

Implementation of strategic management tools improves wound care clinical trial outcomes

Background: Clinical trials are designed to test efficacy and safety of new drugs. Trials testing biologics for wound care is a fast growing field. We have analyzed clinical trials testing fibroblast cell-based agents for chronic venous stasis ulcers (VLUs). These two studies had similar objectives, study design, comparable eligibility criteria and outcomes. **Objective:** To assess performance and compliance in two successive clinical trials testing cell-based therapeutics for venous ulcers in order to identify trends and improvement opportunities. **Methods:** A systemic internal audit of two prospective, randomized wound care clinical trials was conducted at Boston Medical Center. Enrollment rates, earned values, actual and planned costs were analyzed and compared. The schedule performance index (SPI) and cost performance index (CPI) were calculated and factors affecting enrollment rates were identified. Study compliance was assessed based on study protocol deviations. Safety profile was assessed based on severe adverse events reported. **Results:** The first venous leg ulcer study (VLU1), performed between September 2005 and January 2008, randomized 24 patients. The second study (VLU2), conducted between January 2010 and 2011, randomized 16 patients. Due to lack of prescreening in VLU1, the screening failure rate was 54.7 and 33.3% for VLU1 and VLU 2, respectively. The SPI at project completion was 0.58 and 1.0 for VLU1 and VLU2, respectively. VLU1 was behind schedule due to low and inconsistent enrollment caused by study staff changes and inexperience. Implementation of strategic trial management including interim monitoring of SPI, CPI and compliance resulted in VLU2 to be completed on schedule with higher randomization rates. The CPI at project completion was 1.0 and 1.2 for VLU1 and VLU2, respectively, indicating that both studies were conducted according to planned budget. The most common severe adverse event reported for both studies was cellulitis of target wound unrelated to study drug. Compliance assessment revealed 128 deviations for VLU 1 and 36 deviations for VLU 2. Most common categories, for both studies, included out-of-window visit and missed study procedures. **Conclusion:** Internal auditing is a critical tool for improvement of site performance in prospective wound care studies. Implementation of strategic management tools yielded higher enrollment and better compliance rates for the VLU 2 study.

Keywords: clinical operations • compliance management • cost performance index • schedule performance index • strategic project management in clinical trials

Background

Clinical trials are conducted to test safety and efficacy of new drugs and devices and it is estimated that the pharmaceutical industry spends an estimated US\$4 billion, annually, for research and development of cardiovascular products [1] of which biologics for

wound care is a particularly rapidly growing field [2,3]. Although technological innovations have shortened drug discovery and pre-clinical development phases, the clinical testing phase has not made similar progress [1,2]. Costs associated with the implementation of clinical trials have become an increasingly

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important issue [1,2], yet little has been done to develop cost reduction approaches and organized efforts to improve clinical study efficiency and performance [4,5]. Such efforts are important because successful management of clinical projects is predicated on the development and maintenance of a cohesive bond between clinical operations and project management [4,5].

Strategic project management focuses on tracking key study parameters through the life cycle of a project in order to optimize clinical operations and adhere to trial execution timelines [1,2]. Management processes are tailored, within the framework of an organization's

standard operating procedures, to be in place at time of project initiation [1,2]. Prior to the project's execution phase, a detailed examination of its critical path using both historical information and personal experience is necessary. Factors that affect study efficiency and improve compliance need to be identified and monitored [4,5]. For example, since adequate recruitment is vital to the conduct of a clinical trial [4] and projected recruitment rates are often overestimated while the accrual period is underestimated [2,4], the trial must be carefully planned so as to timely meet its scientific objectives.

