Contemporary Clinical Trials Communications 9 (2018) 108–114

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Quantifying and visualizing site performance in clinical trials

Eric Yang*, Christopher O'Donovan, JodiLyn Phillips, Leone Atkinson, Krishnendu Ghosh, Dimitris K. Agrafiotis

Covance Inc., 210 Carnegie Center, Princeton, NJ 08540, USA

ARTICLE INFO

Keywords:
Data visualization
Site performance
Investigator performance
Clinical trial optimization
Alzheimer's disease

ABSTRACT

Background: One of the keys to running a successful clinical trial is the selection of high quality clinical sites, i.e., sites that are able to enroll patients quickly, engage them on an ongoing basis to prevent drop-out, and execute the trial in strict accordance to the clinical protocol. Intuitively, the historical track record of a site is one of the strongest predictors of its future performance; however, issues such as data availability and wide differences in protocol complexity can complicate interpretation. Here, we demonstrate how operational data derived from central laboratory services can provide key insights into the performance of clinical sites and help guide operational planning and site selection for new clinical trials.

Methods: Our methodology uses the metadata associated with laboratory kit shipments to clinical sites (such as trial and anonymized patient identifiers, investigator names and addresses, sample collection and shipment dates, etc.) to reconstruct the complete schedule of patient visits and derive insights about the operational performance of those sites, including screening, enrollment, and drop-out rates and other quality indicators. This information can be displayed in its raw form or normalized to enable direct comparison of site performance across studies of varied design and complexity.

Results: Leveraging Covance's market leadership in central laboratory services, we have assembled a database of operational metrics that spans more than 14,000 protocols, 1400 indications, 230,000 unique investigators, and 23 million patient visits and represents a significant fraction of all clinical trials run globally in the last few years. By analyzing this historical data, we are able to assess and compare the performance of clinical investigators across a wide range of therapeutic areas and study designs. This information can be aggregated across trials and geographies to gain further insights into country and regional trends, sometimes with surprising results.

Conclusions: The use of operational data from Covance Central Laboratories provides a unique perspective into the performance of clinical sites with respect to many important metrics such as patient enrollment and retention. These metrics can, in turn, be used to guide operational planning and site selection for new clinical trials, thereby accelerating recruitment, improving quality, and reducing cost.

1. Introduction

The soaring costs and declining productivity of drug development has intensified interest in tools and technologies that can improve the efficiency of clinical trials. From an operational standpoint, the goal is to complete the study as quickly as possible with as few sites as possible. The number of quality of the sites are important determinants of trial success. Fewer sites reduce logistical complexity and higher-quality sites minimize unnecessary delays in recruiting patients and successfully completing the protocol. Both are important value drivers, as they impact cost-per-patient and time-to-market, thus extending the drug's patent lifespan, the sponsor's return on investment, and the societal benefit of bringing important new therapies to patients in need.

The patient interfacing part of a clinical trial is conducted at independent medical institutions, such as university research centers, hospitals and doctors' offices. Because these independent sites are responsible for patient recruitment and engagement, they have a profound effect upon the number and rate at which patients are screened, enrolled and retained in a clinical trial, and ultimately upon the timeline for completing the study [1]. In addition to keeping the patients engaged and preventing patient drop-out, high performing sites can also increase the availability of data and the probability that a statis-

* Corresponding author.
E-mail addresses: eric.yang@covance.com (E. Yang), chrisod76023@yahoo.com (C. O'Donovan), jodilyn.phillips@covance.com (J. Phillips), leone.atkinson@covance.com (L. Atkinson), krish.ghosh@covance.com (K. Ghosh), dimitris.agrafiotis@covance.com (D.K. Agrafiotis).

https://doi.org/10.1016/j.conctc.2018.01.005
Received 12 November 2017; Accepted 16 January 2018
2451-8654/ © 2018 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

tically significant therapeutic effect can be demonstrated at the end of the trial [1,2].[1]

Thus, the selection of high quality clinical sites during the planning phase of a trial is critical to its success, and improved methodologies to enable this process are of great interest to pharmaceutical companies and clinical contract research organizations (CROs). As a market leader in central laboratory testing and clinical trial management services, it has been our experience that the strongest predictor of a site's future performance is its historical record. Sites that have performed well in the past also tend to do well in the future. While this insight seems obvious, acting upon it is operationally difficult for two reasons. The first is the lack of data. Normally a pharmaceutical company or CRO will only have visibility into their own trials and not those sponsored by other companies and institutions, thus limiting their ability to obtain a sufficient volume of historical information to make robust assessments. The second challenge stems from the fact that the complexity of the clinical protocol itself can have significant impact upon patient recruitment and retention, making it difficult to compare investigators and sites that have not worked on the same trial. Like most “big data” analyses, the challenge is not so much the collection and aggregation of the data, but finding ways to analyze data that have been collected under significantly different assumptions and conditions; clinical trial data falls squarely into that category.

