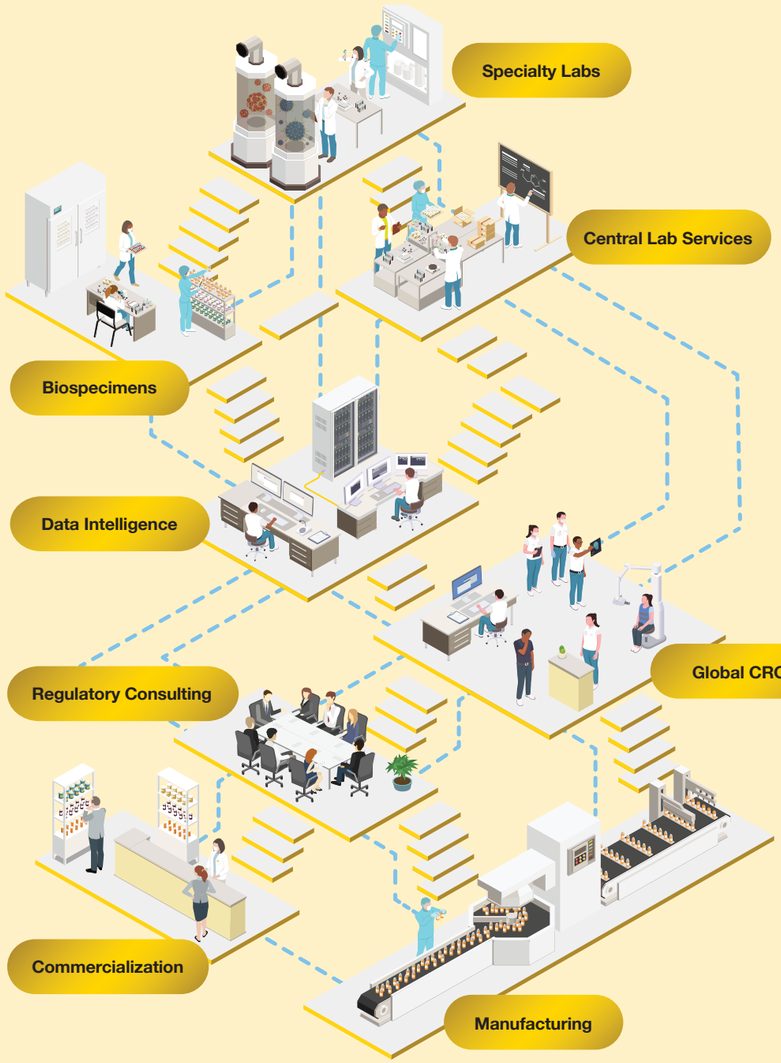

End-to-end capabilities are only the beginning. Precision's global teams and proprietary technologies strategically enhance key milestones across the development life cycle.

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