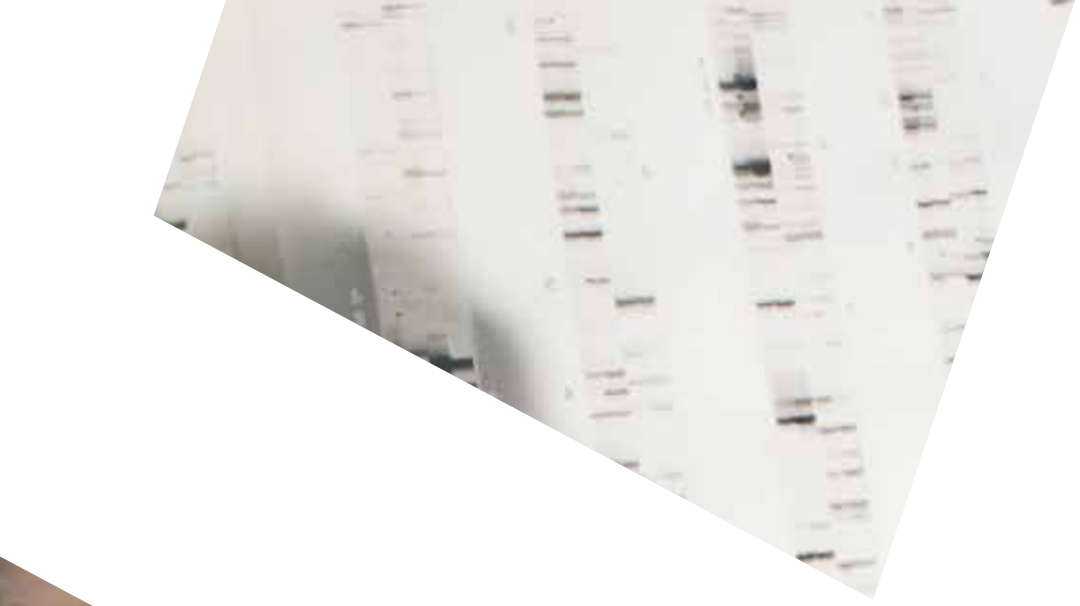


Improving your product's chances of launch

Adaptive and Flexible Trial Designs

›››

We'll help you evaluate your interim data so you can adapt your study design parameters for better outcomes

With Heart

No company wants to spend millions of dollars on a protocol, only to receive a negative result at the end of the trial. Nevertheless, that's exactly what's happening time and again in the pharmaceutical industry. But what if you could know earlier if your initial assumptions and expectations were off, and you had an opportunity to correct them? The good news is that you can.

Adaptive and Flexible Trial Designs give biopharmaceutical companies the opportunity to reduce the risk of failure by evaluating interim data analysis at pre-defined points and adapting the study design parameters accordingly, in order to optimize the outcome.

It's a practice that has been around for 20+ years, however, is still not widely used.

›

Improving a new therapy's likelihood of launch

A 2018 research report evaluating the use of four innovations in Phase II/III studies, *The Innovation Imperative: The Future of Drug Development* by The Economist Intelligence Unit (EIU), on behalf of Parexel, found that Adaptive Trial Designs provide the following benefits:

13% **average increase** in a new therapy's likelihood of launch

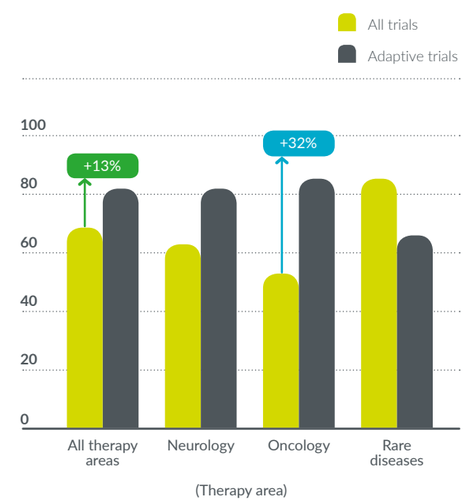
3 **months** average time to recruit 100 patients vs **7** **months** industry average

32% **average** improvement for new oncology therapies

Using Adaptive Trial Designs increases the probability of success of Phase III trials, and therefore impacts the approval rate by regulatory agencies and payers.

