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Research Article

Implementation of quality and risk management strategies in wound care trials

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ABSTRACT

Background: Systematic analysis of risk factors in multiple wound care clinical trials was performed to develop proactive risk mitigation strategies and improve the quality of trials conducted.
Methods: This internal, single center internal quality control (QC) audit of eight recently completed prospective, randomized wound care clinical trials assessed the rate of serious adverse events (SAEs) and compared two wound indications: diabetic foot ulcers (DFU) and venous leg ulcers (VLU). Additionally, adherence to study protocol and compliance with current regulatory requirements was examined based on the rate of protocol deviations over time.
Results: A comparison of SAE occurrences between DFU and VLU studies showed twice as many SAEs per subject in the DFU studies as compared to the VLU studies. The most common categories were infections, both of the wound and of other anatomic locations. The onboarding of new study coordinators and multiple coordinators working independently on one trial over time consistently showed an increase in the number of deviations per active subject, particularly immediately following the date of hire. The most common categories for deviations were out-of-window visits and missed study procedures.
Conclusions: Assessment of potential issues in prospective wound care studies can lead to earlier mitigation of risks, quality improvement in data obtained and increased efficiency of studies conducted in this field. Effective training and retention of research coordinators can reduce the number of deviations, and an understanding of the frequency and types of adverse events can provide an expectation for those conducting trials in a particular indication..

Keywords: Quality control, Process improvement, Risk management, Development of corrective and preventive actions (CAPA), Wound care trials

INTRODUCTION

Clinical trials in the field of wound care require resources, staff's time, and significant effort from both the study sponsors and participating sites. In the clinical trial execution phase, it is necessary to maintain a balance between efficient, expeditious study conduct and data of high integrity that preserves subjects safety.[1] The ability to predict potential issues in compliance subjects and safety during the start up phase of the study and to develop mitigation strategies to reduce or eliminate these risks is a valuable asset in clinical trial management.

With the recent U.S. Food and Drug Administration (FDA) draft "Guidance for Industry: Oversight of Clinical Investigations - A Risk Based Approach to Monitoring" issued in 2013, sponsors and contract research organizations (CROs) have begun to focus on the risks specific to a particular study protocol as they relate to data integrity and protection of study subjects.[2,3] When drafting a monitoring plan, the FDA suggests consideration of, among other factors, the therapeutic area, complexity of study protocol, and study population with regards to specific safety concerns.[2] Adoption of this new monitoring approach has led to greater pressure upon

individual sites to establish their own quality management systems and metrics.

Historically, monitoring and management in clinical trials focused on collecting information and analyzing errors at the end of the study, when it is often too late to address problems.[4] Constant monitoring and analysis of quality throughout the course of a clinical trial can mitigate risk in real time and enable rapid correction of emerging or repetitive problems. The use of key risk indicators in clinical trials prior to the study can assist when creating a monitoring and contingency plan during the initiation phase and can assist with decision making during the course of the study. These key risk indicators are measures of possible future adverse impact, and include error rates and data quality specific to the trial being considered. Some of these indicators are consistent across most or all clinical trials, such as number of queries or time to resolve queries, and some may be specific to a particular indication or type of clinical trial and are determined based on data from previous studies.[4]

This analysis was performed to establish pattern of risk factors at a single center in multiple wound care clinical trials in order to develop proactive risk mitigation strategies and improve the quality of trials conducted. Serious adverse events (SAEs) were used as an indicator of possible safety considerations during wound care trials, and deviations were used to assess protocol adherence and site compliance with good clinical practices. Quality control at the site level in the execution phase of wound care clinical trials is critical to producing high integrity data that protects the human subjects involved in research and helps achieve the study's objectives, particularly as biomedical research moves towards a risk based monitoring approach.

METHODS

A single-site internal audit of eight recently conducted prospective, randomized quality control wound care clinical trials was performed as given in Table 1. These studies have similar objectives, study design, inclusion/exclusion criteria, and outcomes. The rate of serious adverse events (SAEs) and protocol deviations was assessed and compared between two wound types: diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs).

Diabetic foot ulceration is most commonly caused by diabetic neuropathy, either alone, or in combination with peripheral vascular disease. Other complicating factors of the wound can include microvascular disease, decreased joint range of motion, and increased susceptibility to infection of the diabetic population. These wounds are the most common cause of amputation in the diabetic population, and are traditionally treated with off-loading and sharp debridement, however, DFUs are a target for many emerging technologies.[5] Venous leg ulcers are wounds resulting from venous hypertension, which is the result of venous reflux or obstruction. Numerous treatments for these wounds exist, however, the most widely used include some type of debridement in combination with compression dressing.[6] Given the systemic impact of diabetes, it was hypothesized that the DFU subjects would have a greater number of serious adverse events as compared to the VLU subjects.

