Proactive Management of Study Complexity and Amendment Risks Can Return Millions on the Investment

David Nagel, MEd, MBA
Executive Director, Value & Development Consulting
Evidera, a PPD business

Beth Schneider, MSc
Executive Director, Site Intelligence and Activation
Site and Patient Access, PPD

Stephen Powell, MBA
Executive Director, Strategic Feasibility
Site and Patient Access, PPD

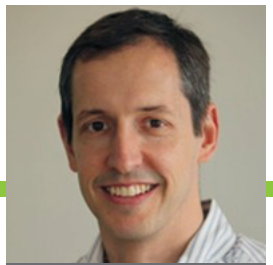
Malcolm Horsley, BSc
Senior Director, Site Intelligence and Activation
Site and Patient Access, PPD

Jennifer Monen, BS
Associate Director, Site Intelligence and Activation
Site and Patient Access, PPD

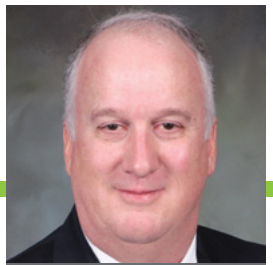
Trends and Problem Statement

Biopharma and biotech companies make significant investments in getting their products to market. Studies are becoming more complex, driven by several factors including eligibility, endpoints, assessments, data collected, and number of sites, etc. This ever-increasing complexity in study design can frequently lead to study cost increases in excess of 25%, in addition to other implications such as difficulty in finding patients, increased effort by sites to conduct a study, more time spent in study start-up, and more costly amendments. For example, in the last two years, 73% of PPD studies have had protocol amendments between receiving the final protocol and reaching first site activated, 83% before first subject screened, and 92% before 50% of sites were activated.

While there is a high level of focus on study costs, and rightly so, the higher cost comes from study delays. One research study[1] looking at lost patent days once a product was launched suggested that the impact on Expected Net


David Nagel


Beth Schneider


Stephen Powell


Malcolm Horsley


Jennifer Monen

Present Value (ENPV) of one protocol amendment on a typical oncology program entering Phase II or III ranged from $35 million to $75 million respectively. Given the significant cost of delays, investing the time and effort to design well thought out study protocols in initial planning will benefit companies in the long run.

What Can be Done to Avoid Lost Revenue?

Companies should assess every study to determine the best options for reducing study complexity, cost, timelines, and amendments while designing the study. Several activities at different times throughout the study design process (See Figure 1) have shown an impact on overall success, including:

- Patient-informed protocol design (PIPD)
- Protocol optimization (PO)
- Finding the right sites (Site ID)
- Protocol de-risking

Patient Input

PIPD refers to any form of engagement with patients to help inform elements of clinical trial study design. Common approaches include conducting patient focus groups, mock trials, patient surveys, and consulting with representatives from patient advocacy organizations. While there are many benefits of integrating PIPD into standard research practices, one key element is optimizing the study design to meet the needs of a given patient population. This has the potential to improve recruitment, patient enrollment and study outcomes; reduce patient burden and study withdrawal; ensure patients follow the assigned assessment schedules and adhere to therapy; and optimize data quality and capture, to name a few. Furthermore, involving patients during the protocol development stage is crucial to ensure the data on outcomes most relevant to patients are being collected.[2]

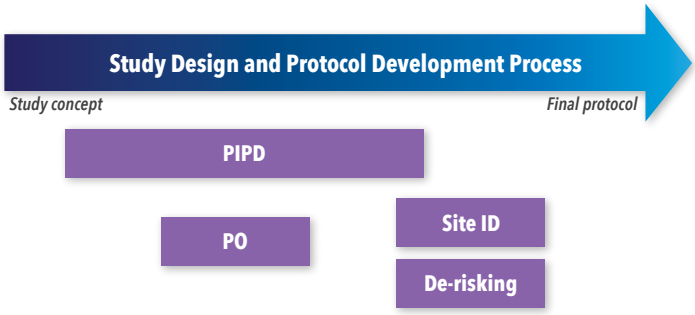
Although the quantitative impact of PIPD is still emerging, previous research has documented a 16% increase in patient enrollment[3] and improved timelines, with recruitment of the first 100 patients reduced by three months.[4,5]

Protocol Optimization

PO can mean different things to different organizations. Here the term is used to describe a set of protocol-focused assessments meant to uncover areas where study complexity can be reduced.