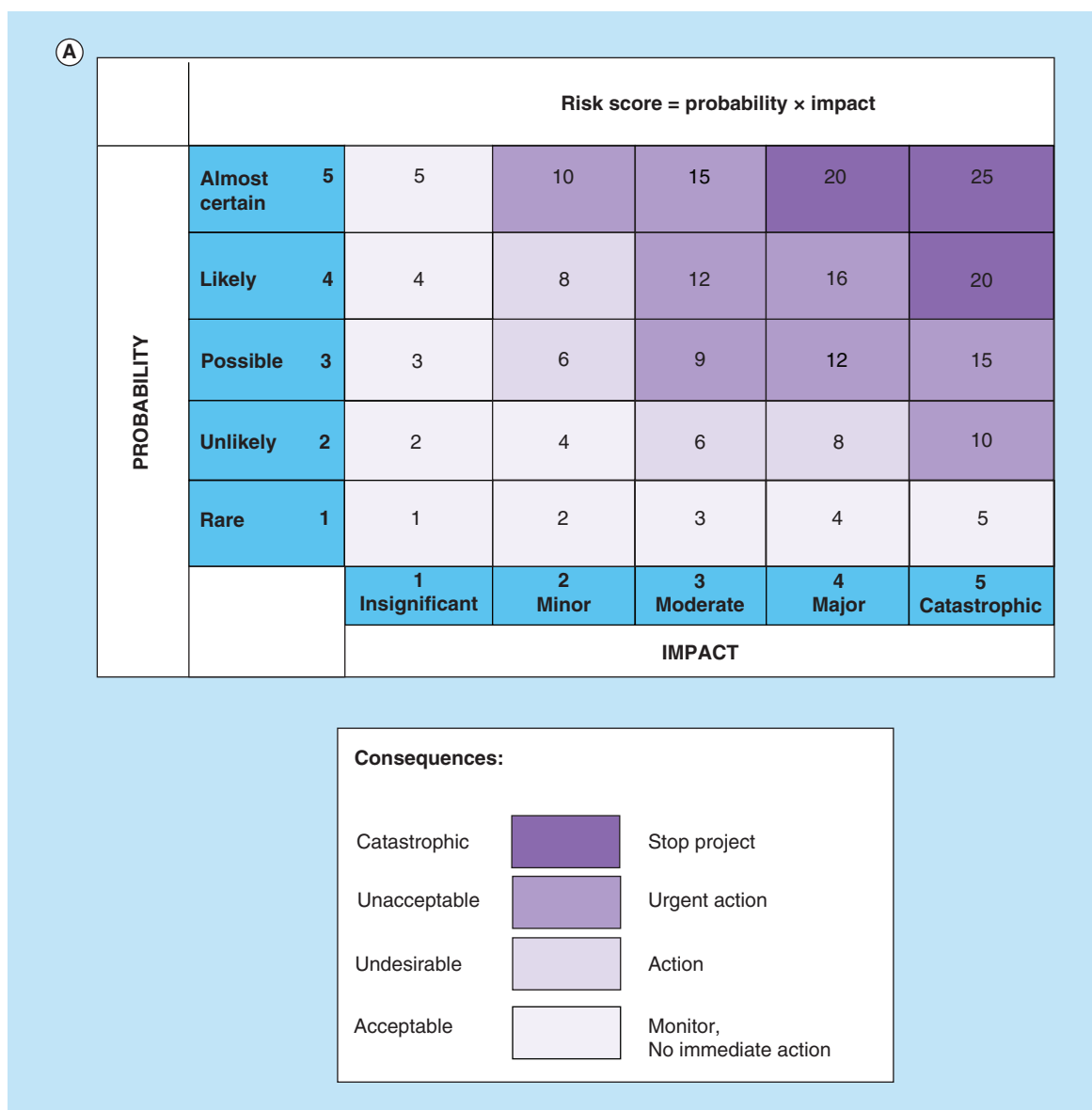
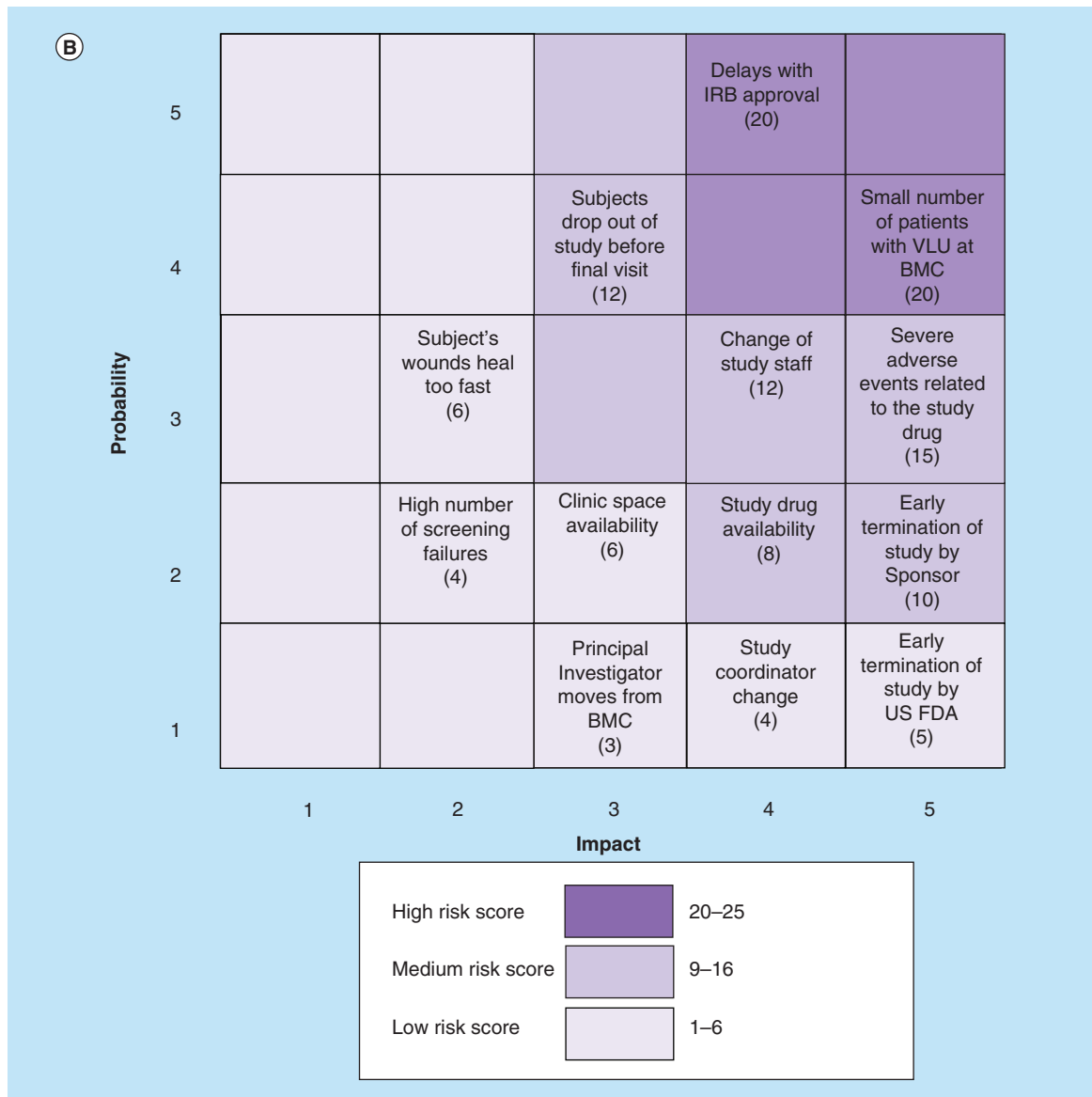


Figure 1. Risk analysis matrix diagram for VLU1 study (see facing page for [B]). (A) An example of a risk score assessment diagram. The categories were each ranked on a scale 1–5 based on their probability of occurrence and impact and the risk score was calculated. **(B)** Risk analysis matrix diagram for VLU1 study. BMC: Boston Medical Center; IRB: Institutional review board; VLU: Venous leg ulcer.



The development of a comprehensive project plan provides the basis for successful trial implementation and execution. The project plan embodies tools to adequately assess anticipated potential obstacles and risks while creating contingency plans. Failure of such a plan can lead to significant delays in the achievement of project milestones, and adversely affect overall study quality and outcomes.

