Phesi

Data-Driven Drug Development



CLINICAL DEVELOPMENT

FEASIBILITY | PLANNING | EXECUTION

ALIGN THE SPONSOR & CRO AROUND PHESI'S DYNAMIC,
DATA-DRIVEN ANALYSIS OF PREDICTABLE TRIAL PERFORMANCE

Clinical trial feasibility, planning, and execution are complex, expensive processes of critical strategic importance to the on-going innovation of the pharmaceutical industry

The headline figure of bringing a single new drug to market is still escalating – now exceeding $2.5 billion[i].

Clinical trials are key to the ongoing innovation of the pharma industry, but they are expensive, with median costs of $3.4m, $8.6m, and $21.4m for Phases I, II and III trials respectively[ii]. These costs are rising: costs-per-patient have doubled in the last decade[iii].

Pharmaceutical clinical teams need to address many complex decisions on trial design (e.g. adaptive vs traditional), protocol design (e.g. inclusion and exclusion criteria), and site feasibility selection

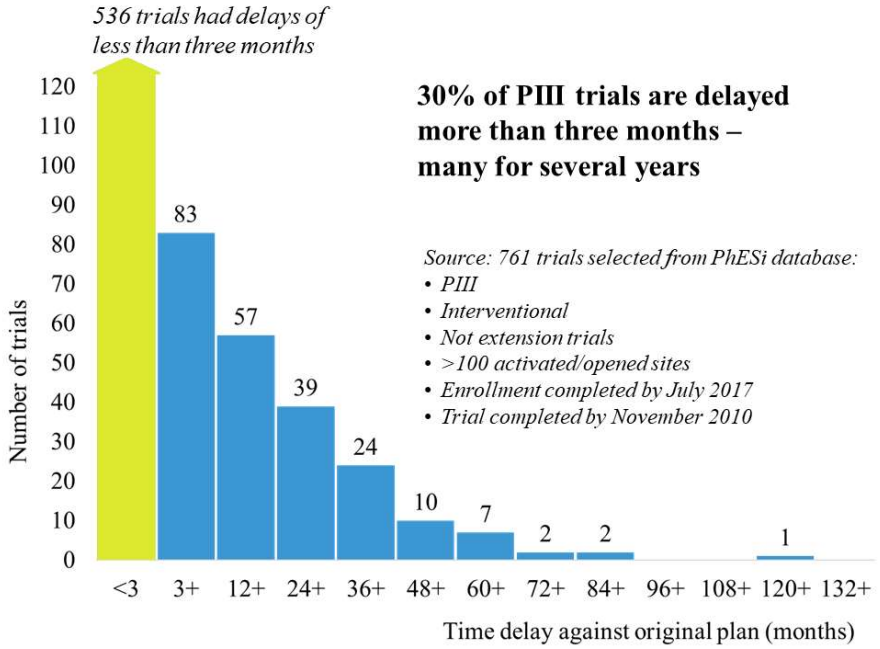
When making these decisions, clinical teams need to be aware of the impact on site activation, patient enrollment and enrollment cycle time.

Many Sponsor organizations delegate trial execution to their partner CRO, with little shared understanding of what is feasible or optimum for their specific trial

Pharmaceutical and biotech companies need to work with CROs to supplement in-house capacity, meeting the peaks of resource demand to execute the number of trials needed to progress innovative drugs through their pipeline.

The global CRO market is now reported to be worth over $30 billion[iv], and is expected to rise at up to 10% CAGR into the next decade[v].

Trial overrun costs are high, and trials are often delayed due to patient enrollment falling behind expectation. Trial "rescue" missions are common.



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Trial feasibility, planning and execution are currently inefficient and ineffective. In one recent example that a client asked Phesi to review, the CRO initiated 210 sites – Phesi's analysis suggested only 148 were needed – the majority of the extra sites never enrolled a single patient. Site performance could have been accurately predicted based on analysis of data within the Phesi database. The resulting overspend in this case study was estimated to be over €2.5 million.

In addition to frequently adding more centers than are needed, because of the inability to predict site performance and the correct number of high-performing centers to run such a study), Phesi often sees Sponsors and CROs simply extrapolating enrollment rate estimates as the candidate moves from Phase II to III often with significant performance issues in the late phase trials.

