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Using Patient Burden Evaluation to Improve Clinical Trial Planning and Execution

Executive Summary

Giving serious, systematic consideration to the burdens a clinical trial places on patients is vitally important for trial planning and execution, as well as improved patient centricity. Until now, patient burden has been qualitatively assessed, but this has not provided a systematic evaluation of the reality of a patient's overall clinical trial experience. Understanding and evaluating patient burden can help meet the challenges of patient recruitment, retention, and adherence. This paper discusses the concept of patient burden, its components (anxiety, pain, invasiveness, etc.), its measurement, and structural aspects of clinical research that hinder its reduction. The Patient Burden Index, or PBI, developed by Medidata is an effective tool for improving trial design, downstream operations, and patient centricity. An example illustrates the application of the PBI.

Patient Burden and Why It Matters

When a study team conceives and develops a protocol for a clinical trial, serious consideration of the burden on the patient is of paramount importance. Typically, the patient burden in a clinical trial is qualitatively assessed, but the reality of a patient's overall experience is not evaluated systematically. The Schedule of Events in a protocol determines the number and types of procedures a patient undergoes during the clinical trial; this can give some insight into the overall level of patient burden and site burden. However, the ability of this process to reflect total patient burden is seriously limited. Specific components of hardship, including a patient's pain, anxiety, and harmful exposure, are not explicitly considered and incorporated into the analysis of a protocol.

Patient recruitment, retention, and adherence are crucial determinants of the success or failure of a clinical trial. These factors continue to challenge the pharmaceutical industry despite the focused efforts of dedicated clinical operations teams. Dropout rates in clinical trials are frequently very substantial, sometimes above 30%.[1] Poor patient retention adversely affects trials by lengthening timelines, adding costs, introducing risk to the interpretation and validity of study data, and delaying or even derailing trial completion and product approval.[2] Poor patient recruitment and adherence to the trial schedule have the same effects.

As the race for patients becomes increasingly competitive, building a clinical trial with a patient-centric approach could be the difference between achieving high patient enrollment and retention rates and suffering protracted enrollment and high patient withdrawal rates. Attention to patient centricity can mean the difference between rapid trial completion and failure to complete a trial.

Patient Burden: Obstacles and Measurement

Patient burden is a well-established concept in medical literature. It has long been accepted and studied as an important construct, as Sloan noted in 2002.[3] The analogous concept of respondent burden in health survey research, defined as the respondent's subjective experience of hardship from psychological, physical, and economic effects of research participation, was defined 25 years earlier.[4]

It is natural to integrate the concept of patient burden into the specialized area of clinical research. Combining the disparate components of patient burden—physical pain, anxiety, harmful exposure, and additional factors—into an overall Patient Burden Index, or PBI, creates a tool that helps us visualize and understand the experience of the patient in a clinical trial. This index, indicating the level of patient burden resulting from a specified protocol, has several major applications.

The concept of patient-centric trial design highlights the goal of bringing awareness of the patient's experience in clinical research to the study team developing a protocol. To minimize the potential negative impact of a trial on patient volunteers, clinical development professionals must create and systematically use a multi-dimensional combination of insights to optimize study design. Constructing a lean study design that achieves the essential clinical and statistical outcomes, with a focus on minimizing the site and patient burden, leads to a more positive patient experience. This ultimately drives downstream operational efficiencies by creating an opportunity to improve patient recruitment, retention, and adherence.

Structural factors in clinical science make it increasingly challenging to reduce patient burden. As the science associated with the clinical development effort evolves, so does the inclination of clinical scientists to expand correspondingly the number of objectives, endpoints, and associated procedures. There is often pressure for a trial to collect information that will lead to increased scientific understanding, especially in trials for which a novel approach to the treatment of a disease is being explored. This goal is understandable, but it can, and often does, override consideration of the minimum requirements necessary to meet the key outcomes of a specific trial. Recent research shows that "for a wide variety of reasons, research sponsors routinely add procedures because their marginal cost is a small fraction of the study budget."[5] Unfortunately, if the clinical activities required to obtain the data that will yield improved science are excessively burdensome for the patients, this situation can greatly reduce patient recruitment, retention, or adherence, leading to delay or even failure in a trial. It has been shown that the higher the burden of a trial, the more patients consider dropping out of the trial.[6]