Table 1: Duration of each study included in the analysis and number of subjects consented.

Study	Duration	No of Subjects Consented
VLU-1	September 2005 – April 2008	53
VLU-2	January 2010 – May 2011	23
VLU-3	October 2012 – July 2014	40
VLU-4	December 2012 – August 2013	17
VLU-5	March 2013 – April 2015	11
VLU-6	October 2013 – December 2014	6
DFU-1	November 2013 - December 2015	24
DFU-2	May 2014 - April 2016	30

As part of standard clinical research operations at our site and as a method of maintaining and assessing metrics in real time, a log of serious adverse events (SAEs) tracking is maintained by principal investigators and study coordinators for each study documenting event start and end date, the date the event was reported to the sponsor and regulatory groups, severity, expectedness, and relatedness to the study procedure or drug. Similarly, a log of protocol deviations is maintained for each study recording the date of the deviation, a description of an issue, and when the deviation was reported to the IRB. These tracking tools were used in this analysis.

Each adverse event was classified into one of the ten categories as given in Table 2 and stratified by relationship to the study product and procedures to better understand the correlation between type of event and wound etiology. An assessment of expectedness of the event was performed by principal investigator or designee based on the study's Investigator Brochure (IB) for drug trials or User Manual for device trials.

Adherence to study protocol and compliance with current regulatory requirements was examined based on the rate of protocol deviations within the context of study personnel changes. In particular, deviations per active subject (including those who were consented, but failed to qualify during the screening period) was calculated to prevent artificial inflation of deviation number at times of higher enrollment.

To elucidate the major causes of protocol deviations in wound care studies, each deviation was categorized into one of the categories as shown in

Table 3. For deviations, Cause-Effect analysis was performed based on the most common reasons for protocol deviations based on our experiences while conducting those trials as given in Figure 5.

Table 2: Categories applied to SAEs.

Category of Serious Adverse Event
Wound Infection (target or other)
Infection (non-wound)
Worsening of Wound (target or other) / Wound Re-Opening
Myocardial Infarction / Cardiac Arrest
Gastrointestinal Problem
Wound Pain
Pain (unrelated to wound)
New Wound
Allergic Reaction
Other

Table 3: Categories applied to deviations in the current analysis.

Category of protocol deviation
Study visit out of protocol window
Study visit missed
Use of prohibited concomitant medication
Test article handling
Study procedure not performed or performed late
Eligibility criteria not met
Other

RESULTS

A comparison of serious adverse events between the DFU and VLU studies analyzed showed an average of 0.30 serious adverse events per subject in the DFU population as compared to an average of 0.15 SAEs per patent in the VLU population (Figure 1). There were no SAEs deemed to be related to the study drug/device or procedure in any of the eight studies analyzed, and most were associated with known pre-existing conditions. Three of the SAEs in the VLU studies were considered life threatening or were ultimately fatal, whereas none of the SAEs in the DFU studies fell into this category. There were a total of 15 SAEs in all of the DFU studies analyzed. Three of the 15 (20%) were considered "expected" based on the known risks of the product or device published by the sponsor in the Investigator Brochure (IB) or User Manual for devices, whereas 4 of the 24 (17%) VLU study subjects' SAEs for the VLU studies analyzed fell into this category as shown in Figure 2. Overall, 18% of SAEs in the DFU and VLU studies analyzed were considered expected.

SAEs related to wound infections were most common in both wound etiologies (Figure 3). Twelve out of the 24 (50%) of the SAEs reported in the VLU studies were related to wound infections, both of the target wound and of additional wounds affecting the subject during the course of the study. Similarly, 7 out of the 15 (47%) SAEs reported in the DFU studies were related to wound infections as given in Figure 3.

DFU subjects had a slightly higher prevalence of gastrointestinal problems and infections unrelated to the wound as compared to the VLU counterparts as given Figure 3. Two DFU subjects reported SAEs in each of those categories, as compared to only one VLU subject. Serious worsening of the wound reportable as an SAE occurred for one subject in each of the two wound etiologies. During the course of the studies, two VLU subjects suffered from a myocardial infarction resulting in death, whereas no DFU subjects suffered cardiac complications during the time period assessed. Serious pain leading to hospitalization was reported by one DFU subject.

