Cytel
Shaping the Future
of Drug Development

Are You Harnessing the Power of Your Clinical Data?

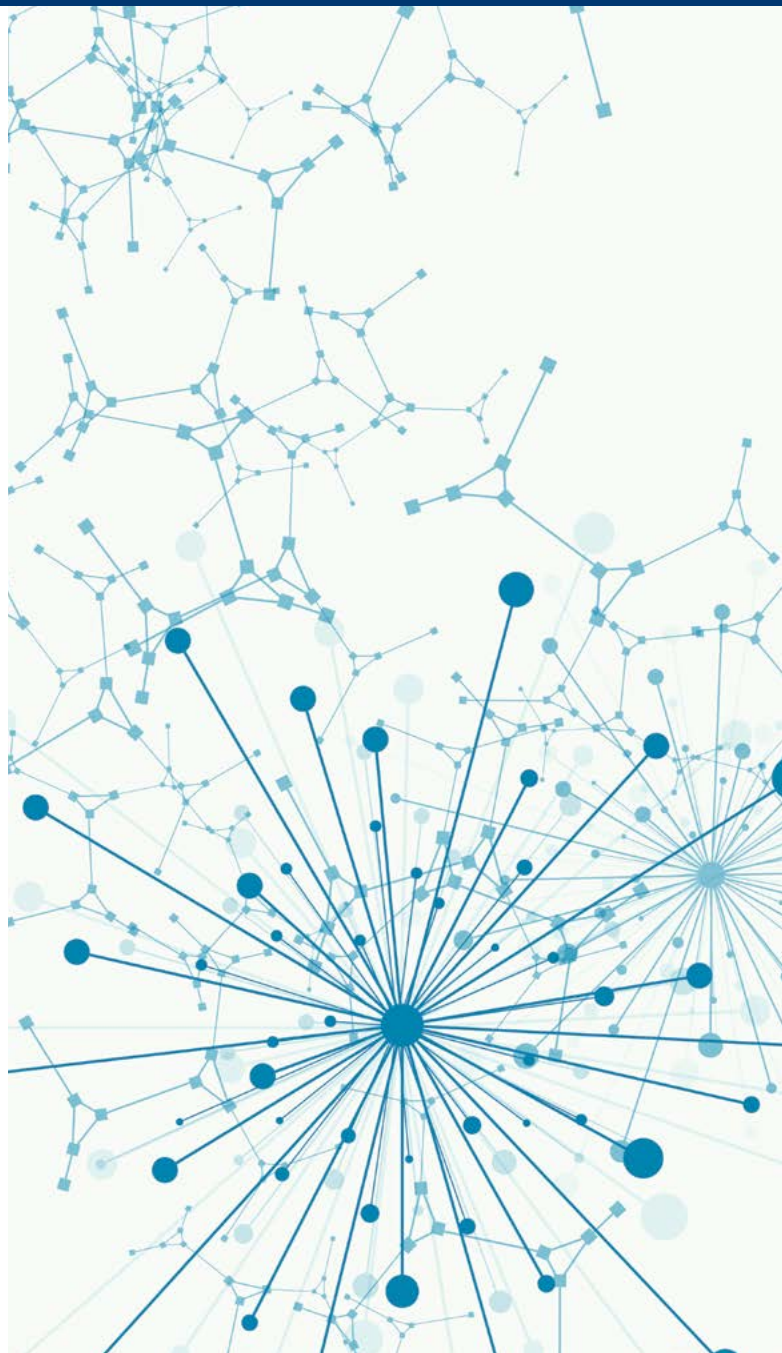
How Small Changes to Your Data Strategy Can Make a Big Difference to Your Chances of Success in Clinical Development

WHY IS PLANNING YOUR CLINICAL DATA STRATEGY CRUCIAL FOR SUCCESSFUL CLINICAL DEVELOPMENT?

> "Someone is sitting in the shade today because someone planted a tree a long time ago"
>
> Warren Buffett, investor, business magnate, and philanthropist

In clinical development, we all strive to deliver therapies that improve patients' lives. However, the clinical data we generate can profoundly impact our success in achieving this goal. A high-quality clinical data package is a fundamental requirement for a new therapy to obtain approval from regulators like the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), as well as other stakeholders such as payers and health technology assessment (HTA) agencies. As such, ensuring data quality can increase your chances of successfully bringing your therapy to market or licensing it to another company.

However, generating high-quality clinical data is far from straightforward, especially if you don't have the appropriate in-house expertise. For example, statistical validity, source type, and clinical relevance are just some of the many factors that can affect the quality of the data produced. What's more, it can be challenging to manage increasingly vast and complex datasets while safeguarding data quality, such as when collecting real-world data using digital devices.



Planning your data strategy, including your trial design, is crucial to ensure the quality of your evidence package so that you can manage risk and increase the chances of successful clinical development.

It can be extremely risky to deprioritize your clinical data strategy. You could lose considerable resource investment with no gains, and companies with a smaller portfolio may jeopardize their viability if their few assets fail to gain regulatory approval. Even more concerning is the risk of having to stop investigation into a promising therapy that could have been life-changing for many patients.