When a developing protocol reaches synopsis stage, the major components of the overall draft are in place yet are still formative—making it an ideal time to step back and look for areas to optimize. A synopsis typically includes objectives/endpoints, study design/schema, number of participants, intervention groups, duration, statistical considerations, standard of care (SOC), and inclusion/exclusion (I/E) criteria. It is at this formative point that a protocol optimization assessment may help surface areas where complexity can be reduced, as well as patient burden, study cost, study duration, and likelihood of amendments.

Figure 1. Timing of Study Design and Protocol Development Activities



PO requires an expert cross-functional team consisting of product development, clinical science, operational strategy, biostatistics, regulatory, and innovation. Such an expert team should be highly experienced and have access to robust data that allows for the conduct of the following assessments:

- Measure study's **site complexity and patient burden**, compare to competitor studies, and recommend adjustments to the schedule of assessments; quantifying site complexity allows for better management of complexity, and several industry tools exist that allow for measurement of the complexity for a site to conduct the study
- Ensure alignment between **objectives, endpoints, and assessments**
- Analyze the **patient eligibility criteria** and recommend adjustments to increase likelihood of showing response and/or increase ability to recruit
- Evaluate **standards of care**, surface regional differences, and anticipate future changes
- Recommend opportunities to deploy **technology** to improve collection of patient-level data, reduce patient visits, and/or reduce number of sites through **virtualization**
- Analyze **trial design and statistical methodology** to recommend alternative designs or methods
- Surface **alternative strategic options** and the relative impact those options will have on complexity, burden, cost and time

Example: Complexity, Patient Burden, and Cost Reduction

Parkinson's Disease Phase III

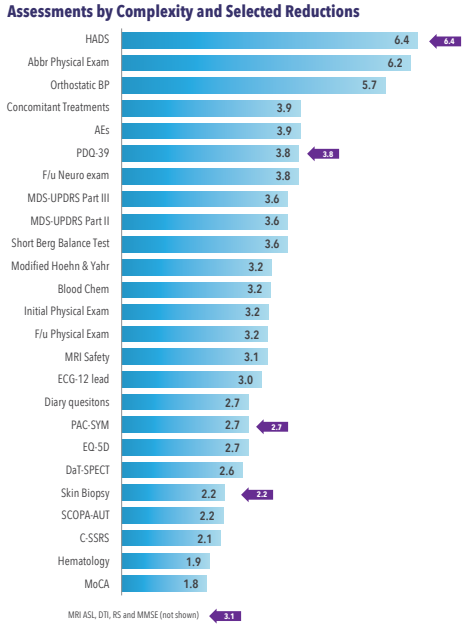
Findings:

- Versus benchmarks, protocol above 75th percentile on all key measures (duration, visits, activities, complexity, and burden)
- I/E criteria restricted use of L-dopa (SoC) which exacerbated burden on over 60% of patients*

Recommendation: Reduction/removal of six assessments (see chart)

PO Impact: Reduction in complexity by 16%, patient burden by 12% and costs by ~$1M

* *TriNetX query for % of patient population treated with L-dopa*



Example: Biostatistics Study Design

Lymphoma Phase I/II Study

PO Recommendation:

- For Phase I, employ modified toxicity probability interval design instead of 6+6 design
- For Phase II, employ enrichment design following basket trial design instead of Simon 2-stage

PO Impact:

- Reduction in sample size[2] and costs ($180K/pt)
- Increased confidence/flexibility in decisions

[2] *Simulations run on Enrichment Design module of FACTS 6.1*

Example: Patient Population and Standard of Care

NS NSCLC Phase III

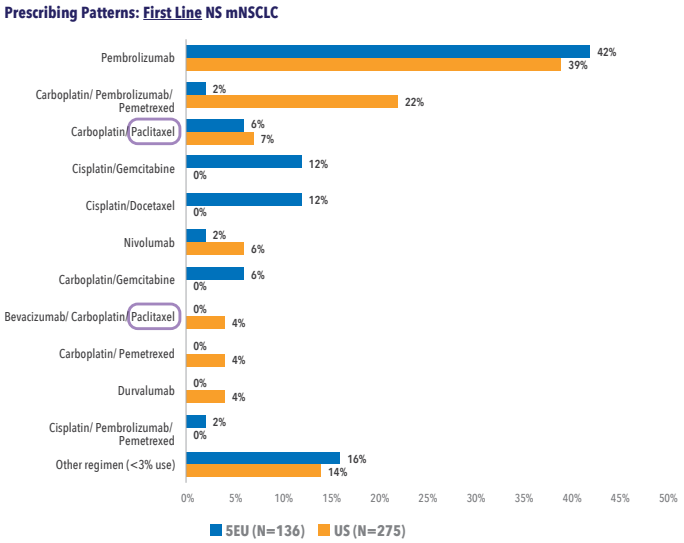
PO Findings:

- Exclusion of prior treatment with taxanes will exclude up to 18% (US) and 13% (5EU) after 2L+
- Most all competitors only exclude prior docetaxel

PO Recommendation: Exclude prior docetaxel use but allow prior paclitaxel use

PO Impact: Avoid excluding approximately 15% of otherwise eligible patients

NS NSCLC = Nonsquamous Non-Small Cell Lung Cancer



+ Ipsos Prescribing Data, Q4 2018, Metastatic, nonsquamous NSCLC (EGFR/ALK WT)

Example: Standard of Care

Asthma Phase IIb

PO Findings:

- Average patient on four respiratory meds++
- Example: ICS/LABA plus LAMA and LTRA
- LTRA often used despite limited efficacy as cheap (generic) and good tolerability**

PO Recommendation: Allow more than one additional controller

++ *McDonald Study (2019): Severe Asthma registry from 26 sites across Australia and New Zealand, 434 patients*

** *Comparison to therapies in MENSA and DREAM studies*

ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonists

The impact of conducting protocol optimization can vary from study to study and each synopsis can yield different areas for optimization. The preceding examples illustrate the types of impact that can be realized.

Finding the Right Sites

Another key to successful study execution is to identify sites with the highest likelihood of success in the given indication and population. Effective use of data is essential in selecting the sites and validating their experience. There are numerous data sources in existence that can be used and more continue to become available all the time. In assessing possible sites, there is no substitute for real-world experience; therefore, the first step is to query experience data to see how sites have performed previously, in terms of enrollment, quality of data, number of monitoring issues, and speed of activation. Many contract research organizations can "score" the sites based on the parameters above to determine which are historically most successful.

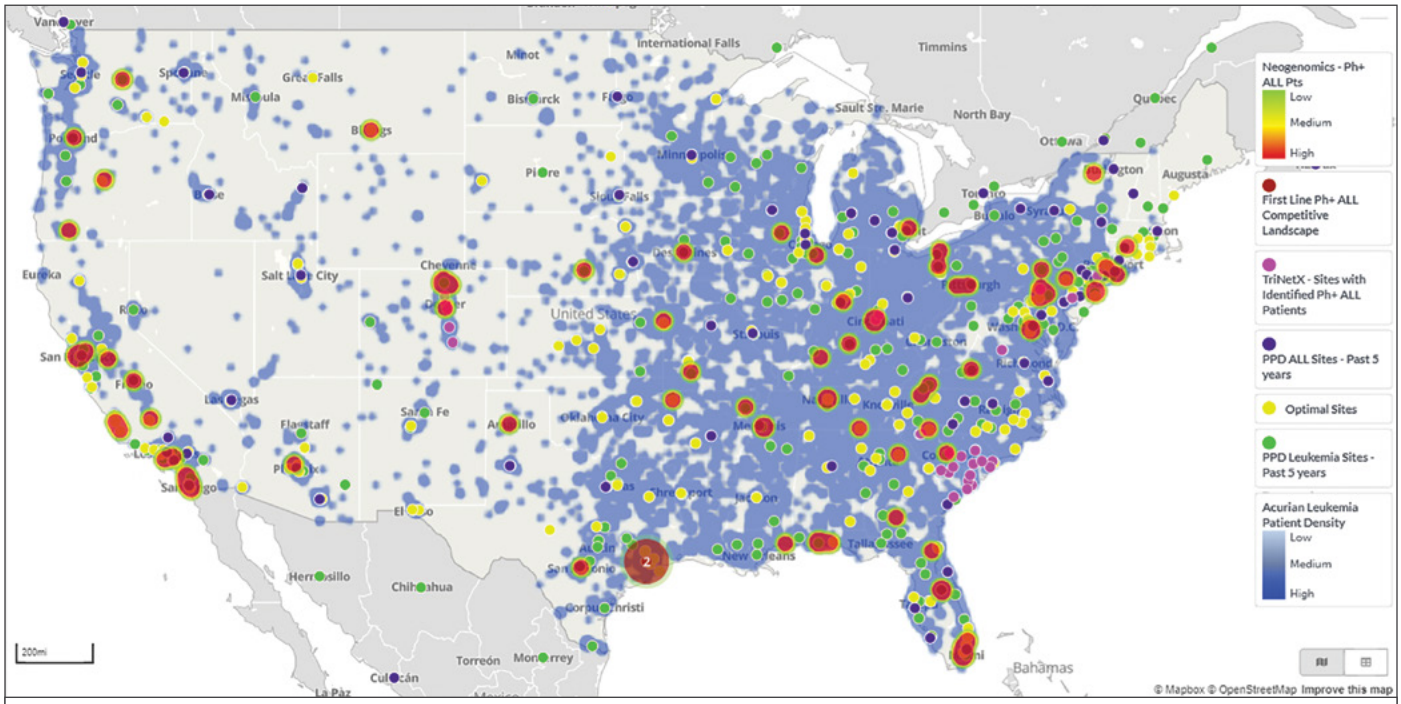
There are, of course, other parameters that should be investigated. Electronic medical records (EMR) data should be examined to determine the actual, demonstrated population for the indication within the practice or institution. One example is TriNetX, a global EMR tool that allows the user to query the data to identify where patients are available. Of course, not all will qualify, but the site totals can be compared to identify which sites have larger potential patient populations. Other sources of data, such as genomics data, can be accessed to identify where patients with the specific genetic trait or marker are located in order to focus on the correct population at the correct sites.