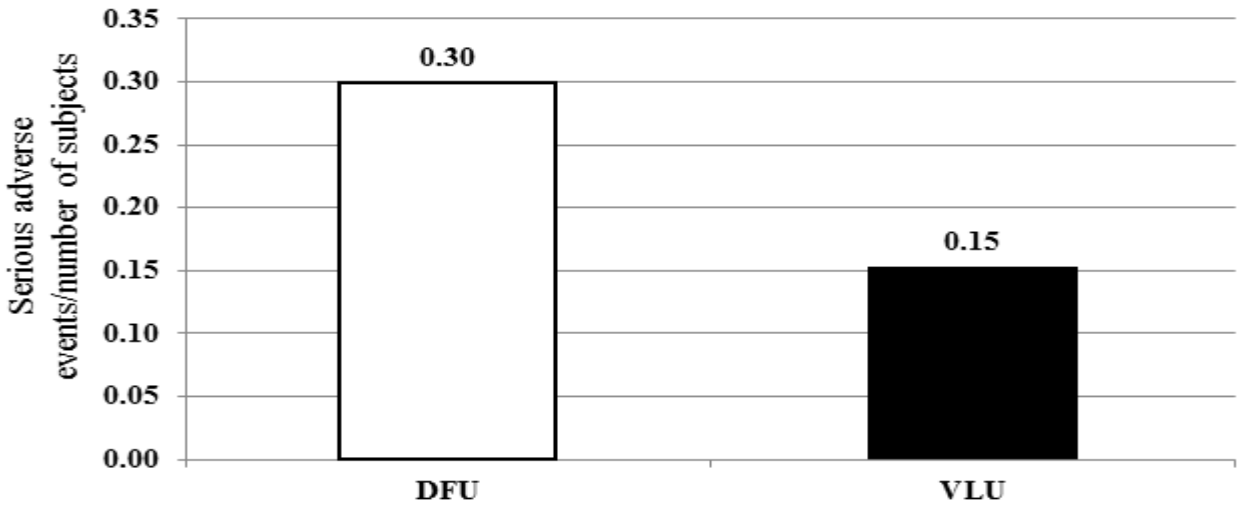

Figure 1: Comparison of serious adverse events (SAEs) per enrolled subject.

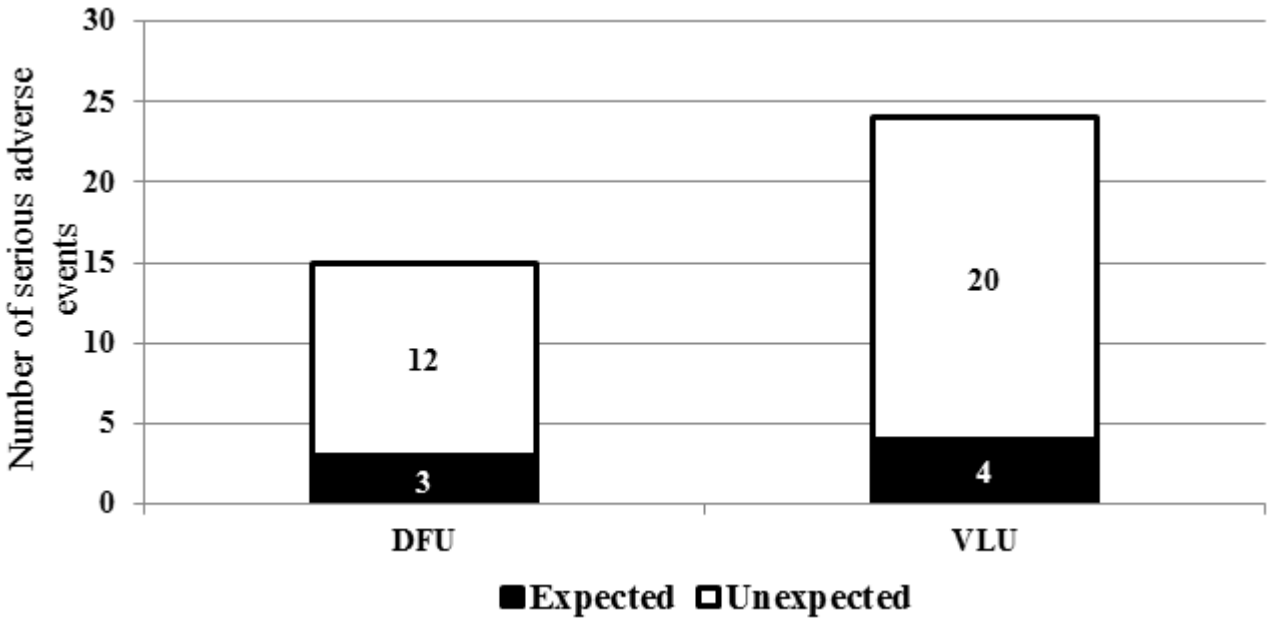

Figure 2: Assessment of the expectedness of SAEs.