Considering all of this, Planning your data strategy, including your trial design, is crucial to ensure the quality of your evidence package so that you can manage risk and increase the chances of successful clinical development. Although most companies devise data strategies for their clinical programs, this often happens quite late in the development process, long after the time when a data strategy is most useful. In the best case scenario, your program will not reap the full benefits of a well-planned data strategy. In the worst case scenario, the evidence package will be of insufficient quality and you will fail to gain regulatory approval for a promising new therapy.

In this eBook, we discuss what is involved in planning a clinical data strategy for the entire duration of a development program, as well as for Phase 1 and Phase 2 trials specifically. We also outline some best practices for planning your data strategy, including tips from Cytel experts working in our Strategic Consulting, Clinical Research Services and Data Management teams. With even small, easy to implement changes to your data strategy, you could enhance your chances of success and ensure the therapies you develop ultimately reach patients.

1 CHAPTER 1: KEY CONSIDERATIONS IN PLANNING YOUR CLINICAL DATA STRATEGY

"A man who does not plan long ahead will find trouble at his door"

Confucius, philosopher and politician

A clinical data strategy doesn't just concern data quality. It also involves identifying where you will source your data and defining your approach to data collection, storage, and analysis. Along the traditional Phase 1—2—3—4 trajectory of the clinical development process, a well-planned data strategy can help to overcome the unique challenges encountered at each stage (see page 6; see also Chapters 3 and 4 for more details on the importance of a data strategy during Phase 1 and 2 studies).

How a Data Strategy Facilitates all Stages of the Traditional Clinical Development Process

A data strategy can help overcome the key challenges you encounter during each of the four stages of the traditional clinical development process:

Phase 1:

Evaluation of safety, toxicity, and tolerability of an investigational therapy in a small group of (usually healthy) people for the first time, to identify safe dosage ranges and pharmacokinetics and metabolism of the drug. Phase 1 trials can involve unforeseen logistical and administrative challenges, such as the timely introduction of data standardization processes and frequent protocol amendments. Without forward planning, these challenges can cause significant delays and increase costs. As such, having a data strategy in place that predicts and manages these unforeseen issues can help you mitigate risk and even expedite the development pathway. A well-planned data strategy will also ensure that early phase trials generate the evidence necessary for later phases of development.

Phase 2:

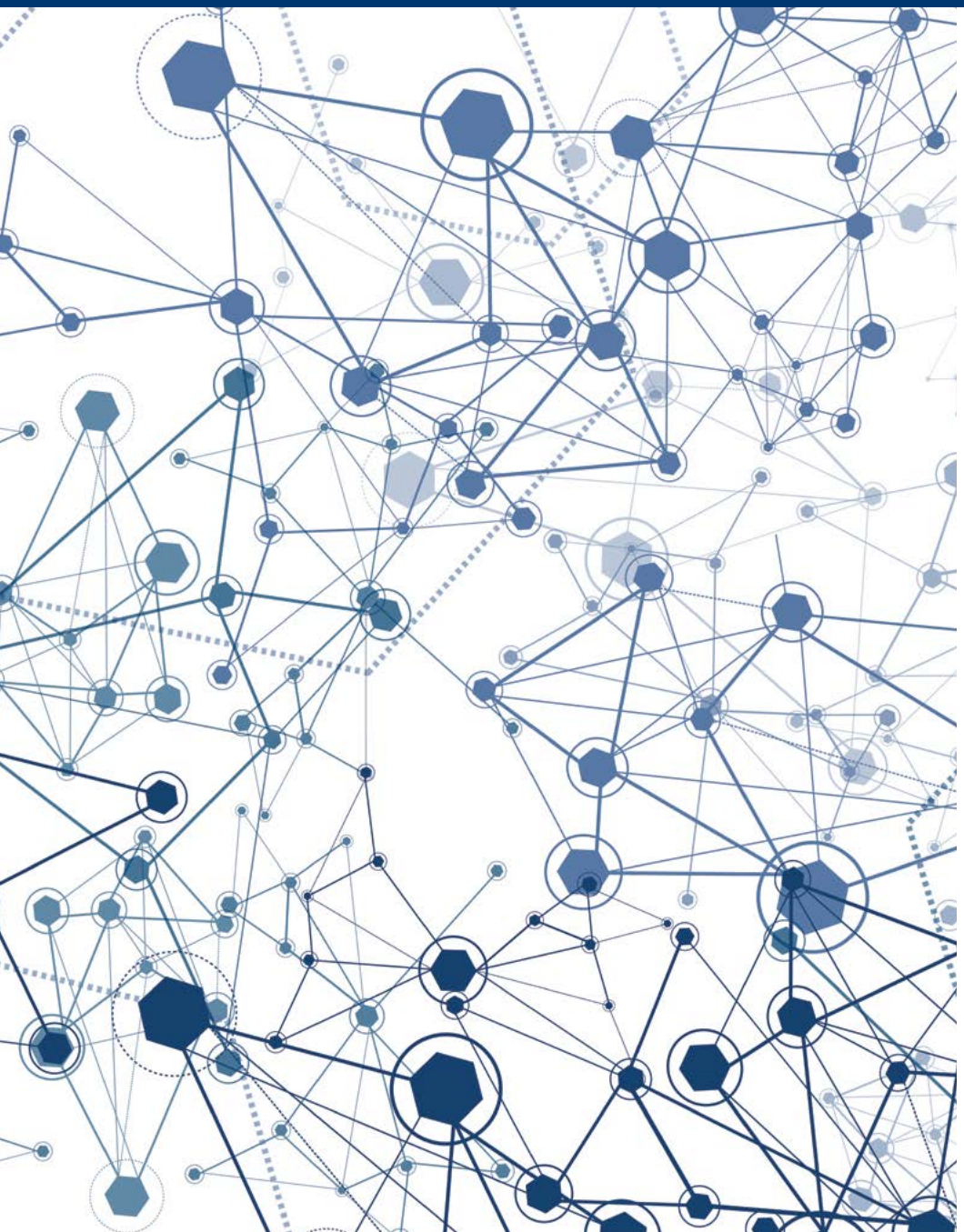
Studies in patient populations with the disease of interest to generate preliminary evidence of efficacy and safety. The key challenge at this stage is to ensure that adequate data is collected to fill in as many present knowledge gaps, as well as plan for future evidence needs. For example, using Phase 1 data and quantitative modeling/simulation techniques can guide the generation of high-quality evidence.

