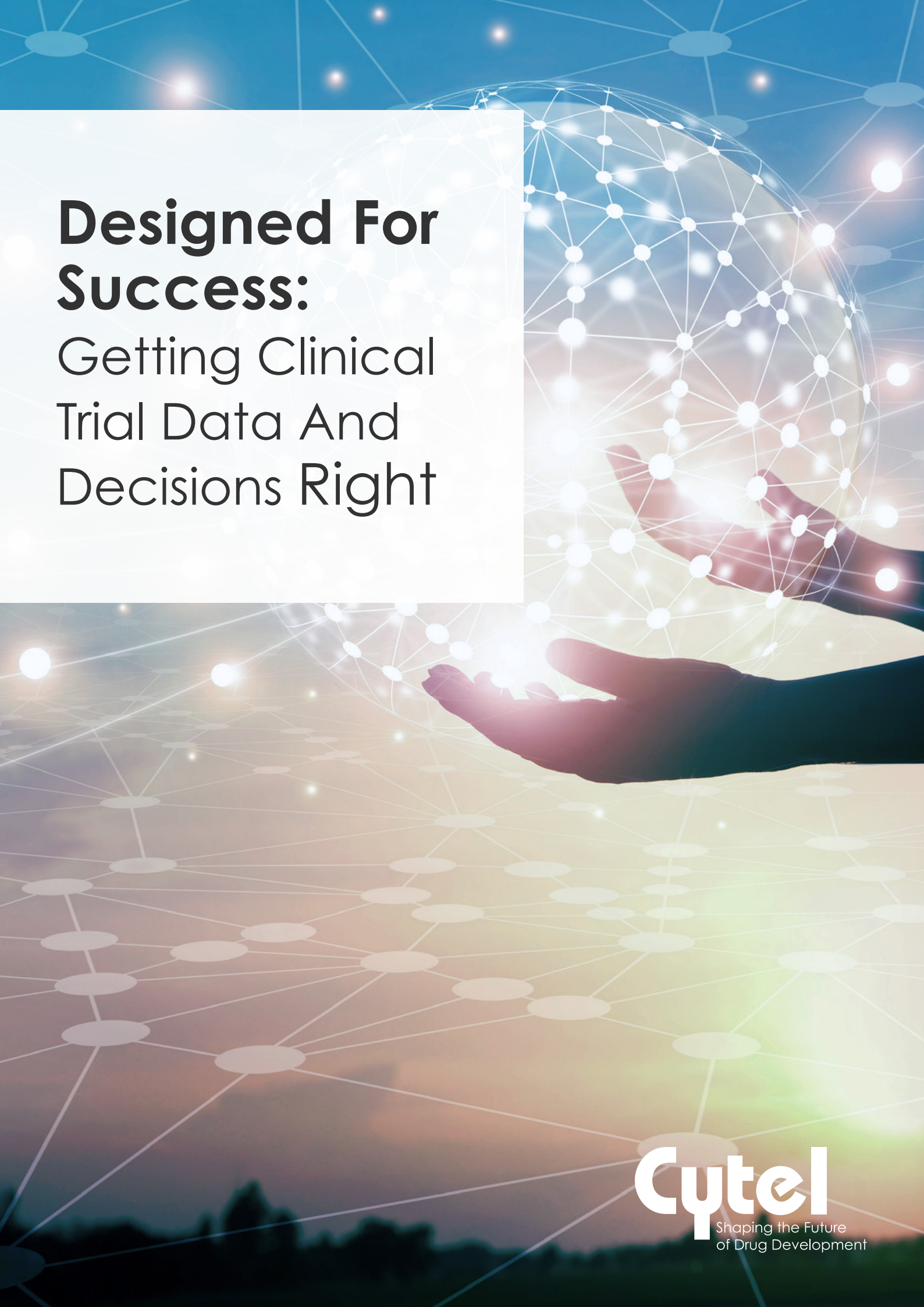


# Designed For Success:

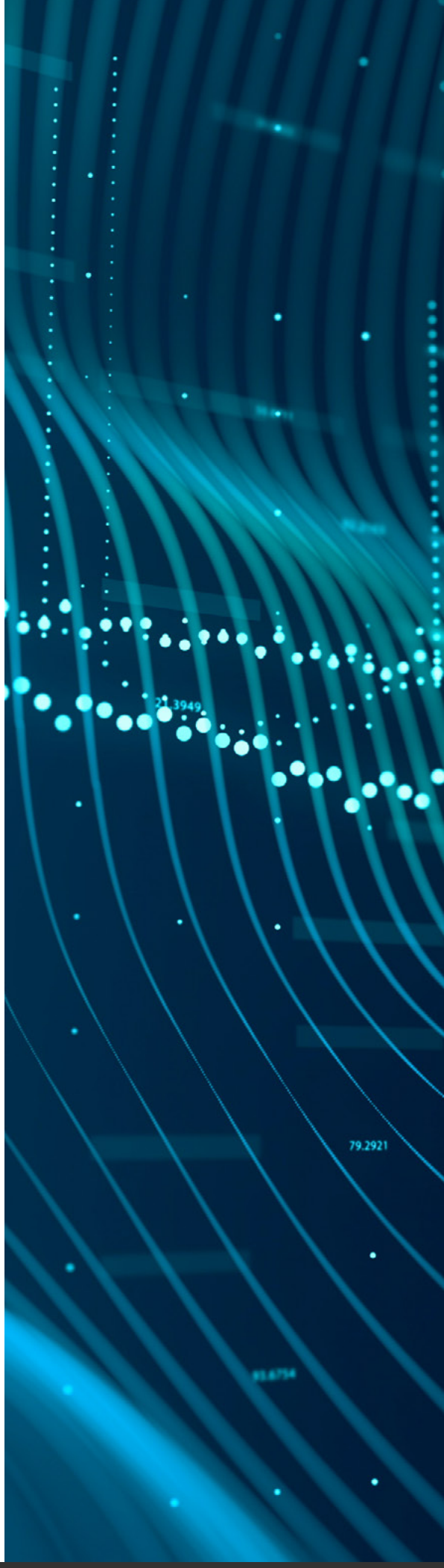
## Getting Clinical Trial Data And Decisions Right

Cytel

Shaping the Future of Drug Development

# Contents





# Introduction

Every structure requires strong foundations if it is to avoid costly remedial work further down the line and a clinical trial is no different. Without the right design, right data and right decisions, an idealised plan cannot be translated into a blueprint for robust study.

This is vital for pharmaceutical and biotech companies alike. Rebuilding and re-running a trial is a costly, time-consuming process and an all too avoidable one too, given that any uncertainties could have been resolved if the development process had been better designed in the first place. But if failed trials are a major annoyance for big pharma, they can be fatal to smaller biotech companies.

Thankfully, the traditional three-phase clinical development process is changing. While big late-stage trials are still fairly common, it's also no longer a surprise to see sponsors refer to phase 1/2 trials, or phase 2/3, and smaller trials that can be progressed to the next phase if an interim data readout supports further evaluation.

Such 'seamless' trials and options like adaptive trials can all increase a study's chances of success. But only if it has the right design and execution.

To explore these issues this report hears from Dr Charles Theuer, president and CEO of biopharmaceutical company TRACON Pharmaceuticals, four-time biotech chief medical officer Scott Harris and clinical development thought leader Dr Nico Merante.

Additional expert counsel is provided by Cytel's senior vice president of clinical research services Irving Dark and its principal of strategic consulting Natasa Rajicic.

# 01
# Data – A Complex Picture

The pharmaceutical world has always been data-rich, but lately it is faced with a data landscape that has become increasingly complex in-line with the rise of the digital and 'real-world' age.