In order to develop and implement strategic management tools to improve performance and compliance of wound care clinical trials we analyzed two similar clinical trials testing fibroblast cell-based agents for chronic venous leg ulcers (VLUs). These two studies had similar objectives, study design, comparable inclusion/exclusion criteria and outcomes. Study progress was assessed by utilizing the schedule performance index (SPI), earned value (EV) and cost performance index (CPI). This was

not intended to be an analytic project but rather exploratory pilot study trying to adopt strategic project management concepts and observe, in a descriptive fashion, their implementation in clinical trials.

Methods

Two consecutively conducted VLU trials were evaluated. Both studies received an institutional review board (IRB) approval prior to any research activities were conducted and were performed in compliance with Declaration of Helsinki. The first trial, VLU1 was conducted between September 2005 and April 2008 and enrolled 53 subjects. Twenty-four subjects were randomized to the investigational treatment. The second trial, VLU2, was conducted between January 2010 and 2011 and enrolled 24 subjects. Sixteen subjects were randomized to study drug. Subject's charts

and electronic records were reviewed retrospectively for the VLU1 study and assessed prospectively for the VLU2 study.

In both studies the planned enrollment rate was estimated as two subjects per month based on number of patients with disease of interest seen for their routine medical care at the hospital and who met eligibility criteria as defined in study protocol. Planned cost assumptions were made based on these enrollment rates and budgets were established according to the costs of specific study procedures. Actual enrollment rates and actual costs were acquired after subject randomization into the study and completion of required study procedures per study protocol.

Study efficiency was measured using the weekly cumulative CPI as defined by the following formula:

Weekly cumulative CPI = EV/actual cumulative costs acquired (AC) [6,7].

Earned value was defined as the percent of cumulative activities completed multiplied by the cumulative activities planned in the budget up to a given point in the study (per study procedures/per visit) [6,7].

Weekly calculation of EV for each subject was used to determine whether the trial was proceeding as planned. Weekly CPI was used to monitor accumulated costs and determine whether the trial was providing a profit to our site. Assessments of accumulated costs allowed us to determine whether we stayed within planned budget and made profit as defined by $CPI \geq 1$. Loss of profit and/or decrease of billing activities from clinical site to the sponsor of the study was defined as $CPI < 1$.

Study enrollment dynamics was monitored using the SPI calculated according to the following formula:

Weekly cumulative SPI = EV/planned value (PV) [6,7]

Planned value was defined as the cumulative activities completed as planned in the budget up to a given point in the study progression (per study procedure/per visit) under the assumption of two subjects enrolled per week [6,7]. An $SPI \geq 1$ implied that the study was operating on schedule and enrolling well. An $SPI < 1$ implied that the study was not enrolling efficiently and that performance was lower than expected.

In addition, instantaneous SPI and CPI values were assessed each week in order to monitor fluctuations in schedule and costs for each study. To that end we utilized the following formulas:

Instantaneous SPI = EV/PV

Where SPI – instantaneous schedule performance index, EV is earned value per specific week, PV – planned value per specific week [6,7].

Instantaneous CPI = EV/AC

Where CPI is instantaneous cost performance index, EV – earned value per specific week, AC – actual costs per each specific week [6,7].

Although SPI, CPI and EV are widely used in business arena as project management tools, this is the first attempt to adopt these parameters to clinical trials.

We performed retrospective risk assessment analysis based on our experiences with VLU1 study. A risk matrix was used during risk assessment to define the various levels of risk as the product of the probability of occurrence and impact categories [8]. These risks were ranked according to the calculated risk score defined according to the following formula:

Risk score = Impact of risk event × Probability of occurrence [8–10].

The impact of a risk event is commonly assessed on an arbitrary scale of 1 to 5, where 1 and 5 represent the minimum and maximum possible impact of its occurrence. Figure 1A describes an example of such a scale [9–11]. Occurrence probability is commonly assessed on a similar scale, where 1 represents a very low probability of risk event actually occurring, while 5 represents a very high probability of occurrence (Figure 1A) [9–11]. Therefore, the calculated risk score has values that range between 1 and 25. This range is arbitrarily divided into three sub-ranges defined as 1–6 – ‘low-’, 9 to 16 – ‘medium-’ or 20 to 25 – ‘high-’ risk category (Figure 1A).

As an example, a calculated risk score of between 20 and 25 may have catastrophic consequences with global impact on the project (Figure 1A). In this case immediate action is required and the project needs to be stopped or placed on clinical hold. On the other hand, a calculated risk score between nine and 16, may lead to actions ranked as unacceptable and require implementation of a mitigation strategy (Figure 1A).

A score between six and eight is associated with consequences that are considered as undesirable. Typically, these kinds of risk factors can cause slight delay, slight local site concern causing study disruption and/or moderate regional concern resulting in action required by the sponsor of the project. Finally, risk scores below 6 are associated with issues of minor concern.

Categories for our analysis were selected based on knowledge and experience gained through the VLU1 study. These categories were each ranked on a scale 1 to 5 based on their probability of occurrence and impact and the risk score was calculated (Figure 1B).

Root cause analysis for two major risk categories was performed by utilizing a fishbone diagram (Figure 2A & B) [12]. This analysis tool, referred to as the Ishikawa or root cause diagram, provides a systematic way of understanding effects and the causes that create those effects [12]. The fishbone diagram has great value in assisting and categorizing the many potential causes of problems or issues in a systematic way and helps identifying root causes [12].