This is a broken model, that will stay broken until the industry adopts a data-driven, predictive-analytics based approach to protocol and site feasibility.

"Our in-house feasibility team have some historical data from comparable trials - bought externally or from records of our previous trials. CROs all have their own different and limited data. It's hard to get a clear view of what is feasible, along with realistic planning estimates for enrollment rate and enrollment cycle time."
- Head of Clinical Operations

Align the Sponsor and CRO around Phesi's dynamic, data-driven analysis of predictable trial performance

When planning and executing a clinical trial, the Sponsor and the CRO will work together more efficiently and effectively if they can be aligned around a dynamic, data-driven, real-time view of trial performance to support planning accuracy.

When seeking similar historical trials to test if plans are realistic, it is critical to consider a complete view of all previous trials, not just those familiar to the Sponsor organization, its joint venture partner or the contracted CRO.

Phesi has the most-comprehensive clinical trials database in the industry. The database covers over 320,000 clinical trials and more than 500,000 clinical investigators today and is growing. The database is highly-granular, covering site activation, patient enrollment and trial performance metrics, and it is updated daily from over 80,000 sources.

Trial planning typically evolves over several months, if not years. Constantly reviewing plans based on real-time updates from similar trials brings new, up to date and valuable insights to trial performance and competitor activity. The updating of plans from a real-time database allows planning to start early, and then be refined as the trial start-date approaches. This dynamic, data led approach avoids the common planning and delivery pitfalls.

Rapidly identifying lessons learned from comparable historical trials needs appropriate, automated data selection and consolidation, plus robust application of predictive analytics.

Phesi's predictive analytics toolsets consolidate comparable trial and site metrics to support trial design, protocol design, site selection and trial execution.

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These metrics include:

- For comparable trials (actuals) and client's trial (forecast):
  - ***Site Activation Curve***: the number of sites activated over time.
  - ***Site Effectiveness Index*** (SEI): the area under the site activation curve - a relative measure of available site capacity that is being utilized over time.
  - ***Enrollment Curve***: the number of patients enrolled over time.
  - ***Gross Site Enrollment Rate*** (GSER): the effective trial-level enrollment rate (patients/site/month).
  - ***Enrollment Cycle Time***: the elapsed time (months) from first enrolled patient to last enrolled patient.
- For potential investigators:
  - ***Overall Score***: this score measures the level of experience for the investigator in participating in multinational, interventional, and industry sponsored clinical trials.
  - ***Competition Score***: this score measures the approximate number of trials initiated in the past 24 months - related to the trial being planned, though not always in the exact patient population.
  - ***Indication Score***: this score measures the investigator's relevant experience in trials in the same indication.
  - ***Performance Score***: this is derived from a set of proprietary statistical models to measure the past performance in site activation, enrollment performance, and patient data quality.
  - ***Most Recent***: the date a trial was most recently started at the site, which indicates that an intact clinical trial infrastructure is in place at the site.

"This shared view of predicted trial performance enabled by Phesi allows the Sponsor and CRO to plan far more accurately and agree on realistic and achievable site activation rates, patient enrollment rates and enrollment cycle times"
- Otis Johnson,
Life Sciences VP

This data-driven view does not replace the work of the Sponsor or the CRO. Rather this vital information input forms the core of the clinical trial feasibility, planning and management processes. Phesi typically finds 20-35% improvements in productivity and reductions in trial costs from taking this approach.

Such an insightful visualization of future trial performance supports collaboration between the Sponsor and CROs at every stage of the process: selecting the best CRO, and day-to-day trial management and monitoring of study performance.

This data-driven approach shows the levers the Sponsor can pull, the scale of the impact of each lever, and the optimum setting of those levers to maximize trial performance, whilst ensuring quality of delivery and managing cost.

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Development teams have limited access to the relevant, complete, granular, historical data

Sponsor organizations today may have in-house clinical feasibility teams, but they are limited to the knowledge of the trials completed in-house – often only a few or no comparable trials.