Real-world evidence is increasingly used to aid the clinical development process. By showing how effectively medicines work outside the clinic it can also add a powerful new dimension to the traditional gold standard of randomised clinical trials, providing information payers need to make difficult decisions about cost-effectiveness.

There are myriad ways in which this data can be generated. Patient reported outcomes measures first emerged as analogue, paper-based tools and they have been turbocharged by advances in, and consumer uptake of, digital technologies over the last decade or so. These range from electronic health records and registries, to patient reported outcomes and data collected from mobile devices like Fitbits or smartphones. But how can companies ensure this flood of data is best aligned to clinical trials?

Irving Dark, senior vice president of clinical research services at Cytel stresses the importance of having statisticians and data managers working closely together right from the start of the process and then throughout any data collection and analysis endeavours in order to manage data complexity[1].

"Traditionally, the statistician would get involved at the beginning with the data manager to look at

1. Adapting for the future of oncology trials
https://deep-dive.pharmaphorum.com/magazine/oncology-asco-2019/cytel-future-adaptive-trials-cancer

As trials continue, they may progress as planned or they can throw up unforeseen results and outcomes. Ensuring that the statistician is integral to this process will provide companies with the resources to respond in a timely and considered manner.

critical variables and form design," he says. "He or she had to check things of that nature, and then the statistician would focus on the analysis plan and interim Data Monitoring Committee, etc."