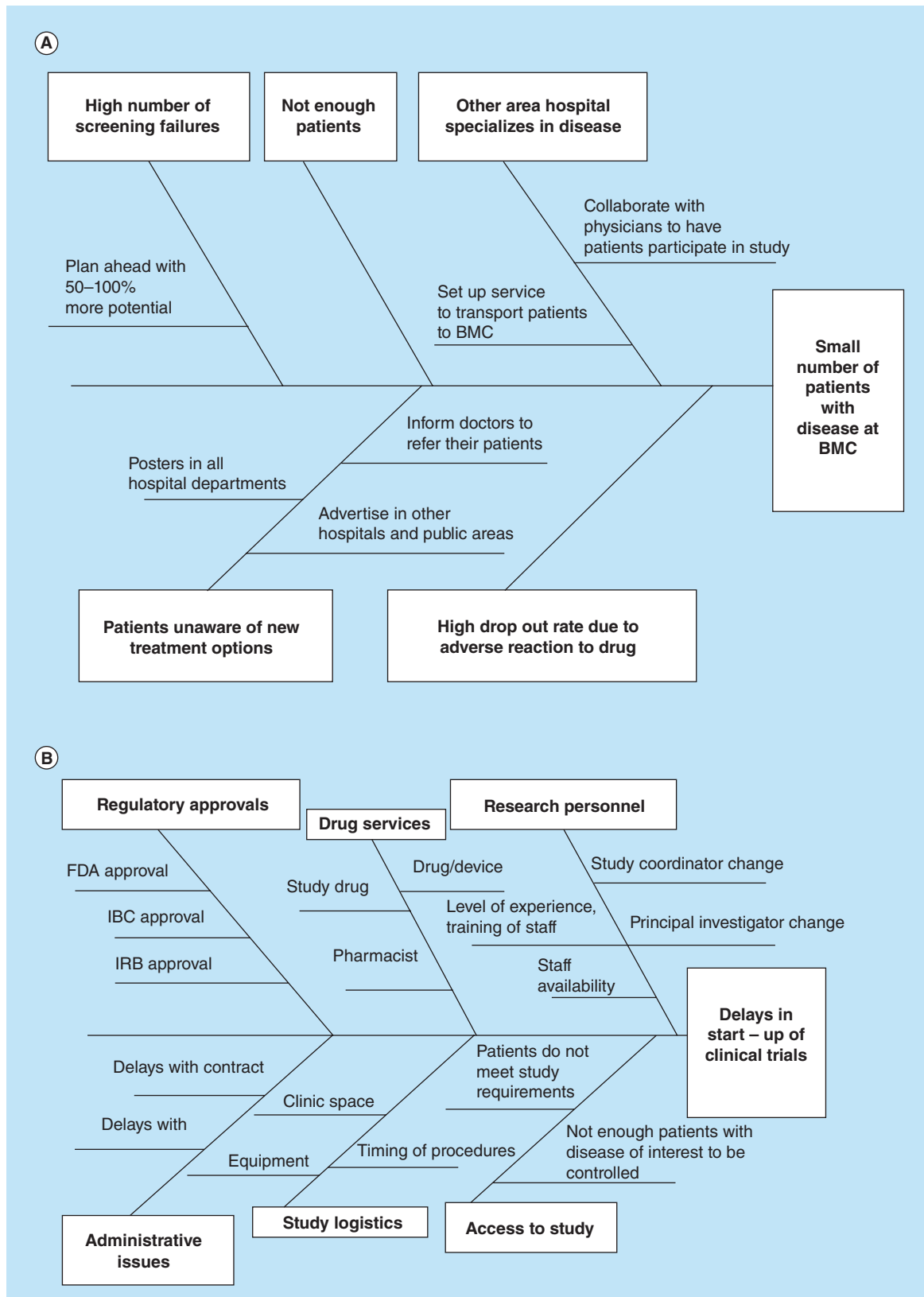


Figure 2. Cause-effect analysis for two major risk categories. (A) Small number of patients with disease at BMC; and **(B)** delays in start-up of clinical trials in the VLU1 study. BMC: Boston Medical Center; IBC: Institutional Biosafety Committee; IRB: Institutional Review Board.