Phase 3:

Studies using larger groups of patients, often lasting several years, to confirm the therapy's efficacy and further evaluate its safety. As the 'race to market' begins at this stage, a well-planned data strategy can help to meet timelines from database set up to database lock while preserving the quality and integrity of the data, such as by implementing optimized systems to enable data standardization and risk-based monitoring.

Phase 4:

Long-term, post-marketing surveillance studies after a therapy is approved by regulatory authorities for indicated use in patients, with safety and marketing groups, as well as prescribers and payers, being key stakeholders. The data strategy plan needs to reflect these various audiences and their different data and evidence needs.



It's no surprise that planning your clinical data strategy can be complex and time-consuming. However, it's easy to underestimate just how much time you need to address the myriad of considerations that underpin the success of your clinical programs. These considerations are not only numerous but also involve making tough decisions that can affect the quality of your data, such as:

- What trial design will you use?
- What data will you need to collect to fill in knowledge gaps?
- How will you collect and analyze the data?
- How will you address regulatory and HTA queries about efficacy, safety and market access?

When addressing these issues, it's vital to draw on your existing expertise and seek guidance when necessary to further build your knowledge. You also need enough time to make informed decisions and implement the best data management practices, which can boost your credibility with regulators as well as HTA agencies and other key stakeholders.

Best Practices for Formulating a Data Strategy

Drawing up a suitable data strategy for your clinical programs involves the following best practices:

Implementing a cross-departmental approach.

Form a governance committee consisting of key stakeholders from all departments involved in the planning and execution of the data strategy, including clinical, biometrics and data management, regulatory, and project management functional groups. The committee helps ensure everyone involved understands the impact of how the data will be sourced, collected, managed, and stored.

Centralizing data collection and analysis.

Implementing a single electronic data capture (EDC) system can improve operational efficiency and costeffectiveness, such as by reducing the time and costs involved in training personnel on data transformation processes. A centralized EDC also helps to standardize data quality across sites, from data collection through to analysis, and can enable full traceability of the data for auditing purposes.

Collecting real-world evidence as well as data on efficacy and safety.

Real-world data, such as patient reported outcomes, social media data, and electronic health records, is becoming increasingly important in HTA studies.

Converting data into knowledge.

Knowledge and actionable insights should be the end-goal for all data strategies, so that companies can make the optimal decisions both for the project and the wellbeing of patients.

As such, it's vital to start planning your data strategy and trial design as soon as possible, prior to starting Phase 1, ideally as you transition from non-clinical to clinical studies. Early planning and consideration of the entire development pathway can significantly benefit your clinical programs, which we discuss in detail in the next Chapter.

2 CHAPTER 2: THE VALUE OF PLANNING A PROGRAM-WIDE DATA STRATEGY, EARLIER

"Before anything else, preparation is the key to success"

Alexander Graham Bell, inventor

The traditionally separated 1—2—3—4 phases are becoming increasingly connected in modern clinical development. This means that a data issue encountered during one phase can now easily have immediate downstream consequences. One way to mitigate this potential issue is to plan your data strategy for the entire duration of your program from start to finish, which we refer to hereafter as a 'program-wide' strategy.