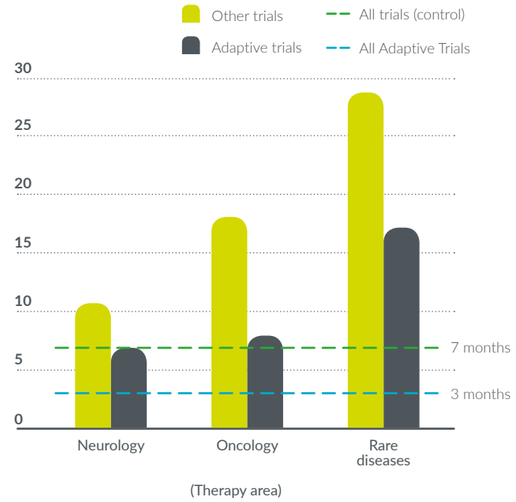
Yet, for something with a long history of measurable results and benefits, the same EIU report found that less than 3% of Phase II/III studies are implementing Adaptive Trial Designs. Reasons for the low adoption include a perceived complexity, lack of workforce expertise, and technology limitations – all challenges that can be overcome with careful planning.

Phase II/III and likelihood of launch (%)



Source: Trialtrove® Pharmaintelligence, 2018. Data:2012-2017.

Average time to enrol 100 participants for adaptive trials vs all trials (months)



Source: Trialtrove® Pharmaintelligence, 2018. Data:2012-2017.

The advantages of Adaptive Trial Designs

By implementing Adaptive Trial Designs you have the opportunity to carefully evaluate clinical data in real-time, allowing you to make informed decisions to change the direction of the study for a better chance of success. These changes could be to sample size, dosage or patient selection.

A well-designed and well-executed Adaptive Trial Design can:

- increase the probability of success for your new therapy
- maximize information from the trial
- shorten development timelines
- reduce overall development costs
- minimize the risk for study volunteers and sponsors
- improve the likelihood of launch and market access

In recent years, regulators have shown more acceptance toward Adaptive Trial Designs. In fact, in 2018 alone the FDA released two separate guidance documents on Adaptive Trial Designs, one clarifying the current state and regulatory framework and another that guides sponsors on key design factors. In addition to following such regulatory guidance, having early conversations with regulators to obtain their understanding and buy-in can have a positive impact on the regulatory review of a submission dossier.

Types of Adaptive and Flexible Trial Designs

Types of Adaptations	Description
Adaptive dose finding	Used to identify the minimum effective dose (MED) and/or the maximum tolerable dose (MTD). Continuous reassessment method (CRM) or a Bayesian Logistic Regression Model (BLRM)
Population enrichment (e.g., based on biomarker or pharmacogenomic data)	Unblinded interim analysis for subsets of interest for identifying sub-populations with significantly higher response to treatment based on scientific rationales. Subjects may undergo biomarker or genomic testing to determine eligibility for participation in the clinical trial or to enable interim decisions to continue with selected sub-populations or the full population
Sample size re-estimation (SSR)	Sample size adjustment or re-estimation based on unblinded interim data while not inflating the false-positive probability at the final analysis
Adaptive randomization	Modification of randomization schedules based on accumulating study data like baseline covariates or responses
Seamless Phase I/II studies – dose escalation and dose expansion trials	Combines dose escalation with an expansion phase to generate first activity data
Seamless Phase II / III	Combines a Phase II and Phase III into one trial, incorporates a decision to adapt the study at an interim analysis and uses data before and after the adaptation in the final analysis
Master protocols	Includes umbrella, basket and platform designs. Master protocols can be very beneficial in the early development to screen different compounds in the portfolio and select the best for each of the indications or test one compound in several indications to select those indications where a compound is particularly effective. Umbrella designs investigate multiple treatments for a single disease whereas basket trials evaluate a single drug in multiple diseases or disease subtypes (e.g., different tumor types that share genomic characteristics). Platform trials evaluate multiple treatments in multiple diseases and permit treatment regimens to be added or removed based on pre-specified decision algorithms
Inclusion of real-world data (RWD)	Real-world data as part of development, forming synthetic control arms

