Original Article

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A data-driven approach to quality risk management

Abstract

Aim: An effective clinical trial strategy to ensure patient safety as well as trial quality and efficiency involves an integrated approach, including prospective identification of risk factors, mitigation of the risks through proper study design and execution, and assessment of quality metrics in real-time. Such an integrated quality management plan may also be enhanced by using data-driven techniques to identify risk factors that are most relevant in predicting quality issues associated with a trial. In this paper, we illustrate such an approach using data collected from actual clinical trials. **Materials and Methods:** Several statistical methods were employed, including the Wilcoxon rank-sum test and logistic regression, to identify the presence of association between risk factors and the occurrence of quality issues, applied to data on quality of clinical trials sponsored by Pfizer. **Results:** Only a subset of the risk factors had a significant association with quality issues, and included: Whether study used Placebo, whether an agent was a biologic, unusual packaging label, complex dosing, and over 25 planned procedures. **Conclusion:** Proper implementation of the strategy can help to optimize resource utilization without compromising trial integrity and patient safety.

Key words: Clinical trial, compliance, quality risk management, risk assessment and mitigation

INTRODUCTION

The current paradigm in drug development entails the conduct of complex and large trials, recruiting patients globally, and often relying on clinical research organization alliance partners to manage the trial execution. With the increasing size and complexity of trials, there is a corresponding need to be vigilant about patient safety, data quality, and trial integrity. Most trials employ resource-intensive approaches to oversee quality, with frequent on-site visits, to identify issues in a reactive manner, and may often fail to effectively address critical risks to quality. The prevailing practice of frequent site visits and extensive source document verification has also contributed to the sky-rocketing cost of clinical research. Accordingly, there is a nascent focus on new approaches to quality risk management by the pharmaceutical industry and other stakeholders in the clinical trial enterprise.[1-4] One approach that is gaining momentum is a holistic strategy to quality management that incorporates risk management principles, borrowing ideas from the manufacturing sector as described in International Conference on Harmonisation Q8, Q9 and Q10.[5-7] Central to the approach is the concept of quality-by-design, which in the context of clinical trials translates into building quality into the trial design (e.g., protocol) and processes to execute the trial rather than managing the quality of the trial retrospectively or in a reactive manner.[8]

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Pfizer has launched a pilot project in partnership with the US Food and Drug Administration that is designed to test one model for prospectively designing quality into clinical trials and systematically managing quality during study conduct.[9] The approach, known as the integrated quality management plan (IQMP), is built based on the following core principles:

1. Quality is built-in at the time of protocol development and systematically managed during study conduct through a process of continuous improvement;
2. Critical to quality factors, and related metrics and associated performance expectations are identified a *priori* and actual performance is measured and actively managed throughout the duration of study conduct;
3. Risks to quality are prospectively identified, prioritized, and mitigated.

In this paper, we discuss a quantitative approach to complement the IQMP efforts using statistical models to identify risk factors that require closer scrutiny both before and during study conduct. Quantitative and data-driven approaches help minimize some of the pitfalls associated with actions taken in a subjective manner. In particular, such an approach, if executed meticulously, tends to provide results that are reproducible and often generalizable. However, the generalizability of the findings is dependent on the quality and magnitude of the data. This would often involve gathering numerical data, in a cost-effective and systematic fashion, from a fairly large number of studies that are representative of future trials.

The rest of the paper is organized as follows. In Section 2, we describe the data and analytical approaches and discuss the results in Section 3. In the last Section, we highlight the implications of the data-driven strategy with regard to optimal resource utilization, and suggest success factors that are critical for an IQMP.

MATERIALS AND METHODS

Data source and description

Data were obtained from seventy-three select ongoing late-stage clinical trials from across a variety of business units and therapeutic areas over several years at Pfizer.

Two separate questionnaires were completed for each study by the respective study teams. The first was a forward-looking assessment seeking to identify the level of risk perceived to be associated with risk factors that are related to eight different risk categories (i.e., asset characteristics, subjects, protocol, locations, site operations, vendors/outsourcing, monitoring, and drug supply). Table 1 lists the prospectively identified risk factors that were collected for each trial. The second was a backward-looking assessment that identified the issues that actually occurred during study conduct based on a standard set of common issues critical to quality requirements. Table 2 lists the issues that were assessed in the course of the trial conduct, and used to define the dependent variable for subsequent statistical analysis.

Statistical methods

To identify relevant risk factors that require closer scrutiny in future quality management initiatives, several statistical methods were employed. Quality issues were defined both as binary (i.e., presence or absence of a quality indicator) as well as counts (i.e., number of issues satisfying quality criteria). In the following, we present the results of the analyses performed using the latter.