Adverse events observed during the execution phase of VLU and DFU studies were analyzed based on prior established expectedness profile and previous reported/documented experiences with the test article (i.e. investigational drug or device).

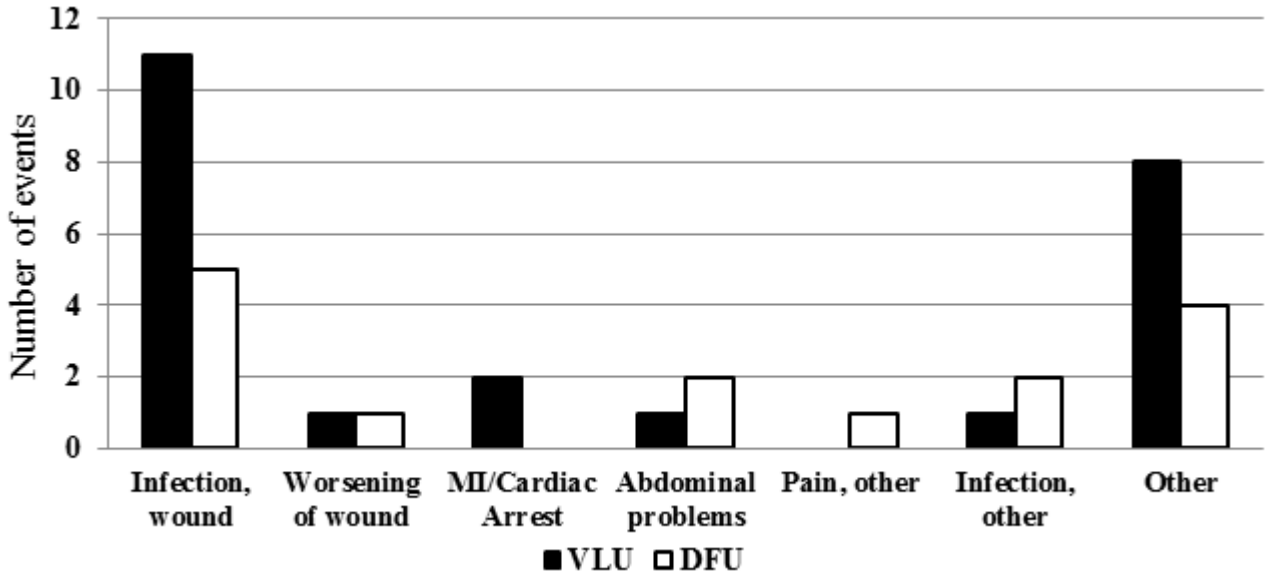

Figure 3: Comparison of the types of SAEs between the DFU and VLU studies.

Adverse events based on our experiences with DFU and VLU clinical trials were analyzed. SAEs related to wound infections represented the most common category in both wound etiologies. None of the adverse events were deemed to be related to the test article but were rather related to pre-existing conditions.

In both DFU and VLU subjects, a high number of SAEs were categorized as "other." For the DFU subjects, these events included an acute deep vein thrombosis, recurrent peripheral vascular disease, and a fever of unknown origin leading to hospitalization. In the VLU population, these events included overgrowth of hypertrophic tissue in the target wound, worsening of venous insufficiency, worsening of coronary artery disease, pulmonary edema, lightheadedness, and two separate incidences of hospitalization due to shortness of breath. A subject in the VLU 1 study was hospitalized due to a tonic-clonic seizure that resulted in removal from the study. This event was deemed not related to study drug and/or procedures by both the site investigator and medical monitor. However,

the subject missed several dosages of study drug and per study protocol was no longer eligible to further participate in the study.