As a company with a market leading laboratory division that conducts clinical laboratory testing for more than 40% of the outsourced clinical trials in the world, Covance has assembled the most comprehensive database in the pharmaceutical industry, spanning more than 13,000 protocols, 1,400 clinical indications, 230,000 investigators, and 23 million patient visits. To enable communication with our clients and clinical sites and to ensure that the laboratory results can be effectively integrated with other clinical trial data, the laboratory samples are labeled with metadata such as anonymized patient identifiers, investigator names and addresses, sample collection and shipment dates, etc. While this information is captured primarily for operational purposes, we hypothesized that it could also be repurposed to compute site performance metrics such as patient enrollment, screen failure rates, drop-out rates, and other site quality characteristics. More importantly, since the central laboratory service is rarely changed during the course of the trial in order to minimize variability, the data that we collect is complete and consistent: if the laboratory part of a trial is conducted by Covance, all clinical test results for all patient visits across the world for that trial are captured and recorded through our systems. This allows us to develop reliable performance metrics and insights at the individual site and protocol levels, which in turn enable us to intelligently identify and prioritize high performing sites when planning a new trial.

From a design perspective, the inherent variability in trial complexity can be addressed in two complementary ways: a) by providing the user dynamic interfaces to explore the underlying data at any level of detail, and b) by normalizing and aggregating site performance in a way that minimizes these inherent differences and allows direct comparison of protocols of widely different designs and complexity. Here, we describe two different visualization approaches designed to address these needs. The first includes an interactive dashboard that allows project managers to drill down to individual sites' historical data relating to site performance and confirm or challenge their intuitions about each site's likely future performance. The second is a way of compressing this information into a single plot that offers unique insights into relative performance and aggregate trends. These two types of visualizations are highly complementary in that they render the information at different levels of granularity, and both have proven their utility in our clinical trial planning efforts.

While it may be tempting to eschew the use of interactive visualization in lieu of optimization algorithms that pick the “best” sites [3], it has been our experience that a great number of additional factors that cannot be easily quantified also play a role in determining whether a site is ultimately selected. These factors are often based on the individual study managers' intuition and prior experience working with the sites. It is generally accepted that a tool that allows an astute user to interact with the data yields better overall outcomes when the data supporting the selection decision is incomplete or qualitative. Furthermore, it has been shown in numerous cases that human intuition married to meaningful visualizations can lead to more optimal outcomes than a purely computational solution [4]. The visualizations described in this work are accordingly tailored to their target audience.

2. Methods

The fundamental hypothesis underlying these visualizations is that the metadata associated with the laboratory kits that we receive from the different clinical sites allow us to reconstruct the complete schedule of patient visits on an anonymized basis, and that these patient visits offer insights into the operational performance of their respective sites. Currently, each kit contains an anonymized patient identifier, a trial identifier, the date in which the sample was collected, and the investigator's name and address, which are important for shipping purposes. This allows us to reconstruct the visit schedule of each patient and associate him/her with a particular investigator and trial. Furthermore, regulatory requirements stipulating that laboratory tests associated with patient safety must be processed within 48 h from sample collection allow us to associate each laboratory kit to a specific patient visit with a high degree of precision. Because safety testing is an integral part of every clinical trial, this assumption is generalizable across the all phases, therapeutic areas and clinical indications.

More specifically, the first kit registered for a given patient in a given trial at a given site marks the time that this patient was first screened for that trial. When the second kit arrives for that same patient, same site and same trial, we can assume that this patient was enrolled in the trial (exceptions such as duplicate screening do exist, but are generally rare). Subsequent kit shipments trace the remaining patient visits in a similar fashion. Further, if a patient has fewer kits than expected, we can safely conclude that the patient has been terminated early. Therefore, by counting the number of different patient identifiers associated with a site, we can determine the number of patients screened. By counting the number of different patient identifiers with two or more kits, we can determine the number of patients enrolled. And by counting the number of kits per patient, we can determine which patients followed the visit schedule and which did not. Finally, by computing the time difference between the first kit of the first patient and the last kit of the last patient, we can estimate the length of time that the site was open. This provides us with robust metrics of clinical site performance, which can be further annotated by additional attributes, such as therapeutic area, clinical indication, geography, etc.

Our initial efforts at exploring this data relied upon the interactive visualization capabilities of Spotfire [5] and Tableau [6]. Figs. 1–5 illustrate representative displays exploring various aspects of patient

[1] It is important to note that we define “good” sites based solely on their operational performance and not on any clinical outcome measures. Given that the majority of experimental drugs fail in clinical trials, selecting sites that report treatment effects in their patient cohorts when there is no treatment effect in the wider population would be highly questionable. Of course, patient enrollment and retention are not the only relevant indicators of site quality. Other factors such as improper subject eligibility or discontinuation, underreporting of adverse events, excessive lab test cancellations and repeats, etc. are equally important. Some of these metrics can be derived from laboratory data, but others require access to a broader range of systems used for clinical trial management and oversight (CTMS, EDC, IRT, etc.). Given the insular nature of the pharmaceutical industry and the fragmentation of the clinical technology and services market, this information is not easily accessible at the scale and coverage described in the present work, and is typically confined within the walls of individual pharmaceutical companies and/or software and CRO vendors. Some cross-company initiatives, such as those sponsored by the TransCelerate consortium, attempt to break down these silos, but they are focused on basic operational capabilities, such as maintaining a shared repository of business contact information and a common portal for portal for engaging with investigative sites.

Download English Version:

https://daneshyari.com/en/article/8519345

Download Persian Version:

https://daneshyari.com/article/8519345

Daneshyari.com