In the univariate analysis, a Wilcoxon rank-sum test was used to identify the presence of association between the risk factors and the occurrence of quality issues. The results of the preliminary analyses were then used to reduce the number of risk factors for inclusion in multiple regression models. Due to the skewed nature of the data, it was necessary to use the non-parametric Wilcoxon rank-sum test for the univariate analyses, and a log transformation for the regression models.

RESULTS

Of the 73 protocols in the database, there were 72 studies that had at least one issue with a mitigation plan. Ten (13.7%) studies had at least one issue without a mitigation plan in place. For a preliminary analysis, a binary outcome was defined using the presence or absence of a specified number of issues with or without a mitigation plan. However, a binary definition tended to involve some degree of subjectivity and arbitrariness. As a result, actual counts of issues observed in a study were used in the definition of the dependent variable and reported in subsequent analyses.

Table 3 gives a partial list of the risk factors and associated *P* values. Based on the univariate analyses, nine risk factors had a significant ($P < 0.05$) or marginally significant ($P < 0.10$) association with the number of quality issues. Incidentally, these factors included some intuitive ones that are known to lead to quality problems. The significant factors were: Unusual packaging/labeling, dosing complexity; a biologic compound, size of planned procedures over the course of the trial, whether investigator discretion was permitted in measurement decisions; whether the drug was self-administered; use of placebo; and number of exclusion criteria. Two of the risk factors, namely the co-sponsorship

Table 1: List of prospectively defined risk factors for quality

Risk factors
Asset characteristics
Does the investigational product have: (1) a novel mechanism of action or (2) have the potential to be the first in class if approved?
Does the investigational product or others in the same class carry a boxed warning or has a product in the class been withdrawn?
Has the product ever been subject to a "clinical development hold" (or comparable regulatory action) by a regulatory authority?
Does the study involve an addictive or likely addictive substance that could be subject to abuse?
Have significant deviation (CT11) cases occurred with this product?
Is the development program for the asset co-sponsored?
Is the investigational product a biologic, vaccine, or small molecule?
Is the investigational product an in-licensed compound?
Is the investigational product or comparator delivered through inhalation or injection?
Number of studies comprising development program
Subjects
Indicate vulnerable populations who will be specifically targeted for enrollment as study subjects. Check each/all that apply:
Adolescents (minors)
Blind/illiterate/deaf
Decisionally impaired (including: Neurologically impaired patients (e.g., stroke, dementia, head trauma), patients with mental disorders, and patients whose consent capacity may be impaired
Elderly
Fetuses/neonates/infants/children
Inclusion/exclusion criteria permit women of child-bearing age to take part in the study
Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response in case of refusal to participate
Other categories of vulnerable subjects including but not limited to, patients with incurable diseases, persons in nursing homes, patients in emergency situations
Pregnant women
Prisoners
Seriously ill (potentially disabling or potentially life-threatening diseases)
N/A
What is the total number of planned/projected study visits per subject?
The subject's medical condition upon entry in the study is likely to be extremely rare, terminal or extremely severe (e.g., risk of blindness, life-threatening infectious disease)
What percentage of subjects are anticipated to have impaired capacity to provide informed consent (e.g., age <18, cognitive impairment, unconscious, illiterate)?
Will the trial recruit subjects with situational factors that may lead to undue influence, coercion or duress (e.g., life-threatening illness or incurable disease, chronic pain, dependent or subordinate relationship with the investigator or sponsor, institutionalized or nursing home patients, impoverished or unemployed, homelessness)?
Protocol
Are subjects allowed to take multiple concomitant medications (that are not background medications) during the study?
Are subjects required to be taken off their background medications prior to or during the study?
Does the protocol require non-routine invasive procedures? Check all that apply:
Endoscopy
Imaging techniques such as X-rays, MRIs, and ultrasound with contrast agents
None
Other
Surgical procedures
Does the protocol require the use of a placebo?
Does the study involve a significant departure from the established standard of care, if one exists?
Is investigator discretion permitted in decisions related to:
Dosing
Inclusion/exclusion
Measurement
Other
N/A
Is there a planned interim analysis?
Novel or unprecedented study design (either to Pfizer or industry)
Number of exclusion criteria
What is the total number of planned or projected subjects for the trial?
What is the anticipated length of the study (e.g., overall expected duration from FSFV to LSLV)?
What is the total number of planned/projected procedures over the course of the trial (refer to protocol schedule of visits-FSFV to LSLV)?
Will there be endpoint adjudication (efficacy or safety)?
Locations
Does Pfizer plan to commercialize the drug or the indication/conditions of use being studied, in each of the countries where the study is being run, or are there some countries where we have decided not to commercialize the drug, or the indication/conditions of use being studied?