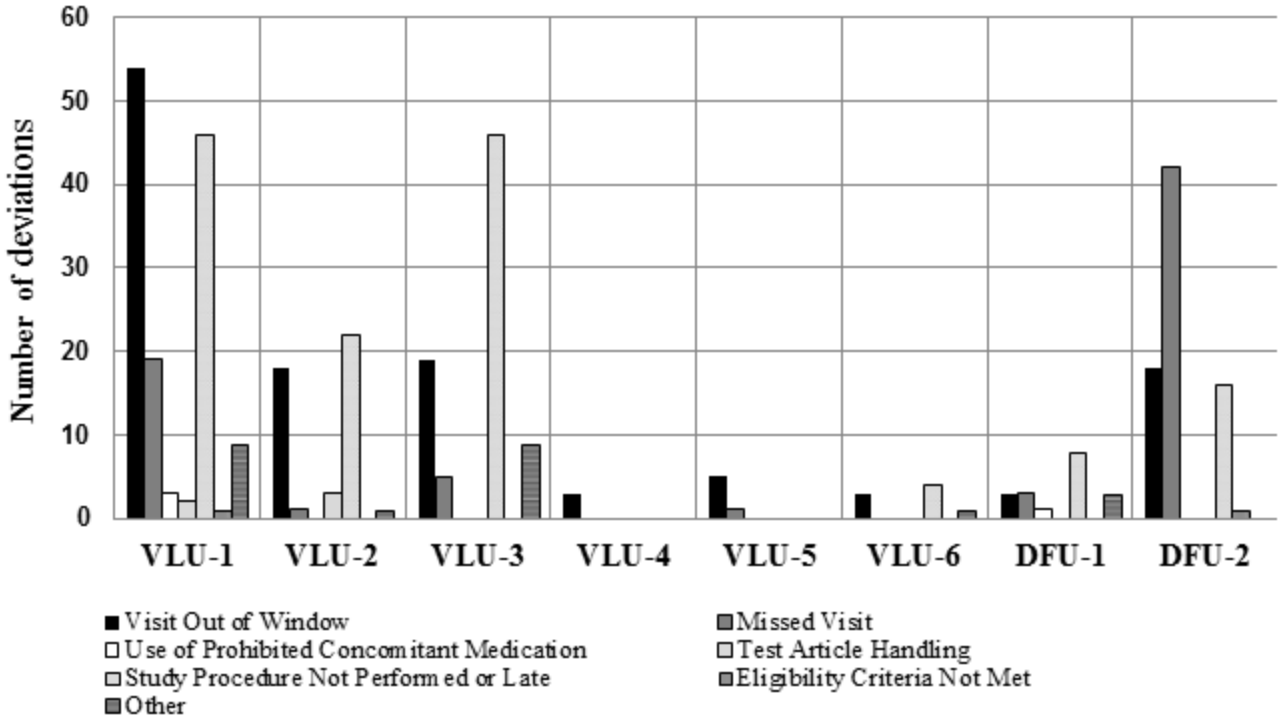

Figure 4: Analysis of the categories of protocol deviations per VLU and DFU studies.

Main categories are based on our experiences while conducting VLU and DFU studies.