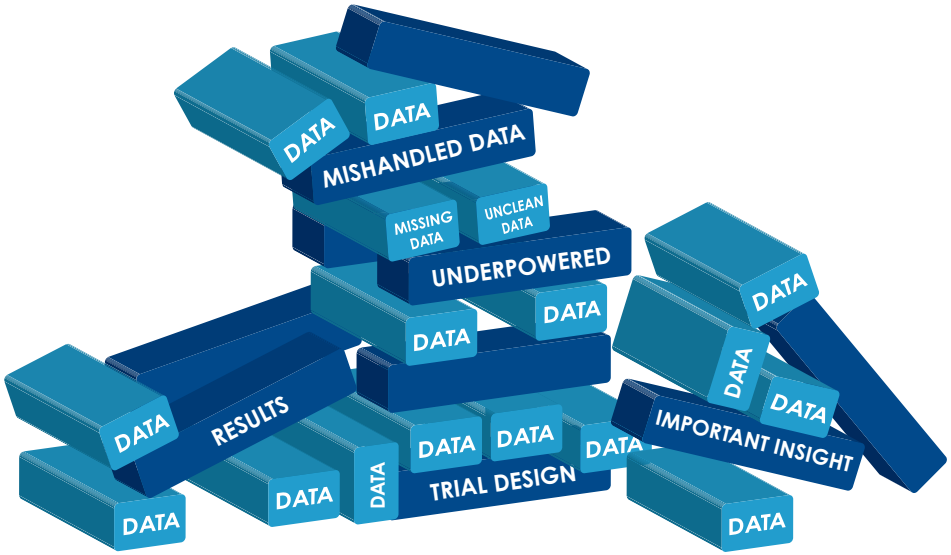
Instead of planning trial by trial, formulating a program-wide strategy for data management and trial design well before starting Phase 1 will enable you to collect the right data, at the right time, in the right amount, and in the right way. As well as obtaining an evidence package of the highest quality, such an approach also shows all stakeholders how you have maintained data integrity throughout your program.

Instead of planning trial by trial, formulating a program-wide strategy for data management and trial design well before starting Phase 1 will enable you to collect the right data, at the right time, in the right amount, and in the right way.

"Like the foundations of a house, if the data is strong it will avoid later collapse"

Clinical Research Services expert, Cytel

This high-quality data package gives you leverage to license out your asset or for your company to be acquired following Phase 2, or to continue to progress successfully to Phase 3. Whatever your business objective, this will not only increase the likelihood of gaining a return on your investments, but also minimize the risk that a promising therapy fails. It also ensures that the time and effort invested by program participants were worthwhile. In the end, your well-planned program and high-quality evidence package will increase the likelihood that your drug will be approved by all stakeholders, including regulators, and that the therapies you develop are valuable to patients, doctors and payers.



Additionally, devising your trial design and statistical analysis plans for the entire development program can also help you to improve its cost-effectiveness, helping you stay on budget without compromising the quality of your data outputs. For instance, by using a historical control group design, you can compare the response seen in a treatment arm against data collected in previous trials, which can save time and money recruiting patients.

A program-wide data strategy can also help inform your market access strategy post-approval, to enable better patient access and market positioning. For example, planning to collect data on social issues, such as how the therapy affects patients' quality of life, is one of the many ways a data strategy can help inform market access once the trial phases are over.

Managing Risks and Streamlining the Development Pathway

Planning a program-wide data strategy earlier will give you enough time to inform risk management by identifying, quantifying, and mitigating potential risks that could jeopardize your clinical programs and increase costs. Having this 'roadmap' in place well before you start Phase 1 means you don't have to act reactively when issues arise and instead have a clear plan for the next steps you must take in the development pathway. The strategies you already have in place will help minimize risks such as costly delays, re-running trials, or even the termination of your program.

> "Planning earlier allows you to make proactive changes according to a holistic vision, rather than just reacting without the next step in mind"
>
> Strategic Consulting expert, Cytel

For instance, to ensure you collect the right data to show regulators and other stakeholders, it is vital to define trial populations and end goals from the start, plan what data you need to collect at each step, as well as identify how innovative features such as historical control group design can facilitate data collection. Moreover, it is essential to have plans in place about how you will handle the data, such as examining data features, implementing bias control measures, or minimizing incomplete data collection. Implementing these strategies has the additional benefit of streamlining the development pathway to accelerate your therapy's time to market, as the next steps in development are clearly signposted to enable the program to continue without delay.