In-house teams examine performance of these trials, supplemented with input from networks and forums in which professionals can share experiences of previous trials.

They may have access to externally collated trial and investigator databases, but these do not have the granular information on site performance needed. How the in-house team interpret and use the data is also critical, and relies on the experience within the team.

There is a substantial risk that this data will be misinterpreted, leading to poor trial planning and execution

Web research of the indication may surface only a small number of top performing investigators, based largely on those most active on the web. Many other relevant, high-performing investigators are frequently missed.

With insufficient information, there is a tendency to return to known and familiar investigator sites despite the investigator not necessarily having knowledge that is relevant to the planned trial.

Development teams frequently use a relationship-based approach, not an evidence-based approach.

CROs often overestimate the required number of sites - adding contingency and cost

Sponsors routinely outsource trial execution to CROs, yet a single CRO will not have all the up to date global data required to make the complex decisions around trial design, protocol design and site selection and activation.

CROs – like in-house teams - are limited to data from the trials they have performed or limited commercial data sets. They do not have a complete dataset of the performance of all comparable clinical trials across the industry. Plus, CROs may have limited experience in a specific disease or geographic area.

Phesi's own analysis shows 25-50% contingency is not unusual. Adding contingency may be done with the best intentions to increase the enrollment, but Phesi's experience shows that those extra sites add little to overall trial performance. These extra sites often recruit few, or no patients – Phesi's analysis shows this is due to the diminishing returns of further lower-quality sites.

Worse, those extra sites will increase the overall enrollment cycle time - adding significant cost with little return.

Instead of contingency, the focus needs to be on better, data-driven planning, across the complex continuum of trial design, protocol design, site selection, and trial execution.

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Phesi's patented predictive analytical tool sets draw on a unique and granular database of historical trial performance, to agree realistic trial design and timescales

Phesi acts as the information broker between Sponsor and CRO, enhancing the relationship.

Our complete database of historical clinical trials shows which CROs have experience with the indication, geography or trial design in question. Sponsors can place CRO planning assumptions in the context of comparable previous trials to show the feasibility of CRO proposals.

Phesi's methods are tried and tested on hundreds of trials over more than 10 years

All trial design and planning decisions are based on a comprehensive, real-time, granular database of historical clinical trial performance. All previous trials are included whether conducted by a Sponsor or CRO. Also revealed are the research as well as the clinical trial interests of the investigator- useful to identify leading and emerging KOLs as well as trialists.

In addition to Phesi maintaining the most-comprehensive and granular clinical trials database in the industry, we have developed patented predictive analytics to understand which trial design, protocols and investigator sites have produced superior performance historically, and to use that insight to optimize trial design, protocol design and site selection.

Phesi analysts work with the client study team as trusted advisors to support the feasibility process and set realistic timescales as part of the process of engaging with CROs

Planning of a single clinical trial can run over 18-24 months: assessing and reassessing the feasibility and the likely performance of the indication, the protocol and the investigator sites.

Phesi analytics are run at the trial level, and the approach can be repeated for multiple trials.

Phesi delivers insights within only a few days. A full initial analysis takes only 2-3 weeks, then iterative updates to capture changes in competitive trials take only 2-3 days.

Our data-driven approach supports Sponsors throughout the clinical development process. The chart below captures the specific inputs we bring through indication feasibility, protocol feasibility, site feasibility and selection and trial implementation.

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Clinical Development Process

Indication Feasibility	Protocol Feasibility	Site Feasibility and Selection	Trial Implementation Management
For the **indication**: • Understand which **competitors** have done (plus, are doing, and plan to do) trials • Understand historical success rates of different **trial designs** (e.g. adaptive vs traditional) • Identify thought-leading investigators, plus potentially **high-performing investigator sites**	For **potential protocols**: • Evaluate the impact of **inclusion/exclusion criteria** on recruitment • Identify **high-performing countries** • Determine the **optimal number of sites** and **patients per site** • Forecast the likely/ optimum **site activation curve** • Forecast the likely/ optimum **enrollment curve**	For the **final protocol**: • Determine a shortlist of desirable **high-performing investigators and sites** • Forecast the planned optimal **site activation curve** • Determine a shortlist of **CROs** with experience/success	For the **ongoing trial**: • Understand which **competitors** are doing, and plan to do, competing trials • Evaluate and track site **performance** • Forecast **enrollment rates** • Forecast **enrollment cycle time** • Recommend **operational adjustments**

Case Study One

An example of supporting a metabolic trial design during indication feasibility.