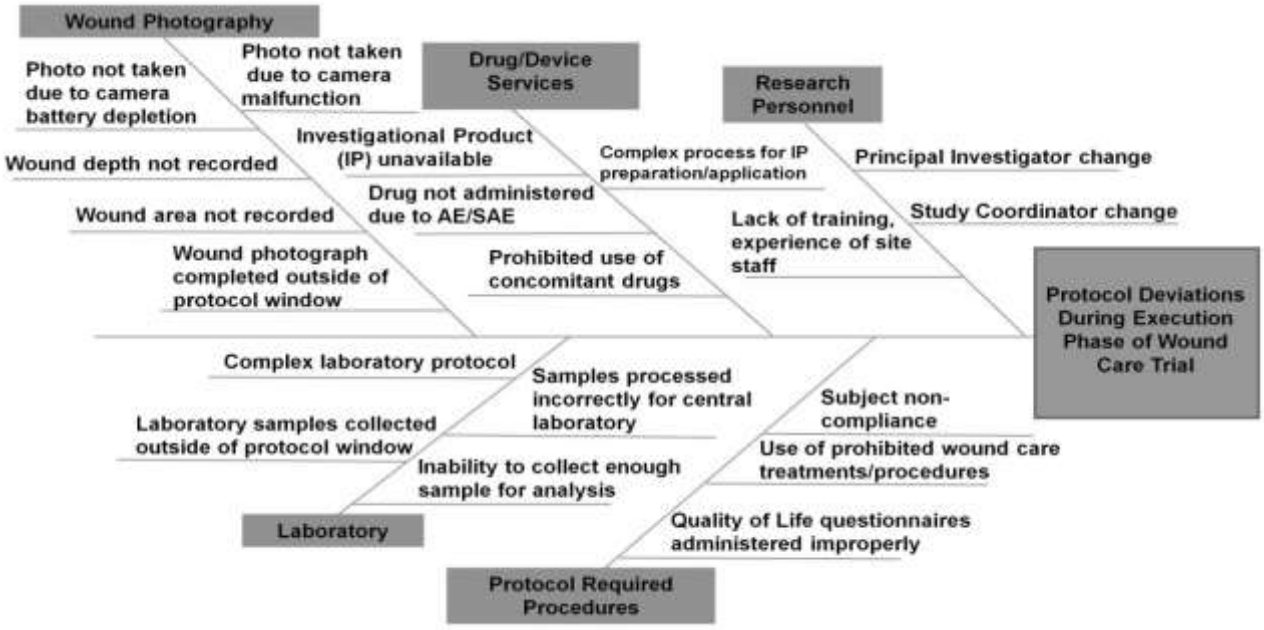

Figure 5: Cause-effect analysis of factors contributing to protocol deviations during execution of the DFU and VLU studies.

An analysis of deviations during the execution of the trials demonstrated that the most common causes for non-adherence to study protocol in these wound care trials were missed visits, visits out of window, and study procedures not performed or performed late, which was consistent between the VLU and DFU studies a shown in

Figure 4. When comparing the trials, deviations were largely dependent on the specific trial, and were unrelated to wound type. For example, 41% of the deviations in the VLU-1 study were due to visits that took place outside of the visit window specified in the study protocol, 14% were due to missed visits and 34% were caused by study procedures not being performed or being performed late. Conversely, in the VLU-3 study, 24% of deviations were due to visits out of window, 6% were due to missed visits and 58% were due to study procedures not being performed or being performed late. Cause-Effect analysis of the category "study procedures not performed or performed late" was performed to further investigate contributing factors leading to this type of deviation as given in Figure 5. This analysis showed that these types of deviations are most frequently associated with wound photography, drug or device services, laboratory testing, and protocol required procedures such as administration of quality of life questionnaires and subject non-compliance. Specific issues contributing to these main categories included improper use of equipment or the continued use of non-functioning equipment, personnel changes, inadequate lab samples, and the use of protocol prohibited drugs or wound treatments.

Deviations were then considered in terms of the number of deviations per active subject over time, to provide insight as to the effect of personnel changes and study staff management on protocol adherence as shown in Figure 6. The on-boarding of new study coordinators consistently showed an increase in the number of deviations per active subject within the months following initial hire, which generally tapered off over time. One example is with the on-boarding of two new study coordinators in September and October of 2013, which showed an increase from no deviations per subject in August 2013 to an average of 1 deviation per subject in November 2013 across these studies. Additionally, multiple study coordinators working on a single study individually with little overlap increased the number of deviations. For example, in VLU-3, managed by four different study coordinators over 21 months, there were a total of 79 deviations and 40 subjects (0.09 deviations per subject per month), compared to 18 deviations in DFU-1, a study managed by one coordinator over 25 months with 24 consented subjects (0.03 deviations per subject per month) as seen in Figure 6. Conversely, a greater number of study coordinators working on one study concurrently with one another was correlated with a decrease in overall protocol deviations, with one or more coordinators acting as a "backup".

VLU-2 was primarily conducted by one research coordinator acting alone, and had a greater number of protocol deviations per subject as compared with later studies, which were conducted at the same time as one another and involved multiple coordinators working on the same projects as given in Figure 6.