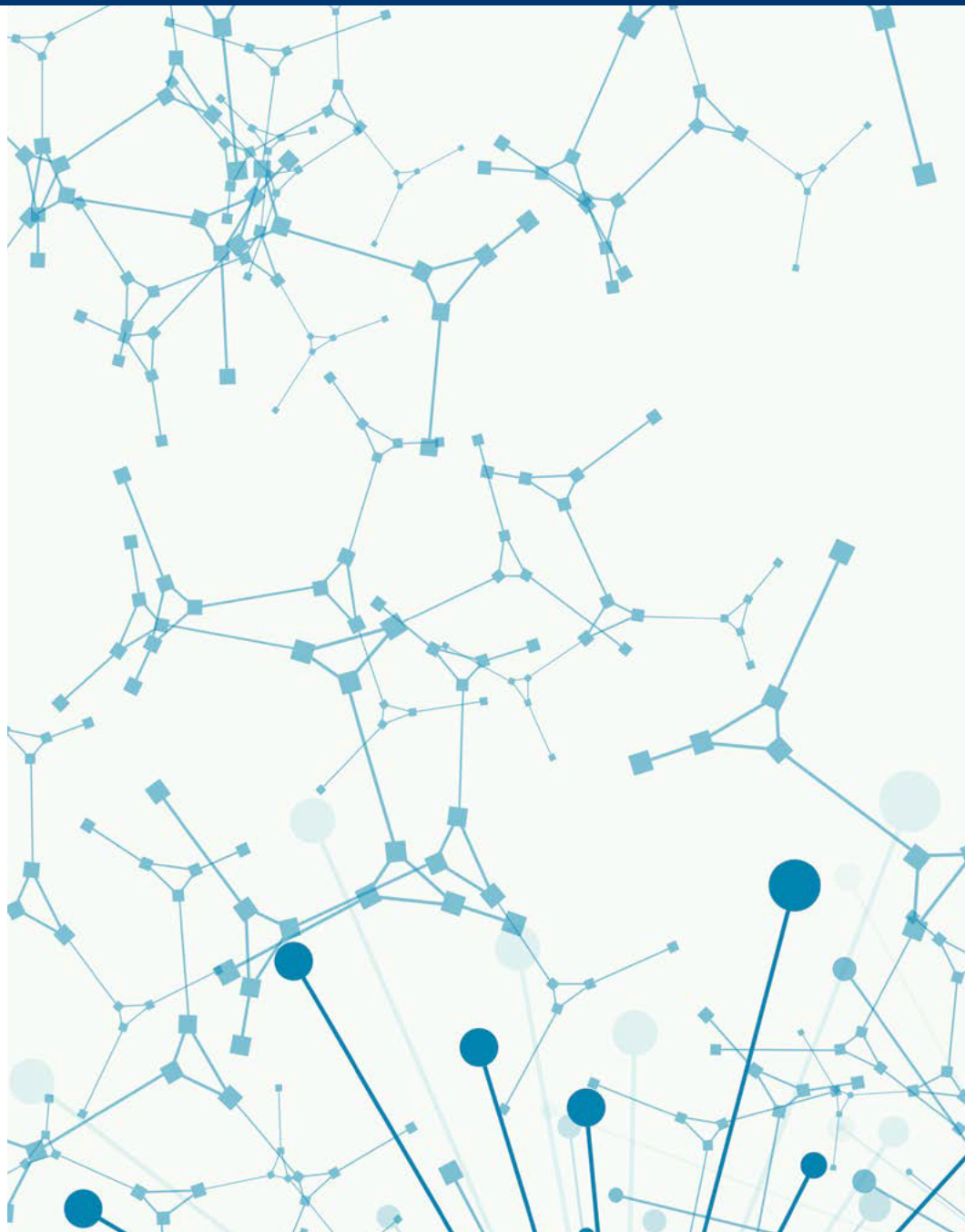
What's more, by planning early, you can use this time to get the plans reviewed by the relevant people, such as data managers, so you can make any necessary amends before the program starts. This is particularly important as changes made late in the development process are very difficult to implement, so having input from stakeholders right at the beginning helps avoid these late-stage changes.

We have so far discussed the benefits of planning a program-wide data strategy. However, it is also valuable to consider how your plan will overcome challenges specific to Phase 1 and Phase 2 trials, which will be the focus of the next two Chapters.

3 CHAPTER 3: PLANNING PHASE 1 – MITIGATING UNKNOWN RISKS BEFORE THEY ARISE

Although Phase 1 studies tend to produce lower volumes of clinical data and are typically shorter in duration than other phases, formulating a data management strategy for these early studies can be more complex than you might expect.

For instance, it can take up to 12 weeks to build a comprehensive database tailored to your program, especially because the study protocol can remain unpredictable during Phase 1 trial set up until First Patient In. Additionally, you will likely need to manage and integrate data from multiple vendors, which can be as many as 15 at a time. As Phase 1 data is typically collected in sets (rather than on an ongoing basis) appropriate resources should be put in place to handle this workflow and address the data as it arrives. Overcoming these challenges can quickly use up time and funding, so having a plan already in place can help you stay within budget while meeting key project milestones.



So how can you ensure your data strategy will successfully minimize the risks and associated costs you might encounter during Phase 1? Planning your strategy with a knowledgeable partner early on can help identify and resolve issues *before* they have a detrimental effect on your project.

For example, an experienced statistical team can help build different databases to strengthen your evidence package (including source, outcomes, and comparator databases), look at existing data to inform the trial design, perform pharmacokinetic analyses such as noncompartmental analysis, and devise ways to integrate different data sources and streamline processes. This can significantly reduce how much time and funds you need to spend fixing unforeseen issues.