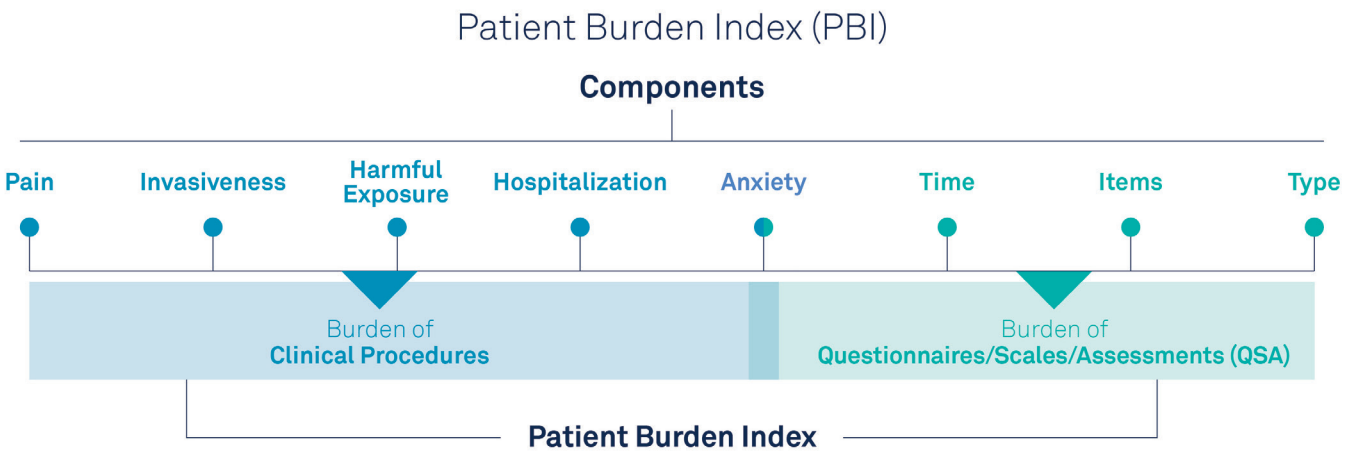
A tool that assesses overall patient burden by using patient-based metrics for the components of hardship can enable patient-centric trial design. Explicit display of the additional patient burden produced by clinical procedures beyond those needed to achieve a trial's required clinical and statistical outcomes can be a powerful tool for shifting the thinking on trial design. Medidata has developed Edge Design Optimizer to meet this need. Edge Design Optimizer improves study design through a systematic, metric-based approach to selecting procedures based on their alignment with specified objectives and endpoints that are considered essential.

Until recently, the burden placed on the patient by a clinical trial could only be surmised through subjective interpretation of the experience resulting from the procedures in the Schedule of Events. This does not allow those responsible for protocol development to evaluate the trade-off between the knowledge gained from clinical activities beyond those needed to achieve the trial's key outcomes and the increased burden imposed by these activities. Medidata has addressed this opportunity by investing three years of R&D effort to build and validate the Patient Burden Index (PBI). The PBI provides a quantitative measure of the burden to the patient on a per-procedure basis. Based on the number of times each procedure is experienced by the patient over the course of the trial, the overall PBI can be quantified at the protocol level and benchmarked against studies of similar disease area and phase. The patient burden and site burden of a trial can now be assessed quantitatively by evaluating the PBI and site burden scores at the study level.

How Was the Patient Burden Index Developed?

To create a quantitative index from eight components that are largely qualitative, Medidata's data scientists built an algorithm that constructs the PBI for sponsors and CROs based on:

- **Anxiety:** Level of anxiety caused by a procedure
- **Pain:** Level of physical pain caused by a procedure
- **Invasiveness:** Level of physical invasiveness caused by a procedure (e.g., blood draw, device implantation)
- **Harmful Exposure:** Level of exposure to harmful substances or radiation caused by a procedure
- **Hospitalization:** Hospital admission required or not required
- **Time:** Amount of time required to complete a survey or interview
- **Items:** Number of questions or items in a survey or interview
- **Type:** Questionnaire, survey, assessment, etc.