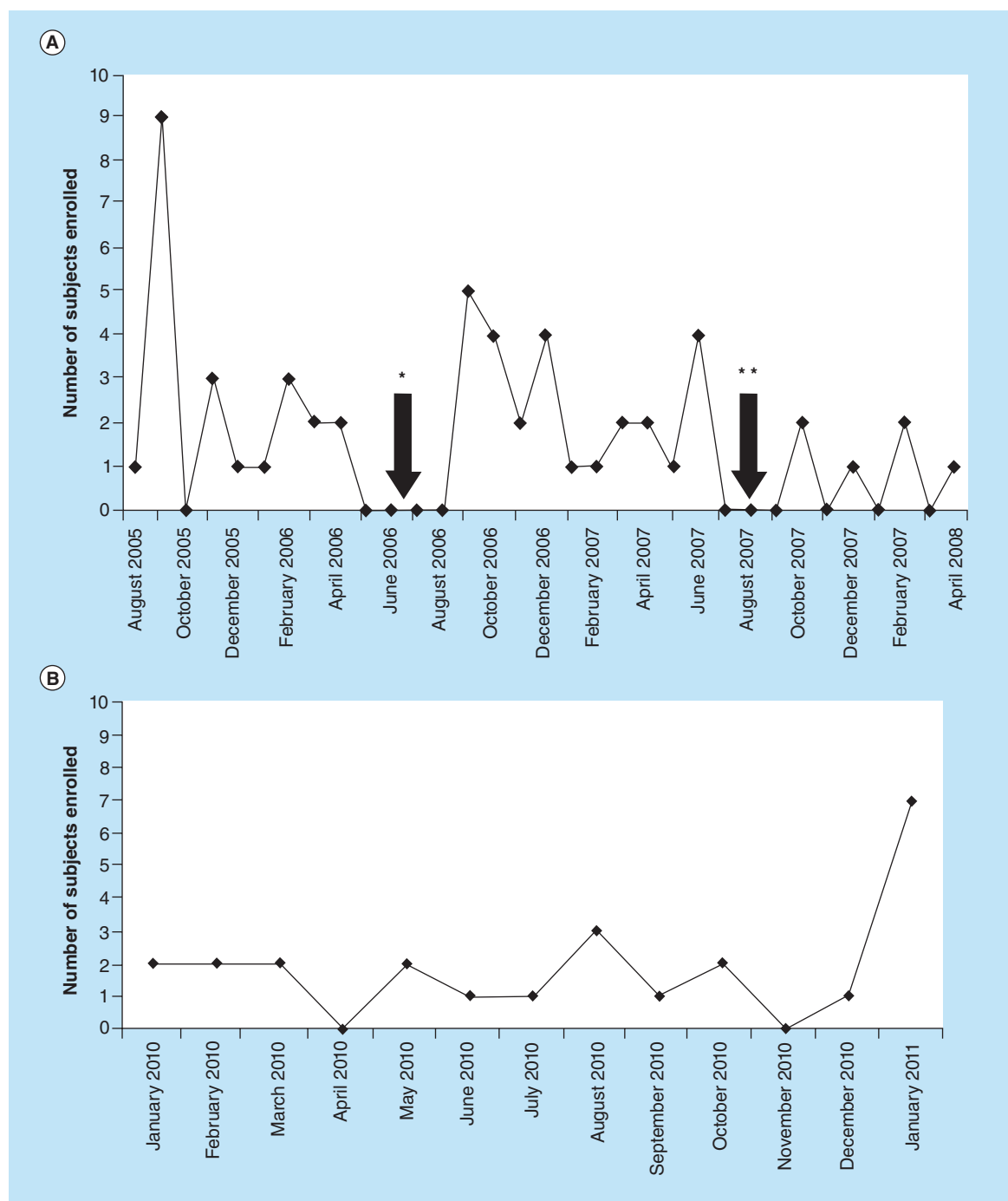


Figure 3. Enrollment dynamics for analyzed studies. (A) Study VLU1 enrollment profile and (B) Study VLU2 enrollment profile. The arrow marked with * corresponds to the transition of the leadership of the study from a principal investigator in the Department of Dermatology to one in the Division of Vascular and Endovascular Surgery. The arrow marked with ** corresponds to a change of study coordinator.

Study compliance (e.g., drop-out rates, deviations, adherence to study protocol, and so on) and safety profile was monitored in conjunction with the implementation of strategic management tools in order to assess their value on the improvement of study efficiency and performance.

Results

Assessment of VLU1, revealed that there was a decrease in subject enrollment associated with the change in study coordinator, transition of the study between clinical departments and the change in principal investigator (Figure 3A). The VLU2 study demonstrated

smoother enrollment dynamics (Figure 3B), which can be attributed to better study performance monitoring and improvement in study personnel training.

In our risk analysis matrix (Figure 1B), based on our experience with VLU1, the following categories were ranked as high impact and high probability: ‘small number of patients with VLU disease’ was ranked as 4 out of 5 in probability, 5 out of 5 in impact and the derived total calculated risk score was $4 \times 5 = 20$. Other significant risk factors of high impact linked to start-up activities included delays with IRB/regulatory approv-

als with an impact 4 out of 5 and probability 5 out of 5 with a derived calculated risk score of $5 \times 4 = 20$ (Figure 1B). In comparison, a medium risk was associated with change in study staff with impact 4 out of 5 and probability 3 out of 5 and a calculated risk score of $4 \times 3 = 12$ (Figure 1B).

The factor of ‘small number of patients with VLU disease’ and ‘delays with start-up activities’ were subjected to more detailed analysis in order to assess what contributed to their occurrence. Specifically, root cause analysis of VLU 1 study was performed retrospectively