A specialist can also help you establish an appropriate data review process for each key decision stage, such as building in enough time for sample analysis and data transfer. They can also implement a consistent data handling approach and analytical rules across studies to reduce your oversight burden.

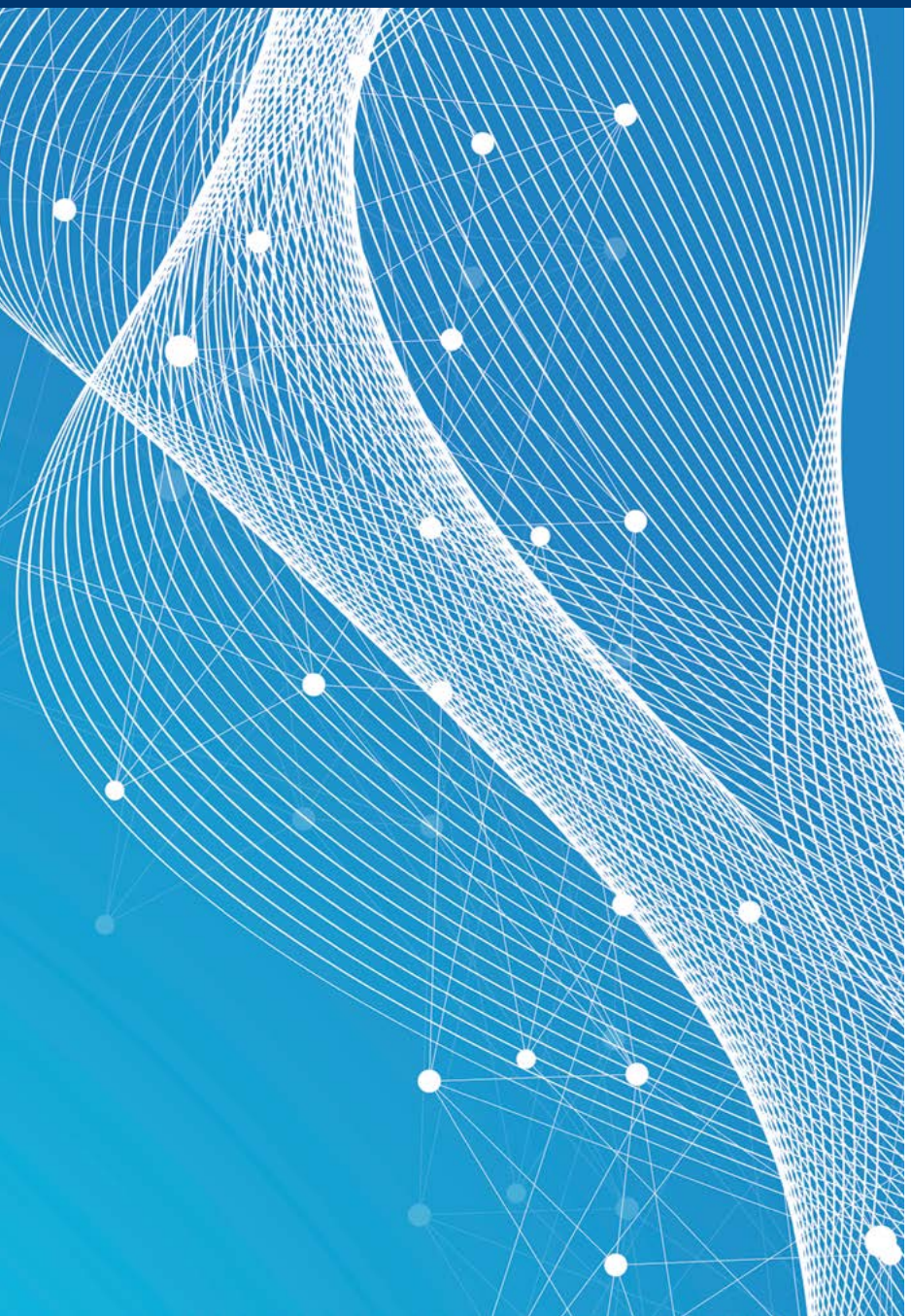
Preserving the Integrity of Your Trial Designs

An experienced partner can help you plan and execute adaptive trial designs, which can help you get the most value out of your clinical programs. Adaptive designs enable shorter treatment duration, smaller trial size, and greater statistical power than traditional fixed trials, enabling you to identify dose ranges, suitable patient populations, and therapy performance for a fraction of the cost. Doing this in the early stages of development gives you rich insight in deciding how to get optimal results in later, more expensive large-scale trials.

What are Adaptive Trial Designs and Why Use Them?

Adaptive designs for clinical trials use accumulating results to change the trial's course (in accordance with pre-specified rules). They can be applied across all phases of clinical development. Trials with adaptive designs are typically more efficient, ethical, and informative, and they often make better use of time and funds, and might require fewer participants. Thorlund et al. (2018) describe some common types of adaptive trials, such as:

- **Sample size reassessment:** If interim results are worse than expected, the sample size can be adjusted to ensure the trial has sufficient power;
- **Response adaptive randomization and abandoning inferior doses:** Newly enrolled patients are assigned to a more promising treatment arm after interim analysis;
- **Adaptive enrichment:** Changing the recruitment eligibility criteria to enrol patients from a more favourable subgroup who are more likely to benefit;
- **Seamless designs:** The continuation of one phase to enrich a subsequent phase, such as to determine the initial allocation ratio and planned total sample size.