Predictive analytics can also be used to not only show the expected activation of sites and enrollment of patients, but also to do scenario modeling as part of a protocol analysis. This can allow the formulation of alternative, potentially more effective, ways to achieve study objectives.

Once data results are generated from these sources, an analysis should be done to marry results of where patients are located with where the most successful sites are located. PPD, for example, can show this visually using our Site and Patient Visualization Tool (SPVT) that provides information regarding the patient populations by number, location, and source (See Figure 2). Identifying sites with the highest population of available patients also is important to reduce patient burden by limiting travel and inconvenience as much as possible.

In the end, the key to site selection is finding the right sites, with the right patients, at the right location to maximize study success and the ability to deliver new therapies to patients in need.

Figure 2. Visual Depiction of Patient Populations and Sites



Enrollment strategies in North America include leveraging Neogenomics data, TriNetX Sites, and Optimal Network in addition to high performing PPD leukemia sites

Protocol De-risking

Protocol de-risking is another strategy built on conducting a set of protocol-focused assessments; however, its goals, timing, and approach differ from protocol optimization (See Table 1). Protocol de-risking is specifically designed to identify and mitigate areas of avoidable risk within the protocol that are likely to lead to protocol amendments.

> "I just wanted to tell you that having the de-risking team have a look has been really fantastic. The Sponsor was really happy with the de-risking team suggestions and for us [the writing team] it was really nice to get feedback! We REALLY appreciate it."

Protocol De-risking Case Study

OBJECTIVE

Determine the benefits of protocol de-risking review for a Phase II open label oncology trial

APPROACH

A broad range of experts within PPD participated in the de-risking review to engage multiple perspectives.

A protocol de-risking tool that focuses on key areas to specifically reduce the number of amendments was used to guide the reviewer.

Timing of review was determined to be at near-final protocol to ensure it mimicked the final protocol yet changes to the protocol were still feasible.

RESULTS

Critical findings included: risk to a potential protocol amendment due to lack of clear and/or consistent study treatment instructions, study treatment safety, recruitment challenges, and clear study endpoints. Positive feedback was received by the client and author of the protocol. Positive feedback was also received by the de-risking team regarding the use of a guided tool.

CONCLUSION

Implementation of a robust protocol de-risking review by various experts within PPD with the use of a concise tool at the right time helped identify and mitigate avoidable risks that may cause a protocol amendment.

While a protocol, or protocol synopsis/concept sheet, may undergo a de-risking process at any point, the ideal timing is when the protocol is near-final, just prior to regulatory submission. Performing the analysis at this stage addresses the concern that a large percentage of amendments occur before the first patient is enrolled.[6] This timing aims to reduce the probability of receiving competent authority requests for changes, as well as decrease the need for future protocol amendments. As approximately half of amendments are considered avoidable,[6,7] identifying and proactively simplifying and modifying the areas of the protocol, that left unchanged most commonly necessitate a future amendment, reduces overall study timelines and costs related to additional submissions and potential pauses in site activations and/or recruitment of patients.