This client was planning the largest randomized clinical trial in this indication with a limited investigator pool. The client asked Phesi for guidance on the trial design. The client was keen to assess the benefits of adaptive trial design over a more traditional design. The client also needed support with country and site selection.

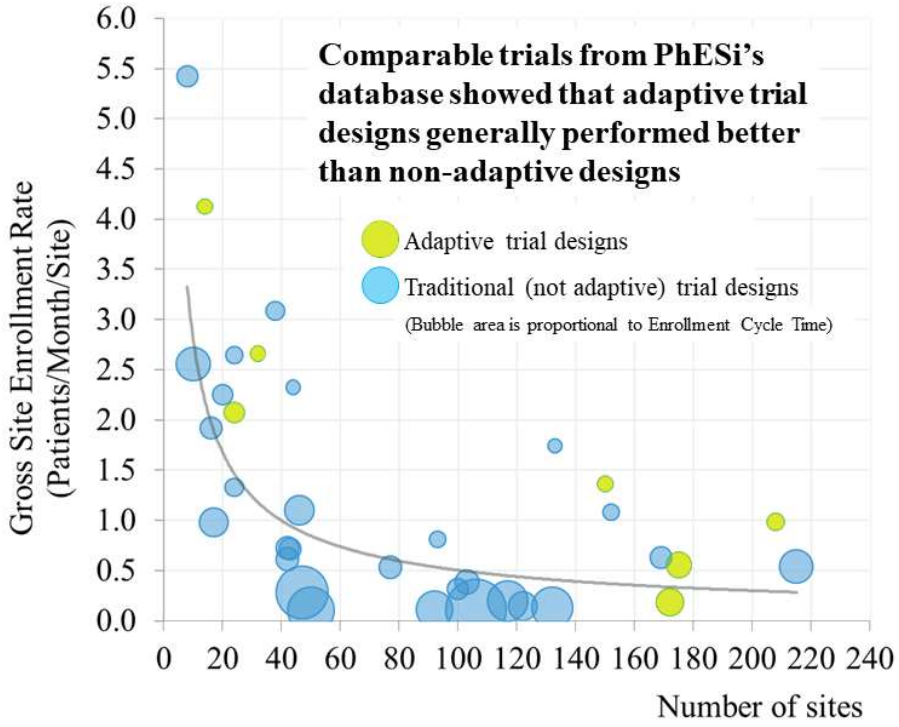
Adaptive vs. traditional trial design for this priority asset in Phase II/III, plus recommendations on site selection and insight on CROs with relevant experience, for a top-20 global pharma client

From Phesi's comprehensive database of clinical trials we selected 39 trials with similar design, targeting three different comparable patient populations.

Using the Phesi analytical tools these historical, comparable trials showed a predictable relationship between enrollment rate and number of sites, across all and each individual patient population. This analysis showed us that a traditional trial design would take 67 months through sequential Phases II and III.

Next, we identified a set of comparable trials covering both adaptive design and traditional design, plus the relevant partner CRO (where the trial was outsourced). This showed that adaptive trials (at least in this comparable indication) had higher patient enrollment rates than traditional trials.

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"Phesi worked with us to show that a particular adaptive trial design would give the best performance. The result was a significantly quicker and cheaper development time on this priority asset"
- Senior Director, Clinical Operations

Phesi showed that the time through Phase II and III could be shortened to 49 months by using an adaptive design. We considered various adaptive designs and recommended the one with the highest likely operational performance. Additionally, our analysis showed that batching site activation would reduce the impact of site fatigue.

With the trial design clear, we then selected and ranked countries and investigator sites (KOls and trialists) based on our site performance criteria in support of the Sponsor and partner CRO. This ensured the final recommended sites had the right experience, plus had previously made satisfactory enrollment contributions on similar trials.