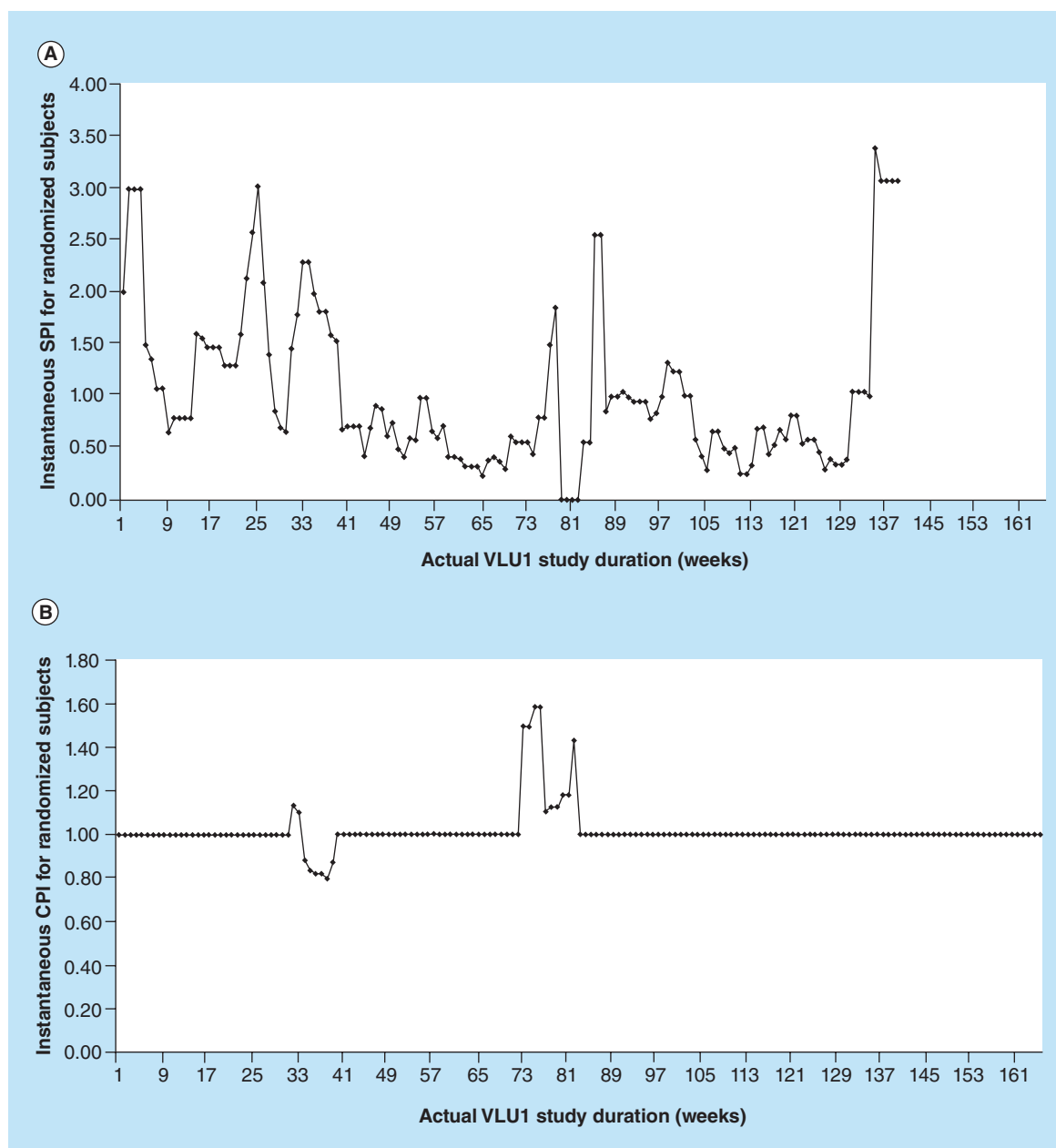


Figure 4. Assessment of instantaneous parameters for VLU1 study for 165 weeks of actual study duration.

(A) Instantaneous SPI; (B) instantaneous CPI.

CPI: Cost performance index; SPI: Schedule performance index; VLU: Venous leg ulcer.

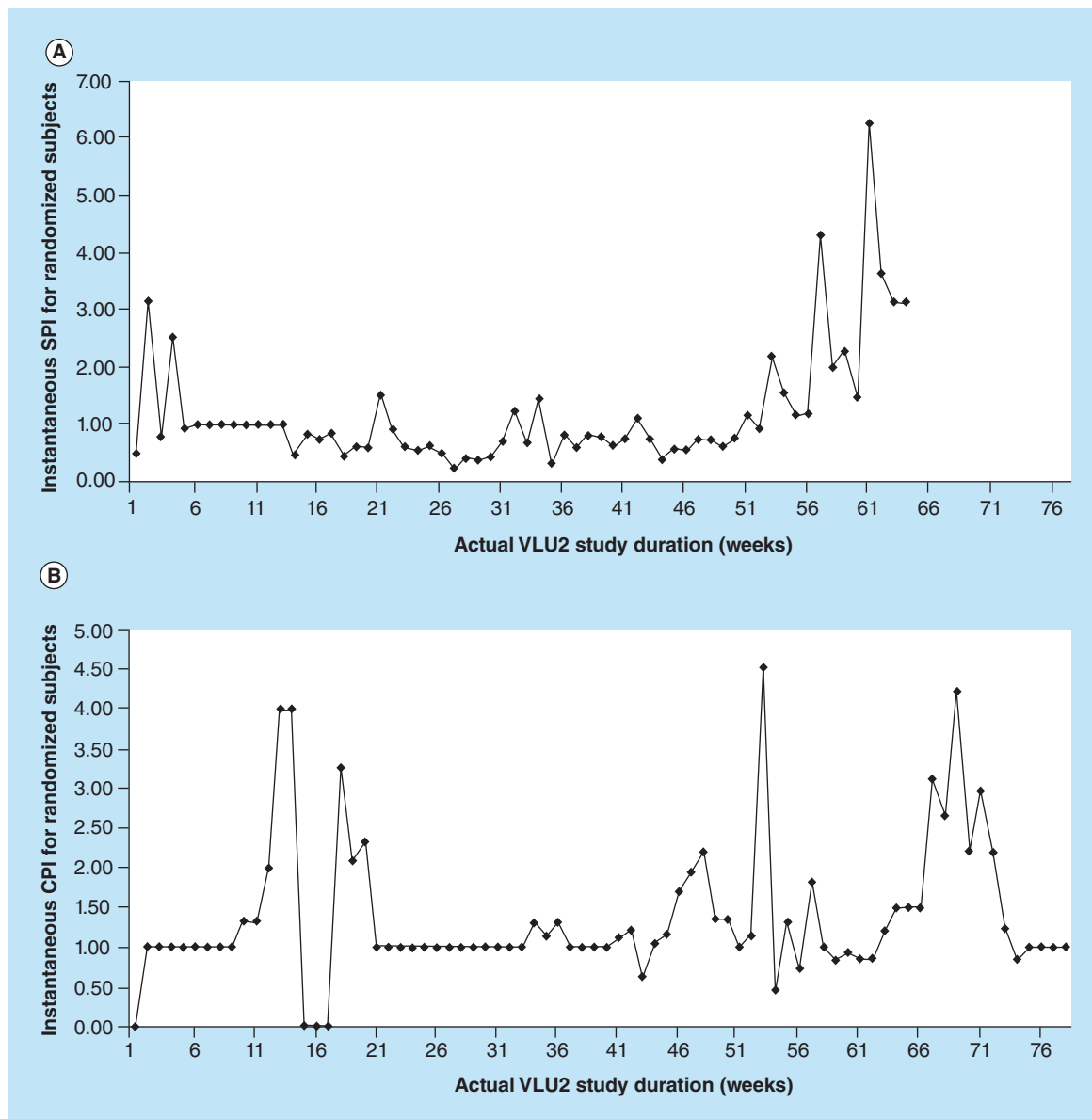


Figure 5. Assessment of instantaneous parameters for VLU2 study for 77 weeks of actual study duration.

(A) Instantaneous SPI; (B) Instantaneous CPI.