Similar to protocol optimization, protocol de-risking utilizes a team of operational experts with experience in biostatistics, project and clinical management, feasibility, data management, regulatory, pharmacovigilance, medical writing, and product development. The most common causes of avoidable protocol amendments include **design flaws**, **inconsistencies/errors**, and **recruitment challenges**.[6-8] The cross-functional team concentrates their analysis and associated recommendation in these areas, as well as customizes the review according to project-specific needs. The following critical data, process, and risks are typically assessed, and associated recommendations provided:

- Clear definitions and alignment between **endpoints, objectives, and assessments**, and strategy for monitoring critical data
- **Eligibility criteria** to ensure relevance to study endpoint, clarity, consistency, alignment with applicable guidelines and regional differences, and level of restriction is appropriate for the phase, objectives, and targeted patient population
- **Logistical challenges** in patient recruitment, retention, study supplies/equipment, investigational product/study treatment, and study procedures
- **Study visit assessments** to ensure frequency, length, and complexity are appropriate and as minimal as required to meet objectives
- Clarity and comprehensiveness of **safety reporting and data collection** procedures
- **Randomization, stratification, and blinding** for feasibility and challenges in execution, as well as completeness needed for statistical analysis plan
- End-to-end **consistency review** to identify areas of conflict or confusion

Several pilots were conducted to demonstrate the potential benefits of protocol de-risking.

Table 1. Comparison of Protocol Optimization and Protocol De-risking

	Protocol Optimization	Protocol De-risking
Goal	Reduce time, cost, site complexity, and/or patient burden	Reduce or mitigate protocol amendments
Emphasis	Mostly strategic focus with some operational elements	Mostly operational focus with some strategic elements
Input Timing	Protocol synopsis	Near-final full protocol
Turn-around Time	~3 weeks	~1 week
Data Intensity	High	Moderate to low
Scope	Seven optimization areas: • Patient Population • Standard of Care • Protocol Design • Competitive Landscape • Regulatory Review • Statistical Review • Virtualization Assessment	Six de-risking areas: • Entry Criteria • Study Treatment • Study Design • Endpoints • Statistics • Ethics/Safety

Conclusion

Lowering study complexity and mitigating amendment risk requires a full complement of activities throughout the design process. Effective strategies include starting with early and ongoing patient-informed protocol design, adding protocol optimization and site identification at the synopsis stage, and concluding with thorough protocol de-risking assessments. The impact of these activities is likely to differ from protocol to protocol, but on average, they have demonstrated significant impacts. Lower complexity and fewer amendments mean faster study enrollment and completion, which equates to patients having earlier access to new therapies and companies seeing significant returns on their investment. ■

For more information, please contact David.Nagel@ppd.com, Beth.Schneider@ppd.com, Stephen.Powell@ppd.com, Malcom.Horsley@ppd.com, or Jennifer.Monen@ppd.com.

REFERENCES

1. Levitan B, Getz K, Eisenstein EL et al. Assessing the Financial Value of Patient Engagement. A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project. *Ther Innov Regul Sci.* 2018 Mar; 52(2): 220–229. doi: 10.1177/2168479017716715.
2. US Food and Drug Administration. Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations – Draft Guidance for industry, Food and Drug Administration Staff, and Other Stakeholders. Available at: https://www.fda.gov/media/130917/download. Accessed September 7, 2020.
3. Crocker JC, Ricci-Cabello I, Parker A et al. Impact of Patient and Public Involvement on Enrolment and Retention in Clinical Trials: Systematic Review and Meta-Analysis. *BMJ.* 2018 Nov 28;363: k4738. doi: 10.1136/bmj.k4738.
4. Economist Intelligence Unit. The Innovation Imperative. 2019. Available at: https://druginnovation.eiu.com/. Accessed September 7, 2020.
5. Levitan B, Getz K, Eisenstein EL, et al. Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project. *Ther Innov Regul Sci.* 2018 Mar;52(2):220-229. doi: 10.1177/2168479017716715. Epub 2017 Jul 17.
6. The Association of Clinical Research Professionals. Are You Wasting Money on Unnecessary Protocol Amendments? April 11, 2017. Available at: https://acrpnet.org/2017/04/11/wasting-money-unnecessary-protocol-amendments/. Accessed September 7, 2020.
7. Getz KA, Stergiopoulos S, Short M et al. The Impact of Protocol Amendments on Clinical Trial Performance and Cost. *Ther Innov Regul Sci.* 2016 Jul;50(4):436-441. doi: 10.1177/2168479016632271.
8. Internal Regulatory Affairs Amendment Data from 2017/2018.