Each component was assessed and placed on a scale of severity, and then further developed and validated internally. The subjective measures of pain and anxiety were validated through surveys with clinical site staff and patients.

The Society of Clinical Research Sites (SCRS) partnered with Medidata, executing the validation process as an unbiased source of site staff and patient survey respondents. A random sample of investigator site personnel and patients was surveyed across several therapeutic areas (TAs) to gauge the patient experience and perception of various procedures.

SCRS selected sites specializing in a variety of TAs. Each site collected responses from physicians, other healthcare professionals with direct patient access, and patients. Surveys included procedures typically performed uniquely within a specific TA and additional, more general procedures that are commonly performed across many TAs.

In the survey, patients rated the pain and anxiety of procedures they had experienced and their perception of the pain and anxiety of procedures they had not experienced. Physicians and healthcare professionals were asked about their perceptions of the same procedures to complement the responses from the patient respondents. The PBI algorithm will continue to evolve in subsequent versions as the measurements are refined, based on continued validation and experience with the PBI.

How Does PBI Enhance Edge Design Optimizer?

Prior to the addition of PBI, Edge Design Optimizer could benchmark a protocol against industry peers and enable optimization of a study by providing the line of sight necessary to understand how specific procedures impact trial cost and site burden. With the addition of PBI, Edge Design Optimizer enables the assessment of both site burden and patient burden, giving sponsors and CROs the novel ability to develop site-centric and patient-centric trials.

In the protocol development stage, the PBI optimizes study design and procedure selection through systematic evaluation of the Schedule of Events. Procedures can be modified or eliminated when patient burden is high but information yield for core objectives is limited.

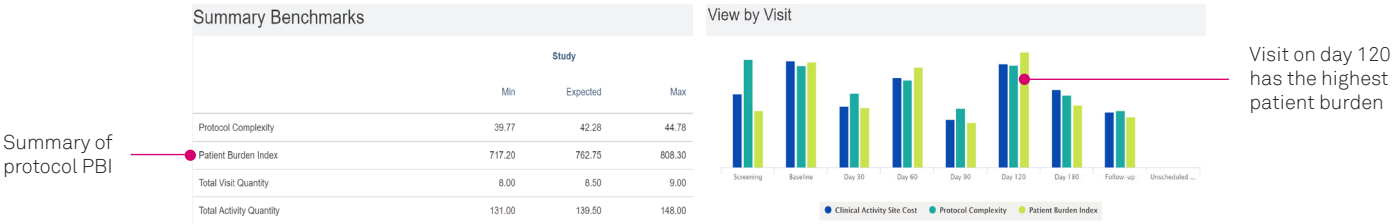
Edge Design Optimizer with PBI displays the data and visualization to improve study operations planning by providing insights to downstream operational impact. A burdensome procedure may be necessary based on the efficacy, safety, or regulatory objectives of the study, but strategic planning for the most burdensome visits of the study can mitigate the risk of excessive patient dropout that will compromise the trial. Visualization of the cost and burden implications on a per-visit basis supports the proactive operational planning needed to reduce the risks of missing enrollment and study milestones.

Operationalizing the Insights from Edge Design Optimizer

As a study is analyzed in an iterative process over the course of its development life cycle, it is possible to consider the potential operational impact of a study design based on a view of the patient burden on a per-visit basis.

In the example below, the visit on Day 120 had the highest patient burden of all study visits. The sponsor examined the types of procedures being conducted at that visit and the objectives/endpoints to which those activities were aligned; several high-burden procedures supported exploratory objectives. To mitigate the risk of patient dropout at Day 120, the sponsor made a strategic decision to remove these procedures from the visit. Alternatively, if those procedures had been deemed essential to the trial at the Day 120 timepoint, the visualization of patient burden suggests a need to bolster operational plans with additional retention strategies at that visit.