Phesi confirmed that an adaptive trial design was both feasible and desirable. PII/PIII could be completed sooner, with fewer patients, and at significantly lower cost. We provided a shortlist of potential high-performing investigators, plus guidance on the related experience of CROs.

Case Study Two

An example of analyzing inclusion and exclusion criteria in the cardiovascular protocol design during protocol feasibility and evaluating the impact on expected enrollment

Protocol design including inclusion exclusion criteria, treatment window based on competitor analysis for a Phase II study for Bayer HealthCare Pharmaceuticals

This client was designing and planning a Phase II study for a cardiovascular (CV) indication. This treatment was first-in-class and first to target this particular CV dysfunction. The client requested insights from similar historical studies, specifically to consider what may impact the trial's operational performance.

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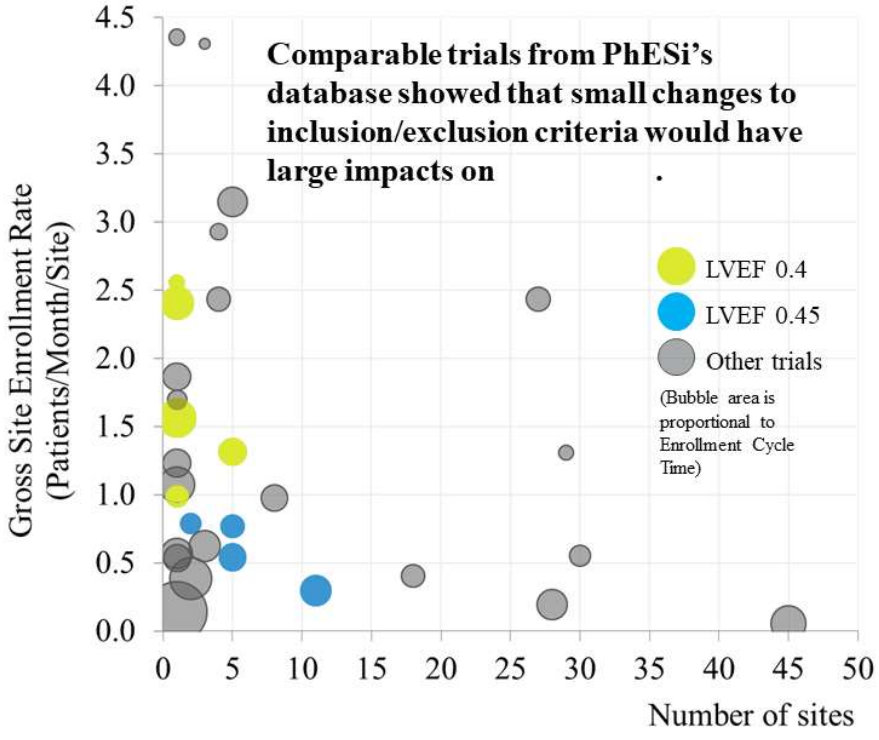
From Phesi's comprehensive database of clinical trials we selected 37 trials with comparable design, and targeting similar patient populations (excluding observational, surgical, ancillary trials and prematurely terminated trials).

Using Phesi's proprietary analytical techniques, these historical, comparable trials showed a predictable relationship between enrollment rate and number of sites. The relationship between enrollment cycle time and numbers of sites and patients, showed that 60 patients could feasibly be recruited from five sites over 28 months.

Further analysis of the comparable trials showed that screen-failure rates would be significant, and we predicted how many patients should be screened to achieve the target recruitment.

Phesi assessed the inclusion and exclusion criteria to ensure the protocol was feasible, and to quantify the impact on enrollment rates.

"To get a challenging but still realistic plan for site opening and patient enrolment in a clinical trial continues to be anything but trivial, in spite of a multiplication of available data. We are increasingly relying on a multitude of information sources in order to enhance reliability and precision of our forecasts. Phesi has repeatedly provided important input in that process that we value highly."
- Steffen Roellinger, Senior VP Global Development Portfolio & Operations, Bayer HealthCare Pharmaceuticals



We evaluated potential countries and recommended a single European country, based on availability of patients and experienced investigators, quality medical records, and a homogenous racial composition.