CPI: Cost performance index; SPI: Schedule performance index; VLU: Venous leg ulcer.

in order to improve the VLU2 study performance (Figure 2A & B). This analysis revealed that lack of in-hospital advertisement of the clinical trial in other departments and areas of the hospital (e.g., specialty clinics waiting areas, hospital lobby, among others) may contribute to unawareness of the trial by potential research subjects (Figure 2A). High drop-out rates can be addressed by monitoring of adverse events by study doctors and high screening failure rates can be mitigated by putting efficient prescreening procedures in place (Figure 2A). We have determined that these two contributing factors once mitigated can yield increased enrollment rates and improve compliance.

Assessment of instantaneous SPI and CPI parameters for the VLU1 study demonstrated many fluctuations over the 165 weeks of actual study duration (Figure 4A & B) compared with those parameters for the VLU2 study during 77 weeks of actual study duration. (Figure 5A & B). We concluded that these fluctuations in SPI and CPI instantaneous parameters in VLU1 study occurred because this study was not well controlled or monitored with regards to schedules or costs and several risk factors may had an impact on the study performance and efficiency. Remarkably, SPI and CPI parameters increased dramatically during the last 20 weeks for the VLU2

study (Figure 5A & B). This can be attributed to successful implementation of strategic management techniques and improvement in risk management.

Compared with planned SPI parameters, which were estimated based on the assumption that two subjects would be enrolled per month for each study (Supplementary Figure 1A & 2A), the actual cumulative SPI at 50% of study completion was 0.39 and 0.74 for VLU1 and VLU2, respectively (Supplementary Figure 1B & 2B). VLU1 was behind schedule due to low and inconsistent enrollment caused by study staff changes and inexperience (Supplementary 1B). As a result, the VLU1 study duration was extended by 26 weeks (165 weeks total) to reach enrollment goals. The VLU2 study was completed in 77 weeks as planned (Supplementary Figure 2B).

The cumulative CPI at project completion was 1.0 and 1.2 for VLU1 and VLU2, respectively, indicating that both studies were on planned budget. However, the VLU2 study was more cost efficient and made more profit (Supplementary Figures 1B & 2B).

Implementation of strategic trial management tools, such as interim monitoring of SPI, CPI and compliance, resulted in the completion of the VLU2 study as scheduled with higher randomization rates compared with the VLU1 study (Figure 6A & B).

Screening failure rates were 54.7 and 33.3% for the VLU1 and VLU2 studies, respectively. The higher screening failure rate for the VLU1 study was attributed to the lack of prescreening activity.

The most common severe adverse event reported for both studies was cellulitis of target wound unrelated to study drug (Supplementary Figure 3A & B). The compliance assessment revealed 128 deviations for VLU1 and 36 deviations for VLU2 (Supplementary Figure 4A & B). The most common categories for both studies included out-of-window visits and missed study procedures (Supplementary Figure 4A & B).

As a result of strategic management tools implementation, study compliance was improved: number of protocol deviations and adverse events was decreased in the VLU2 study by 28 and 33.3%, respectively (Supplementary Figures 3 & 4).

Discussion

The success of a clinical trial heavily relies on the strong bond between clinical trial operations and project management throughout the life cycle of the trial [9,13]. It is crucial to perform a risk analysis at the beginning of the study and reassess this analysis as the study progresses [9,13]. Likewise it is important to develop a specific knowledge of the strengths, weaknesses and pitfalls of assumed risks in order to

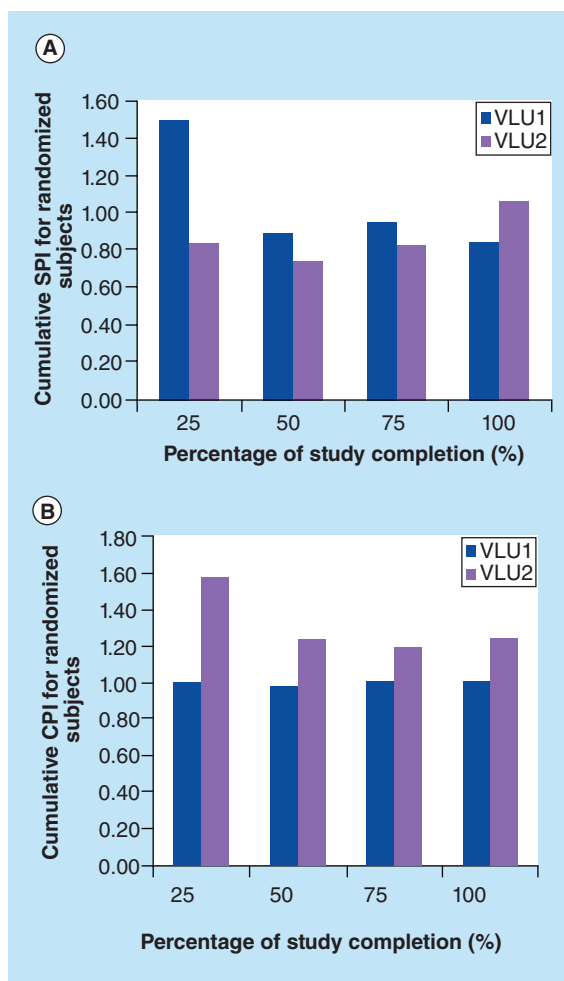


Figure 6. Comparison of two studies progress at different completion points based on randomization rates.

(A) Cumulative SPI for VLU1 and VLU 2 studies; (B) cumulative CPI for both studies.

CPI: Cost performance index; SPI: Schedule performance index; VLU: Venous leg ulcer.

devise a comprehensive strategy to mitigate them [13]. In doing so, important aspects inherent in proper planning, implementation and execution of projects should be considered [8,9].

Based on our retrospective review of the VLU1 study risks (Figure 1), we were able to perform a root cause analysis for two major risk categories for the VLU1 study (Figure 2A & B).

If competing physicians within a hospital specialize in treatment of the disease under investigation the investigator's access to the study population may be affected and this may lead to lower than expected patient enrollment. (Figure 2A). One way to address this risk factor is to make such physicians co-investigators in ongoing clinical trials and make them own a part of the project.