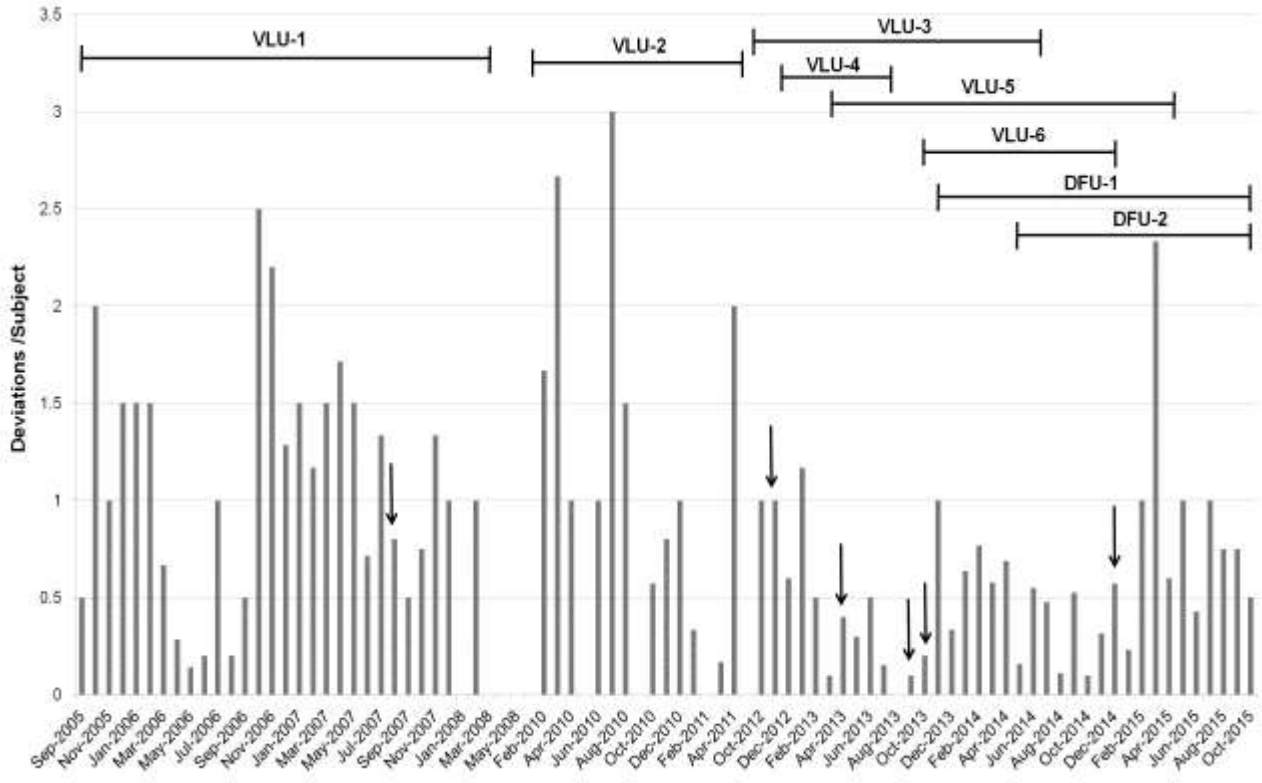

Figure 6: Collective protocol deviations per enrolled subject as a function of time.
Arrows indicate a change in research coordinator. Bars indicate study duration for individual studies.

VLU-1 had the greatest total number of deviations, contrasted with VLU-2 which had a 66% reduction in deviations as compared to VLU-1. The number of deviations in the rest of the studies analyzed was never as high as VLU-1, (Figure 7) which can be attributed to implementation of quality improvement techniques, better training of study personnel and proactive assessment of risks. An increase was seen when comparing DFU-1 to DFU-2, which could be the result of larger number of subjects enrolled, as seen in Figure 7, or the fact that there was coordinator turnover during the study, as compared with DFU-1 which was managed by only one coordinator for its duration.

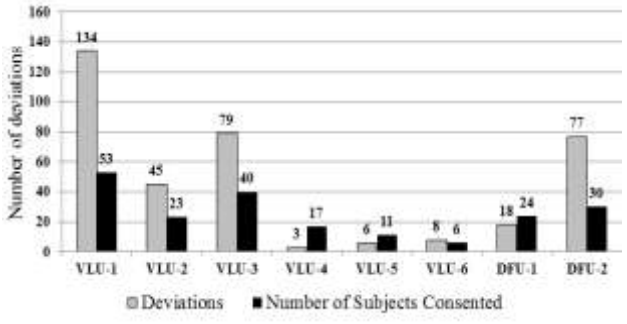

Figure 7: Assessment of total number of protocol deviations as compared to enrolled subjects.

DISCUSSION

Clinical trials in wound care are often initiated to evaluate the safety and efficacy of a particular drug, device, or technique as it relates to the treatment of wounds of a specific etiology. The recording and analysis of quality metrics can be used to identify trends or activities that may detract from the desired outcomes of a study, or that could compromise the integrity of the data collected or present risks to the subject safety.[1] Risk-based monitoring guidelines recently issued by the FDA triggered the need for development of more robust quality assements tools and effective metrics. These can help to assess and mitigate potential risks and pitfalls during study execution phase at the participating clinical site level.