But he adds: "The statistician and data manager need to work hand-in-glove throughout the continuum of the trial, because ultimately your results are only as good as the data that's behind them."

There are several things companies can do in order to optimise their trial data. It starts with having the right trial design and a fit-for-purpose protocol, with both needing to incorporate the patient voice. Once up and running, data collection must be streamlined, duplication of effort or data avoided and appropriate use made of new technologies, for example in data visualisation. Underpinning all of these requirements is close collaboration between a CRO and trial sponsor, with clarity on all aspects of their partnership.

As trials continue, they may progress as planned or they can throw up unforeseen results and outcomes. Ensuring that the statistician is integral to this process will provide companies with the resources to respond in a timely and considered manner.

# 02
# Crafting The Right Study Design

Natasa Rajicic is principal of strategic consulting at Cytel and has been a practicing biostatistician for over 20 years. She says the input of a statistician with broad experiences in different quantitative strategies in the trial design process can help to mitigate all kinds of data problems, particularly when they require trials needing to be changed or amended midway[2].

"Including the statistician early in the design can help de-risk the trial and the programme from the beginning," Natasa says, noting the importance of assembling the right team for getting clinical trial data and decisions right.

Not having a statistician close by at all times may well turn out to be a bad move if the trial hits problems or needs to be tweaked, according to Natasa. Non-statistical functions do not necessarily know when a statistician's input is needed, so not having a statistician as a core member of the team can prevent the team from having a valuable and timely strategic input.

In addition to the need for pharmaceutical companies to prepare themselves to make better decisions about studies, they also need to ensure they are doing all they can to 'walk the talk' when it comes to patient-centricity. Such an approach to study design is vital for ensuring that the data you collect is meaningful to patients and that the trial will have reproducible value in the real world.

Clinical development thought leader Dr Nico Merante outlines a new way of working towards this that he terms an 'outside in' model for clinical development. Instead of traditionally starting with a molecule, with this model a clinical study really starts with patients[3].

2. Keeping clinical trials on track
https://pharmaphorum.com/r-d/keeping-clinical-trials-on-track

As such their viewpoint should be incorporated within the design and plan itself.

“The system should engage with patients from an early stage. It would be beneficial to include their input when study protocols are designed and study objectives are decided, for example. In case of paediatric studies, both parents should be carefully listened to.

“This approach allows us to improve the quality of the development plan and study designs, to engage with patients early and to include more meaningful endpoints in the protocol. It serves to gather knowledge and experience from patients’ perspectives, through a more accurate patient reported outcome data analysis, and to understand what really, really matters to people in relation to the disease condition they suffer from,” Nico explains.

3. Patients in the driving seat
https://pharmaphorum.com/r-d/patients-in-the-driving-seat

The system should engage with patients from an early stage. It would be beneficial to include their input when study protocols are designed and study objectives are decided, for example.

# 03
# The Art Of Statistics

Particularly in the early stages of the research process, statisticians play a vital role helping to get trials, as well as entire development programmes, into shape.

They can take a broad development view to synthesise existing information and better inform the planning of future trials, help plan for the right data to be available at each step of the development path and beyond, as well as forecast the optimal timing of various decision time points.

However, if a statistician is brought in too late it can be hard to reverse any issues that have already been created by a study's original design.

They (the statistician) can take a broad development view to synthesise existing information and better inform the planning of future trials, help plan for the right data to be available at each step of the development path and beyond...

# 04
# An Adaptive Design Picture

One emerging area where that expertise is needed is for adaptive trials that see regulators accept data from smaller studies for accelerated or conditional approval that later needs to be confirmed by data from a larger trial.

It's often used for an increasingly niche-oriented approach to cancer drug development in which developers are advancing clinical development programmes that do not conform to the traditional three-phase approach.

One of the companies at the forefront of this shift is San Diego's TRACON Pharmaceuticals, a clinical stage biopharmaceutical company whose efforts are focused on the development and commercialisation of novel targeted therapeutics for cancer, as well as wet age-related macular degeneration and fibrotic diseases.

Its president and CEO Dr Charles Theuer says the benefits of an adaptive trial design were demonstrated in the phase 3 TAPPAS angiosarcoma trial his company ran[4]. The TAPPAS trial was designed to include an interim analysis that limited exposure of patients to the study drug in the case that the drug was ineffective, defined the final sample size of the trial if the drug was effective in the overall population of angiosarcoma patients, and also allowed for the enrolment of a certain responsive subpopulation of patients in the case of limited activity. In this case, the trial was terminated for futility and the number of patients exposed to an agent that was not producing sufficient clinical effect was minimised.