Delays with start-up activities can be addressed by improving communications with regulatory authorities (e.g., IRBs), setting up and testing study logistics (clinical space, pharmacy availability, and so on) prior to first patient enrollment, resolving all space/scheduling conflicts prior to initiation of the study, training study personnel ahead of time (Figure 2B).

If a delay occurs in the start-up phase of a clinical trial it can dramatically impact study progress. Duration of enrollment can affect participation of a particular clinical site in the trial. It is vital for clinical trial to shorten start-up phase in order to have smooth transition to execution phase and allow more time for enrollment of research subjects.

Findings of risk analysis were implemented to improve performance of the VLU2 study. Specifically, by addressing 'root causes' determined in VLU1 root cause analysis, the start-up time and clinical trial accrual rates was significantly improved in VLU2 study.

In clinical trials strong strategic management initiatives involve the creation of simple processes tailored to monitor the efficiency at the onset of the project to achieve a smooth execution [13]. It is important to create tools that integrate all functions outlined in the project plan to allow enough flexibility to make adjustments as needed throughout the progression of the project [8–9,13]. In order to achieve

Executive summary

Background

- Costs associated with the implementation of clinical trials have become an increasingly important issue.
- The development of a comprehensive project plan provides the basis for successful trial implementation and execution. The project plan embodies tools to adequately assess anticipated potential obstacles and risks while creating contingency plans.

Methods

- In order to develop and implement strategic management tools to improve performance and compliance of wound care clinical trials we analyzed two similar clinical trials testing fibroblast cell-based agents for chronic venous stasis leg ulcers (VLUs).
- Study efficiency was measured using the weekly cumulative cost performance index (CPI). Study enrollment dynamics was monitored using the schedule performance index (SPI).
- Study compliance was assessed based on deviations according to the following categories: missed visits, out-of-window visits, drop-out rates, missed study procedures and study drug discrepancies. Safety profile was assessed based on severe adverse events reported.

Results

- We performed retrospective risk assessment analysis based on our experiences with VLU1 study. A risk matrix was used during risk assessment to define the various levels of risk as the product of the probability of occurrence and impact categories. Root cause analysis was performed for two major risk categories.
- Due to lack of prescreening in VLU1, the screening failure rate was 54.7 and 33.3% for VLU1 and VLU2, respectively. The SPI at project completion was 0.58 and 1.0 for VLU1 and VLU2, respectively. VLU1 was behind schedule due to low and inconsistent enrollment caused by study staff changes and inexperience.
- Implementation of strategic trial management including interim monitoring of SPI, CPI and compliance resulted in VLU2 to be completed on schedule with higher randomization rates. The CPI at project completion was 1.0 and 1.2 for VLU1 and VLU2, respectively, indicating that both studies were conducted according to planned budget.
- As a result of strategic management tools implementation, study compliance was improved: number of protocol deviations and adverse events was decreased in the VLU2 study by 28 and 33.3%, respectively.

Discussion

- In clinical trials, strong strategic management initiatives involve the creation of simple processes tailored to monitor the efficiency at the onset of the project to achieve a smooth execution.
- It is important to create tools that integrate all functions outlined in the project plan, which will enable managers to improve the efficiency of clinical trials, reduce costs and achieve milestones in a timely manner.

Conclusion & future perspective

- Internal auditing is a critical tool for improvement of site performance in prospective wound care studies.
- Although SPI, CPI and earned value are widely used in a business world as project management tools, this is a pilot attempt to adopt these parameters to clinical trials.
- Implementation of strategic management tools yielded higher enrollment and better compliance rates for the VLU2 study. We hope that these tools will be widely adopted to monitor efficiency and performance of clinical trials.

this goal at the planning stage, we decided to focus on two major parameters that are indicative of study progress and intimately interconnected: enrollment rates and costs. We have developed and utilized instantaneous and cumulative scheduled performance and cost performance indexes. This allowed us to monitor study progress throughout life cycle of the project and intervene, if necessary.

Implementation of these strategic management tools led to the more efficient study conduct for the VLU 2 study compared with the VLU1 study (Figure 6). Also, enrollment goals were achieved in a much shorter period time. Utilization of CPI and monitoring of instantaneous and cumulative CPI allowed both the VLU1 and VLU2 studies to stay within the planned budget (Supplementary Figures 1A & B, 2A & B). However, the VLU2 study was more cost efficient and more profitable (Supplementary Figures 1B & 2B).

Overall, utilization of CPI and SPI management tools resulted in better compliance rates (number of protocol deviations and adverse events was decreased in the VLU2 study by 28 and 33.3%, respectively (Supplementary Figures 3 & 4), faster achievement of enrollment goals, shorter accrual periods and containment of the planned costs. We would recommend these strategic management tools to be utilized in the other therapeutic fields when conducting clinical trials. We believe it will allow researchers and project managers to improve the efficiency of clinical trials, reduce costs and achieve milestones in a timely manner.

Conclusion & future perspective

The development of a comprehensive project plan as a foundation, including tools to adequately assess anticipated potential risks with contingency plans, will provide the basis for successful implementation and execution of a clinical trial. Identification of key study personnel with relevant skills and appropriate experience leads to successful and efficient study execution. The development of a training program

for study personnel must be established so as to effectively implement strategies. Priority should be given to the development of effective models of communication. This ensures efficient interactions among the members of the project team internally and externally. It is also important to track key study parameters (e.g., SPI, SPI and EV) in order to measure the true study progress at any given point of time.

In this article we have developed and successfully implemented strategic management tools such as SPI and CPI which yielded higher enrollment and better compliance rates for the VLU2 study as compared with the previously conducted VLU1 study. Thus, internal auditing with incorporation of these project management tools was crucial to improvement of clinical study performance.

As costs associated with conducting clinical trials continue to raise it will be critical to control completion of major milestones, increase efficiency and improve quality of clinical research projects. Adoption of widely accepted strategic management tools can assist project managers overseeing clinical trials in achieving these goals and enable them to assess performance of a project during execution phase, improve quality and mitigate risks in a proactive fashion.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/full/10.4155/CLI.15.30

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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