To take advantage of the many benefits that adaptive trials offer, it is vital to address the various challenges involved. For example, as adaptive designs often require altering the trial's parameters midstream, statistical issues in these designs can be complex. Therefore, it is valuable to have experienced biostatisticians on hand who can help you preserve the trial's integrity as well as interpret and report the findings correctly (Pallmann et al., 2018). If brought in too late, your partner cannot fully apply this expertise, and you will lose the opportunity to enhance the quality of your data as well as the cost-effectiveness of your program.

> "We recommend consulting someone with expertise in and experience [of adaptive designs] well enough in advance. The statistician can advise on appropriate analysis methods and assist with drafting the statistical analysis plan as well as pre-trial simulation studies to assess the statistical and operating characteristics of the proposed design, if needed"
>
> Pallmann et al. (2018), page 6.

4 CHAPTER 4: PLANNING PHASE 2 – ENSURING A HIGH-QUALITY EVIDENCE PACKAGE

> "Plans are of little importance, but planning is essential"
>
> Winston Churchill, former Prime Minister of the United Kingdom

The evidence you collect during Phase 2 studies must convince regulators of your therapy's efficacy and safety, so it can be successfully progressed to Phase 3 or licensed to another company (or even incentivize the acquisition of your company if that is your business objective). This evidence can also boost understanding of the needs of patients and prescribers to confirm that the therapy is commercially viable. It is therefore imperative that your data strategy overcomes the key issues you will encounter.

One major challenge is collecting the data you need to address any knowledge gaps in your Target Product Profile. Moreover, as many Phase 2 studies rely on data collected from earlier Phase 1 trials, it is vital that this data is translated into showing evidence of efficacy and safety.

What are the Characteristics of a Target Product Profile (TPP)?

A Target Product Profile (TPP) involves identifying gaps in knowledge that need to be filled by your clinical development program data to gain regulatory approval. The gaps you need to fill include:

- **Indications:** Which diseases?
- **Population:** Which patients and where?
- **Clinical efficacy:** Does it work effectively?
- **Safety and tolerability:** What kind of adverse events and how many?
- **Stability:** How long can it be stored in the field?
- **Route of administration:** How is it given to patients?
- **Dosing frequency:** How often and how long must it be given?
- **Cost:** Will it be affordable to the target population?
- **Time to availability:** How long will it take to develop?

How Can You Generate the Clinical Data You Need?

One solution is to use a Quantitative Pharmacology and Pharmacometrics (QPP) approach to produce the data needed to fill in knowledge gaps. For instance, expert pharmacometricians can devise modeling approaches to guide your Phase 2 studies, such as providing the optimal range of doses and the best active control. QPP approaches can also help you make critical decisions through exposure-response population modeling, simulation of safety and/or efficacy endpoints, and population pharmacokinetics modeling to identify significant covariates of exposure.

Additionally, Bayesian approaches can help to update the information that accrues during a trial to allow for smaller trials, more precise dose-escalation, and better patient care. Working with a knowledgeable partner can help leverage the predictive power of Bayesian approaches. For example, Bayesian analyses can predict timelines, re-estimate sample sizes, and determine how a current cohort of patient will respond to treatment (based on historical data or available patient-outcome information), all while minimizing the risk of introducing bias or impairing interpretability.

Addressing Commercialization and Market Access Requirements

It's important you generate data that satisfies not only regulators but also payers and HTA agencies so that patients can ultimately use your new therapy. One solution is to seek additional guidance from market access experts to ensure you are generating suitable data to show to payers and HTA agencies, such as the cost-effectiveness of the therapy versus comparators and its affordability to the target population. Specialists in model-based meta-analysis (MBMA) can also help with competitive benchmarking, such as identifying comparative effectiveness, simulating new studies, and generating target values for decision-making.

5 CHAPTER 5: TOP TIPS ON OPTIMIZING YOUR DATA STRATEGY PLANNING

Cytel specialists working in the Strategic Consulting, Clinical Research Services and Data Management teams have shared their top 10 tips on optimizing your approach to planning a clinical data strategy.