We'll help you get started with Adaptive Trial Designs

The biopharmaceutical industry's hesitation toward Adaptive and Flexible Trial Designs could be attributed to a variety of factors including: a perceived complexity; vast, new & fragmented data; a lack of workforce expertise; cultural barriers; and an overall resistance to change. Also impacting adoption is a historical reluctance on the part of regulatory authorities, often taking longer to give regulatory approval to therapies where Adaptive Trial Designs were used, but this is changing.

We have been successfully helping clients understand, evaluate and implement Adaptive Trial Designs for years. Our Adaptive Trial Design Center of Excellence provides services for the planning and execution of adaptive trials, as well as the technology to support their execution.

See what we can do for you

- Statistical expertise to develop Adaptive and Flexible Trial Designs to optimize study plans and clinical development plans
- Biostatistics expertise in planning and execution of adaptive trials, Bayesian adaptive dose finding, sample size re-estimation, seamless designs to combine phases of development, performing simulations of design and decision scenarios
- Integrated technology components through Parexel Informatics including EDC, ePRO, IVR, supplies simulation and forecasting
- Technology developers who provide flexible data platform solutions to gather, synthesize and analyze the data from different sources
- Regulatory experts that have relationships with different regulatory agencies and can speak to the regulatory agencies expectation to maximize acceptability of the particular development plan
- Project leadership with experience in managing Adaptive Trial Designs

We have all the experts you need to help you develop the design and execution of your trial.

We're here to help you save valuable resources and development time

Our extensive experience has taught us that early and careful planning is the best way to successfully implement Adaptive Trial Designs and overcome any operational challenges. In addition to leveraging our team of experts, we'll bring together your key players across the clinical development spectrum during the planning process. This allows us to run through scenarios and potential adaptations, anticipating where issues could arise so we can mitigate any potential roadblocks. Sometimes it may be only a minor tweak or two that is needed (if at all), while in other cases more significant changes are required.

CASE STUDY: ADAPTIVE DESIGN IN PHASE II SCHIZOPHRENIA

Situation:	4 arm study: placebo, 2 doses of test drug and active control, powered for an effect size of 0.6 for PANSS total score at day 28 between the test drug doses and placebo
Challenge:	› Uncertainty around the achievable effect size as assessed by the treatment difference and the variability › Is sample size adequate to identify an efficacious dose statistically?
Solution:	› Perform an interim analysis after ~50% patients randomized and treated for 4 weeks › Depending on the results of the interim analysis either continue study with no change, stop the study for futility, or increase sample size › Predefined criteria: stopping criteria as conditional probability less than 30% › Simulation of scenarios of possible outcomes before study start › Sample size re-estimation depending on observed effect size › EDC and external data (third party vendor) set up to facilitate timely interim analysis › Ensure timely data entry by sites and transfer of vendor data › Ongoing blinded data review and data cleaning
Outcome:	Successful execution with decision to increase the sample size by 20% after the interim analysis, leading to a successful outcome of the completed study in identifying a dose to be tested in a confirmatory Phase III study.

Your Journey. Our Mission.®

We're always available for a conversation

To learn more about our Adaptive and Flexible Trial designs, please contact:

Parexel International Corporation
195 West Street, Waltham, MA 02451, USA
+1 781 487 9900
info@parexel.com

Offices across Europe, Asia, and the Americas
www.parexel.com

parexel®