Finally, we identified all competing trials, and in this case concluded that competition for patients should not be a significant factor on operational performance.

In just a few days, this client received a clear and feasible design appraisal with recommendations for the trial, based on the evidence from the selected comparable historical trials. The client also received operational guidance based on known issues in previous similar trials.

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Case Study Three

An example of re-planning to establish a feasible plan, when an ongoing metabolism trial has fallen significantly behind performance expectations.

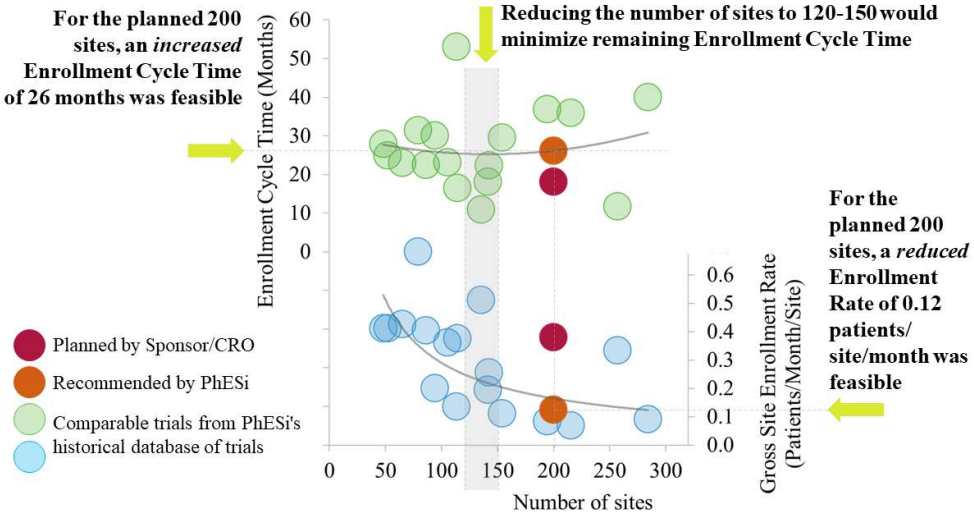
Refocused limited resources on fewer, higher quality sites, raising enrollment rate and agreeing a realistic cycle time, all in a highly competitive trial environment, for a PIII trial for a global pharma company working with a CRO

A major global pharma was executing a priority Phase III trial in Gastroenterology. The trial was experiencing significant recruitment challenges, with competitive studies enrolling the same patient profiles.

Phesi was not involved in the original planning, but when called in by the client, we found that site activation was significantly below expectation for a trial of this type. Phesi was told that the CRO was proposing to add further sites, despite the trial management resources already being diluted across many open sites and study budgets being under pressure.

Phesi quantified the level of competition geographically by showing all current, recruiting, competing trials from our real-time, comprehensive database. This confirmed that many of the chosen sites were in highly competitive locations for similar trials and patients.

We identified 17 comparable historical trials, largely PIII, with similar designs and number of patients. Using these comparable trials, we agreed realistic and feasible site activation rates, patient enrollment rates and enrollment cycle time. This data guided a targeted action plan to get the trial on track.



"Phesi showed us within days how resources were spread too thinly over too many sites (many no longer screening patients). Based on evidence of historical similar trial performance, we could see that we could close many sites, increase enrollment rate, and reduce the planned enrollment cycle time. The way Phesi based all this on their evidence-base of historical trials meant we could rapidly agree a successful plan with our CRO"
- Senior Director, Clinical Operations

We identified the poor-performing sites to close, and agreed that new sites were not necessary. Our deep analysis showed clearly that a higher overall enrollment rate could be achieved by focusing on fewer higher-performing sites, avoiding the cost of adding further sites, as suggested by the CRO.

Phesi worked with the Sponsor and the CRO to agree an achievable plan to complete the trial, backed up with extensive evidence from historical comparable trials.

Enrollment completed on the exact date that Phesi predicted.