He says: "We were studying the very rare tumour type of angiosarcoma, and we did not have the luxury of doing a randomised phase 2 study prior to embarking on the pivotal phase 3 study.

4. Adapting for success
https://pharmaphorum.com/views-and-analysis/cancer-clinical-trials-tracon-cytel

The adaptive design that we chose took into account two factors. One is, we were unsure of the treatment effect. Second, we were also unsure whether the drug could be selectively more active in a certain subpopulation of angiosarcoma."

Theuer says that although the company was "disappointed" with the trial's negative outcome, it proved that an adaptive design can prevent an expensive trial flop further down the line. "Innovative clinical trial designs help everybody.

They emphasise studying the drug in the right population, and then once you've identified the right population to study the drug, they allow you to enrol the fewest patients to prove benefit from a statistical perspective."

Armed with data from the stepwise approach to trial design advocated by Theuer, pharmaceutical and biotechnology companies can have more control over the development process and reduce the risks of trial failures further down the line.

The approach could also allow drugs that really are effective to produce meaningful clinical data in much smaller trials at decreased costs, and minimise ethical dilemmas facing trial sponsors.

Scott Harris is a four-time biotech chief medical officer and currently serves as a principal at Middleburg Consultants, a pharmaceutical consulting organisation. He sees adaptive trials being particularly important for smaller biotechs that can't afford to take a big hit when a large trial fails and need ways to generate suitably compelling data for regulators from the smallest, and therefore least costly, patient group[5].

There is a universal issue with finding the right patients, and therefore any way to reduce numbers needed for meaningful results will save development time, which is vitally important in today's highly competitive market.

5. Flipping the paradigm – how should biotechs harness adaptive trials? https://pharmaphorum.com/r-d/views-analysis-r-d/flipping-the-paradigm-how-should-biotechs-harness-adaptive-trials

# 05
# The Regulatory Environment

Once the ideal clinical trial design has been crafted, it's critical to achieve a successful regulatory decision on the study plans – and this is where preparation is key.

In cases where adaptive trial models are used the statistician will have drawn up an adaptation plan spelling out how information will be used, and details such as the interim analysis.

Cytel's Natasa says: "Having all of that spelled out and planned in advance gives the regulators confidence that you know what you're getting into, and that you've thought it through and have contingency plans."

It also reduces the chance of messy results that may have been affected by poor decision-making during the clinical trial process.

Her message is clear – the journey through clinical trials is as important to regulators as the outcome, and statisticians can provide vital advice and insight throughout to keep things on track.

The final piece of the jigsaw is regulatory authorities like the FDA itself. Although the US agency updated its guidance on adaptive clinical trials in 2018, Scott Harris from Middleburg Consultants would still like to see more leadership from the regulator so that biotechs can feel more confident that data from adaptive designs will be accepted for review.

All that's needed now, he says, is a little more promotion from bodies like the FDA, who need to make it clear that they are ready and willing to accept adaptive designs.

> …the journey through clinical trials is as important to regulators as the outcome, and statisticians can provide vital advice and insight throughout to keep things on track

# 06
# The Finished Picture

The final piece of the puzzle for ensuring that clinical trials are designed for success requires sponsors to work effectively with CROs, such as Cytel, as well as with data monitoring committees (DMCs), the independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing.

Cytel's Irving says that proactive communication is key, as well as consulting with each other early and often. "It's really a collaborative effort between the sponsor, the DMC and the CRO in making sure that it's an efficient process.

"It's important to have a well-run organisational meeting with the DMC early on. There you can identify potential issues, discuss details of future meetings, and think about how the data's going to be presented in order to ensure efficiency thus minimising the need to go back and ask sites further questions."

With planning and forethought, fit-for-purpose data and the right design, pharmaceutical and biotech companies can craft intelligent, responsive clinical programmes that stand on firm ground for the future.

# Further Reading

**Adapting for the future of oncology trials**
https://deep-dive.pharmaphorum.com/magazine/oncology-asco-2019/cytel-future-adaptive-trials-cancer

**Keeping clinical trials on track**
https://pharmaphorum.com/r-d/keeping-clinical-trials-on-track

**Patients in the driving seat**
https://pharmaphorum.com/r-d/patients-in-the-driving-seat

**Adapting for success**
https://pharmaphorum.com/views-and-analysis/cancer-clinical-trials-tracon-cytel

**Flipping the paradigm – how should biotechs harness adaptive trials?**
https://pharmaphorum.com/r-d/views-analysis-r-d/flipping-the-paradigm-how-should-biotechs-harness-adaptive-trials