(*continued*)

Table 1: List of prospectively defined risk factors for quality (continued)

- Indicate which regions will be used in the study:
  - North America
  - Africa Middle East
  - European Union Business Unit markets
  - European Union Emerging Markets
  - Asia Pacific Emerging Markets
  - Asia Pacific European Union
  - China
  - Latin America
  - Other
- Will the study involve sites (or likely involve sites) which do not already have the infrastucture to support the needs of the study (trained personnel, recordkeeping systems, medical technology, GCP infrastructure [regulations, EC, experience and training] etc.)?
- What is the # of countries planned/projected in which the study is or will be conducted?
- What is the total number of planned/projected sites?
- Is a government or non-governmental organization involved in the execution or funding (including reimbursement for study drug) of the study?

Site operations

- Does the study involve, or likely to involve investigators not previously involved in a regulated clinical study (e.g., FDA)? What percent (as applicable)?
- Were any of the following identified for Principal Investigators on the study during due-diligence? Check all that apply or N/A:
  - Conflicts of Interest
  - DEA, OIG Watch list
  - FDA 483s
  - GSA list
  - State medical licensing issues
  - Undergone a for-cause audit by Pfizer resulting in critical or major findings
  - N/A
- Relative to other studies in this therapeutic area for this indication and phase conducted in the past 5 years, is the planned number of subjects per site for this study >, < or comparable (=) to this standard?

Outsourcing/vendors

- What is the total number or vendors that are or expected to be utilized by Pfizer for this study (e.g., Vendors retained directly by Pfizer as FSP, CRO, or sub-contractors [such as data management, labs, shipping companies], excluding individual consultants)?
- What is the total number or vendors that are or expected to be utilized by the alliance partner for this study excluding individual consultants?

Monitoring

- Is there a formal, study-specific communication and training plan provided to the study monitors?
- What is the average number of monitoring visits for each site (actual or projected)?
- What is the planned percentage (%) of study visits to be completed via telephone?

Drug supply

- Which of the following apply to the investigational product or comparator drug? check all that apply or N/A:
  - Controlled substance
  - Light sensitivity
  - Other
  - Reconstitution required for administration
  - Special requirements for investigational product shipment, storage, distribution, disposal
  - Temperature/humidity control
  - N/A
- Is the investigational product or comparator drug packaging or labeling unusual or is required dosing complex?
- Will the inhaled or injected investigational product (and/or comparator drug) be self-administered or be administered by site personnel?
- Does the dosing interval present scheduling challenges to ensure protocol compliance?

CT = Clinical Trial Standard Operating Procedures, MRIs = Magnetic Resonance Imaging, FSFV = First Subject First Visit, LSLV = Last Subject Last Visit, GCP = Good Clinical Practice, EC = Ethics Committee, DEA = Drug Enforcement Agency, OIG = Office of the Inspector General, GSA = General Services Administration, FSP = Functional Service Provider, CRO = Clinical research organization, FDA = Food and Drug Administration

of the development program and the number of vendors used to manage the study were marginally significant.

The median numbers of issues for study drugs that require unusual labeling or involve complex dosing were 18, compared to only 10 when the opposite was the case. Similarly, a biologic compound tended to result in greater median number of issues than a non-biologic study drug (13 vs. 9, respectively). The results for the other significant and marginally significant risk factors trended in the same direction.

The above risk factors that were identified in the univariate analyses were then included in a multiple regression analysis. The regression analysis further identified five risk factors with significant predictive values when taken jointly: Whether study used Placebo, whether an agent was a biologic, unusual packaging label, complex dosing, and over 25 planned procedures.

It should be noted that the multiple regression approach was limited by the size of the data that was available for