Top Tip 1 Make sure everyone in your company works towards the same goal: getting a therapy approved that will help patients, that doctors will trust, and that will be commercially successful

Top Tip 2 Start planning your data strategy and trial design as early as possible prior to Phase 1

Top Tip 3 Conduct simulations of trial designs based on program-level considerations to identify the probability of Phase 3 success

Top Tip 4 Consider using adaptive trial design to increase the efficiency, cost-effectiveness, and flexibility of trials while maintaining statistical rigor

Top Tip 5 Optimize your data collection methods; only focus on the data you need to make informed decisions and address regulatory queries

Top Tip 6 Your planning should focus on continual improvement throughout the program, so try to avoid thinking of your program as distinct phases when devising your data strategy

Top Tip 7 Ensure biostatisticians and data managers are working effectively together to optimize efficiency and data quality

Top Tip 8 Implement systems and processes that enable efficient data standardization and transformation, which can help with regulatory submission planning as well as yield opportunities for new insights

Top Tip 9 Work with a knowledgeable, reliable partner with a track record of planning successful data strategies and try to approach it as a partnership

Top Tip 10 Maintain a communicative relationship with your partner; establish your goals and expectations from the very early stages for optimal project management

Rethinking Your Data Strategy to Advance Clinical Development

As data becomes more complex and interconnected in modern clinical development, it is vital that we implement ways to fully exploit this rich information to improve patients' lives. Data is the foundation underpinning your clinical programs, and one way to reinforce this foundation is to employ a data strategy.

In this eBook, we've outlined how to ensure your data strategy is rock-solid. Planning carefully, following the industry's best practices, helps deliver an optimal approach and trial design suited to your clinical program. This includes planning early, well in advance of starting Phase 1, and formulating a program-wide strategy that considers the entire duration of the development program.

Working with a knowledgeable partner can help you formulate and execute a data strategy that goes beyond your in-house capabilities, so you can gain the substantial benefits offered by a seamlessly implemented and highly effective plan. These benefits include minimizing risk to your clinical programs, gaining returns on your investments, and making life-changing therapies accessible to patients who desperately need them.

Why not speak to us to find find out more?

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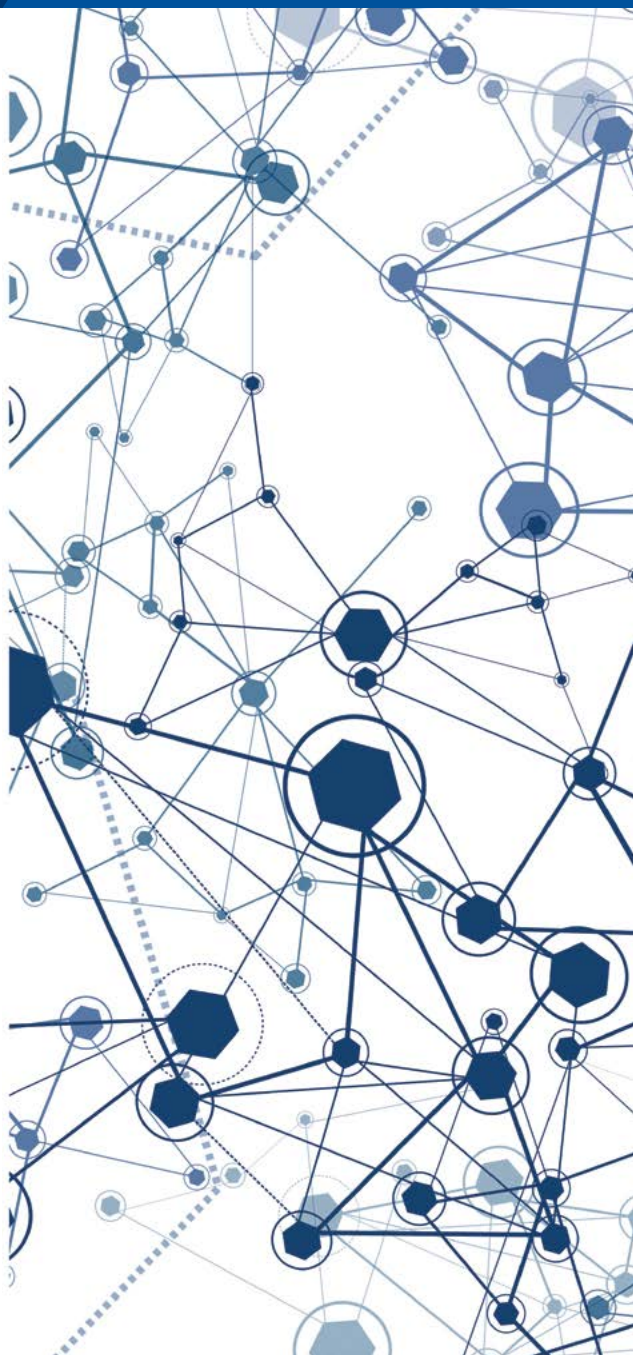

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About Cytel

As a pioneer in evidence generation, with deep expertise in advanced analytical solutions, Cytel is uniquely equipped to unlock the value from increasingly complex data. Life sciences companies count on Cytel to deliver exceptional insight, minimize trial risk, and accelerate the development of promising new medicines that improve human life. Cytel provides data-focused clinical research services and software solutions for the design and analysis of clinical trials, including industry standards East®, StatXact®, and LogXact®. With operations across North America, Europe, and India, Cytel employs 900 professionals, with strong talent in biostatistics, programming, data science, and data management.

For more information about Cytel, visit www.cytel.com

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