Before using Edge Design Optimizer



After using Edge Design Optimizer and realizing protocol improvement opportunities

What's Next?

Clinical trial sponsors and CROs are realizing the positive impact that data-driven decision-making can have on trial planning and execution. This requires not merely having highly informative data, but embracing data-driven insight and discarding methodologies that fail to use data-based actionable information. To develop and execute site-centric and patient-centric trials, clinical R&D and clinical operations personnel should collaborate in designing and developing protocols, from the initial concepts to the final steps in the protocol development and execution lifecycle.

Edge Design Optimizer, now with PBI, is a crucial assessment tool that visually presents opportunities for study design improvement. It allows clinical operations professionals and clinical scientists to engage efficiently in well-informed, data-driven discussions. These two groups share the common goal of designing and executing a study that can recruit and retain patients in order to achieve clinical and statistical outcomes, while reducing patient burden and site burden whenever possible.

About Medidata Solutions

Medidata is reinventing global drug and medical device development by creating the industry's leading cloud-based solutions for clinical research. Through our advanced applications and intelligent data analytics, Medidata helps advance the scientific goals of life sciences customers worldwide, including nearly 850 global pharmaceutical companies, biotech, diagnostic and device firms, leading academic medical centers, and contract research organizations.

The Medidata Clinical Cloud® brings a new level of quality and efficiency to clinical trials that empower our customers to make more informed decisions earlier and faster. Our unparalleled clinical trial data assets provide deep insights that pave the way for future growth. The Medidata Clinical Cloud is the primary technology solution powering clinical trials for 17 of the world's top 25 global pharmaceutical companies and is used by 16 of the top 20 medical device developers—from study design and planning through execution, management and reporting.

info@mdsol.com | mdsol.com | +1 866 515 6044

Citations

1. National Research Council, 2010, The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials; Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press, 39.

2. Burgess LJ & Sulzer NU, 2011, Patient Retention Gifts In Clinical Trials—Undue Inducement Or Justified Motivational Tools? South African Medical Journal 101(9):640-641.

3. Sloan J, 2002, Asking the Obvious Questions Regarding Patient Burden, Journal of Clinical Oncology 20(1):4-6.

4. Bradburn NM, 1977, Respondent Burden, Health Survey Research Methods: Second biennial conference.

5. Getz K & Campo R, 2013, Drug Development Study Designs Have Reached The Danger Zone, Expert Rev Clin Pharmacol 6(6), 589–591.

6. National Academies of Sciences, Engineering, and Medicine, 2016. Recruitment and Retention Issues: Patient, Provider, Institutional, and System Barriers. Strategies for Ensuring Diversity, Inclusion, and Meaningful Participation in Clinical Trials: Proceedings of a Workshop. Washington, DC: The National Academies Press. doi: 10.17226/23530.

Additional References

Lingler JH, Schmidt K, Gentry A, Hu L, Terhorst L 2014, Perceived Research Burden Assessment (PeRBA): Instrument Development and Psychometric Evaluation. Journal of Empirical Research on Human Research Ethics 9:46-49.

Massey S, 2016, 5 Ways To Increase Patient-centricity In Your Clinical Trial Operations. Posted at xtalks.com/patient-centricity-in-your-clinical-trial/

Ulrich CM, Knafl KA, Ratcliffe SJ, Richmond TS, Grady C, Miller-Davis C, Wallen GR, 2012, Developing A Model Of The Benefits And Burdens Of Research Participation In Cancer Clinical Trials. AJOB Primary Research 3:10-23.

Ziv S, 2017, How To Design A Better Clinical Trial With The Patient Experience In Mind. Newsweek July 21, 2017.

Ulrich CM, Zhou QP, Ratcliffe SJ, Knafl K, Wallen GR, Richmond RS, Grady C, 2018, Development And Preliminary Testing Of The Perceived Benefit And Burden Scales For Cancer Clinical Trial Participation. Journal of Empirical Research on Human Research Ethics, DOI: 10.1177/1556264618764730.