Table 2: List of prospectively defined quality metrics

Quality metric items
Safety review frequency as per SAF09
Number of subjects that cannot be dosed due to lack of investigational product, comparator (s), and placebo (s) as appropriate
Number of subjects that cannot be dosed due to lack of non-drug supplies
IB review and updates are completed annually or as required for an urgent safety issue
Number of vendors performing study related tasks without an appropriate written agreement and oversight in place
% of investigators (principal and sub investigators) trained on study-specific requirements for each study
% of investigational product shipments without approved investigator initiation package or equivalent in place
% of SUSAR reports not distributed to applicable investigators in compliance with timelines outlined in the CFR and local country regulations
% of TMF completeness
Number of expedited safety reports submitted in greater than the required timelines, 7d for life-threatening events or death and 15d for all other SAEs
% of investigators not notified promptly using alert letters for new observations related to adverse effects and/or safe use of the study drug as appropriate
Number of SAEs reported from site to sponsor in greater than 24 h of investigator awareness
Number of GMP incidents related to improper manufacturing, packaging, storing or shipping of investigational product leading to a customer compliant
Number of inappropriate dosings due to site receipt, storage, preparation, handling, and dosing per number of dosings that occurred
Number of protocol deviations due to improper delegation of duties or site staff conducting tasks without appropriate training
Number of subjects randomized that do not meet inclusion/exclusion criteria
% of subjects with inadequate informed consent
Number of protocol deviations related to study procedures
Number of protocol deviations due to prohibited concomitant medication or vaccinations
% of visits meeting data entry target timelines of within 4 calendar days
% of unresolved queries in database with an editing status of “site review” or “unreviewed” for longer than 30 calendar days
% of unresolved queries in database with an editing status of not equal to “site review” or “unreviewed” for longer than 30 calendar days
% of randomized subjects that are in the clinical database
Number of unresolved queries in the database for greater than 30 days
% of defined patient data not received from vendor for current loading cycle
% of vendor data queries remaining unresolved at next data load
% of TMF on-time submissions
Number of vendor (s) not meeting approved timelines and quality of deliverables as established in the scope of work and project materials

SAF = Safety Standard Operating Procedure, IB = Investigator Brochure, SUSAR = Suspected Unexpected Serious Adverse Reaction, CFR = Code of Federal Regulations, TMF = Trial Master File, SAEs = Serious Adverse Events, GMP = Good Manufacturing Practice

Table 3: Summary of univariate analysis

Risk factor	No		Yes		Wilcoxon *P* value
	n[a]	Median	*n*[a]	Median	
Packaging/labeling unusual; dosing complex	61	10	12	18	0.001
Biologic	44	9	29	13	0.003
25+ planned procedures over course of trial	22	7	51	13	0.007
Investigator discretion permitted in measurement decisions	63	10	10	13.5	0.017
Self-administered	60	10	13	14	0.026
Use of placebo	41	10	32	13	0.026
20+ exclusion criteria	44	9.5	29	13	0.029
Development program for asset co-sponsored	60	11	13	13	0.052
>5 vendors-alliance partner	54	10.5	19	12	0.070
Government or non-governmental organization involved in execution/funding	68	11.5	5	9	0.105
Subjects required off background meds prior to/during study	49	10	24	13.5	0.140
Clinical development hold	48	12.5	25	9	0.142
Dosing interval/scheduling challenges	67	11	6	13.5	0.168
Any investigator not previously involved in regulated clinical trial	46	11	27	12	0.204
Novel Mechanism of Action or potential 1st in class	47	11	26	11.5	0.270
Investigational product/others in class boxed warning/withdrawn	48	11	25	12	0.398
Undue influence/coercion/duress	54	11	19	10	0.431
Endpoint adjudication for efficacy or safety	58	11.5	15	11	0.452
Novel or unprecedented study design	70	11.5	3	10	0.495
Significant departure from established Standard of Care	70	11	3	12	0.676
Sites w/o infrastucture to support study needs	64	11	9	10	0.814
Significant deviation cases occurred with investigational product	10	12.5	63	11	0.879
Injection	36	12	37	11	0.881

Number of studies responding yes or no to a given risk factor.

analysis. In addition, there were a few instances where the relevant data were missing. Despite those limitations, the approach has the potential to guide risk mitigation activities by identifying those risk factors that require increased attention.

DISCUSSION

In this paper, we proposed the use of a data-driven approach to enhance an integrated quality management strategy. While the results presented in the paper are intended to illustrate the approach, with robust and more reliable data, the approach can serve to identify risk factors that may need to be mitigated more closely. A meticulous application of the approach has the potential to maximize resource use in risk mitigation activities.

The advantages of quantitative and data-driven approaches rest largely on the ability to make decisions based on objective, rather than subjective, criteria. This in turn requires numerical data collected from a fairly large number of studies, to ensure result validity and generalizability. To the extent possible, the data collection method should be simple and cost-effective.

In any quality risk management exercise, success in ensuring patient safety and trial integrity is a function of several variables. Most notably, fancy models or complex quality management plans cannot be a substitute for strict adherence to Good Clinical Practice. In addition, it is important to collaborate and share experiences with other internal and external stakeholders, including regulatory bodies. For optimal impact, it is also essential to establish the necessary infrastructure, including processes, tools, and systems to make the quality management plan and findings of quantitative exercises scalable implementable.

A key feature of any continuous improvement project is the need to revisit current thinking and update operating models, informed by accumulating data. Accordingly, the quantitative analyses proposed in this paper should periodically be updated and refined using new data and until a reasonably steady state is achieved.

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