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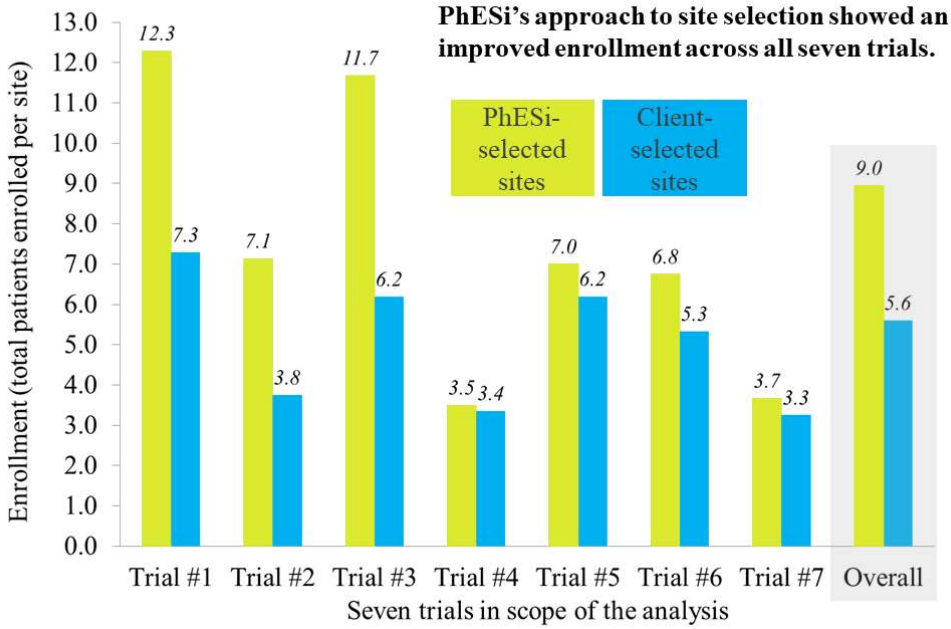
Case Study Four

Site feasibility and selection was significantly enhanced, showing how enrollment could be improved, along with avoiding site activation costs on those sites unlikely to contribute patients

An example of site feasibility and selection - evaluating the impacts on expected enrollment.

The client was conducting site feasibility and selection on multiple trials in type-2 diabetes. The client wanted to understand how expected trial performance would be impacted by alternative site selection from Phesi.

Phesi analyzed seven client clinical trials, and recommended alternative site selections for each trial. We also stated the expected enrollment from each site, and compared the overall enrollment from the Phesi selected sites against the client selected sites. We repeated this for each trial individually, plus across all seven trials.



"Phesi demonstrated to us that they could achieve superior site selection from their database of investigators and sites from previous trials, evaluated with their unique metrics"
– Clinical Program Manager

This analysis showed how trial performance could be improved across all seven trials, through Phesi's improved site selection. The client was shown how this analysis could be implemented as an ongoing process improvement within the client's in-house processes. The expected cost saving of this process improvement was around $17 million per year in site activation costs alone

i http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf

ii http://www.nature.com/nrd/journal/v16/n6/full/nrd.2017.70.html

iii http://www.pharmafile.com/news/511225/clinical-trials-and-their-patients-rising-costs-and-how-stem-loss

iv http://www.fiercebiotech.com/r-d/global-cro-market-expected-to-rocket-to-59b-by-2020

v http://www.outsourcing-pharma.com/Clinical-Development/CRO-market-to-reach-45.2bn-by-2022

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Contact Phesi To Discuss If Your Planned And Expected Clinical Trial Performance Is Realistic Based On Our Complete Database Of Historical Clinical Trials And Patented Predictive Analytics Tool Sets

- Are you currently planning a clinical trial (in CDP, protocol, or site selection phase)?
- Do you have a clinical trial that has fallen behind planned timelines?
- Are you concerned that your CRO is adding further poor-quality sites to the plan (and cost), reducing enrollment rate and increasing enrollment cycle time?
- Are you concerned about the large and growing cost of clinical development, and looking for ways to make it a more efficient, effective, and cost-effective process?
- Are you looking to better understand the costs and impacts of any contingency funds requested?

Do you want insights into comparable trial design and factor this into your design?

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