Site monitoring by the sponsor or a designated contract research organization is dependent upon the site for quality control and assurance techniques to avoid future problems when the drug or device is launched. Nevertheless, few sites have adequate techniques in place to detect scientific and operational risks via quality systems beyond responses to site audits, which are often reactionary and not based on proactive assessments by site personnel as part of an ongoing quality assessment effort.[7] Even with traditional, non-risk based, full on-site data monitoring (i.e. 100% source verification data collected by the sponsor or CRO), findings during site visits can often reveal missed opportunities for risk identification and implementation of contingency strategies during study execution. Reviewing the risks of a clinical trial protocol during study start up based on the protocol required procedures, known complications for the indication or disease being studied, and potential site related risks such as personnel turnover and data quality is the key to risk-based monitoring. This approach allows monitors to troubleshoot problems and streamline decision making proactively.[8]

The objective of this analysis was to use tools in place at a single site in order to conduct an assessment of potential difficulties in prospective wound care clinical trials, which can lead to earlier mitigation of risks, quality improvement in data obtained, and increased efficiency of studies conducted in wound care. By using SAEs as a representative metric of subject safety in the execution of these clinical trials, and using deviations as a measure of protocol adherence, quality control of trial execution and predictive risk identification was possible. Though it is difficult to predict the risk of severe adverse events for a particular clinical trial prior to study initiation, it is necessary to monitor and evaluate these events during study execution in order to prevent serious safety concerns for study participants.[9] By identifying adverse events that are more commonly affiliated with particular disease states, sponsors and sites can set expectations for what might be seen when conducting different wound care studies and develop strategies for safety and operational risk mitigation.

Our analysis compared subjects with diabetic foot ulcers to those with venous leg ulcers, two largely different conditions that we predicted would be related to unique categories of SAEs. Analysis of the serious adverse events in the eight studies included in this investigation showed twice as many SAEs per subject in the diabetic cohort as shown in Figure 1. Additionally, as expected, these events were more diverse in the DFU population than the VLU population. The SAEs experienced by the VLU subjects were largely related to the target wound itself, or to cardiovascular complications of pre-existing conditions as noticed in Figure 3. Conversely, the events experienced by the DFU population were more diverse and often affected multiple organ systems. Nevertheless, the percentage of serious adverse events that were considered "expected" was greater in the DFU studies as compared to the VLU studies, which may be the result of more repetitive events between subjects across all sites or a greater understanding of the potential risks inherent to the DFU products which were same as the events observed in Figure 2.

There is currently no regulatory guidance on the assessment, classification or reporting of deviations as there is with adverse events and safety reporting. Deviations from the study protocol can lead to compromised subject safety and the collection of inaccurate data, placing the integrity of the trial at risk. Despite proactive actions to eliminate these events, protocol deviations are likely to occur in most clinical

trials.[10] By recording and analyzing these protocol deviations at our site, strategies to reduce these events have been developed and specific trends have been identified that have reduced the number of deviations per subject over time. The dramatic reduction of protocol deviations between VLU-1 and VLU-2 was largely the result of the implementation of strategic quality management tools, such as interim internal monitoring, close supervision of cost and performance goals, and assessment of quality metrics throughout the execution phase of the trial as seen in Figure 7. Cause-Effect analysis for each specific study was also performed and helped elucidate factors leading to increased deviations. For example, study coordinator training was optimized as a preventive action when it became clear that many deviations were the result of inadequate understanding of the research protocol. Similarly, missing or inadequate data was corrected by the creation of detailed case report forms and study visit checklists as observed in Figure 5. This was maintained for all analyzed studies from that point, and is largely the reason for the dramatic decrease in the number of protocol deviations in studies conducted following the VLU-1 study.Our analysis also showed that many of the deviations were repetitive, where the same errors were made continuously until corrected. One example is VLU-3, where 27 out of the 79 total deviations recorded for this study (34%) were related to a malfunctioning camera that was not repaired within a timely manner. This represents 59% of the "study procedures not performed or performed late" category for this study as shown in Figure 4. Early identification of these types of errors and the implementation of strategies to solve these problems is key to reducing the number of repetitive deviations. The collection of specific details of protocol deviations in the wound care trials at our site has allowed us to develop preemptive plans during the study start up phase of future wound care studies targeting possible pitfalls.

An analysis of the number of deviations per enrolled subject over time was conducted which provided insight into temporal trends as well as the effect of study coordinator changes on the number of protocol deviations. Based on the trends, frequent turnover of research staff and lack of coordinator overlap can result in increased protocol deviations as seen in Figure 6. For this reason, it is critical to address the issues leading to site personnel turnover and ensure that study coordinators are adequately trained on the study protocol, Good clinical practices (GCPs), their role on the study and standard research operations prior to assuming their roles and responsibilities on the study. As shown in Figure 6, the studies conducted from December 2012 onward increased study staff and the less frequent change of study coordinators reduced the overall number of deviations per subject. A large part of this improvement was also the result of implementing better research training for new study coordinators, and proactively assessing each coordinator's performance weekly via reported deviations and adverse events and addressing issues as they arise.

One reason for the increase in protocol deviations between DFU-1 and DFU-2, as seen in Figure 7, can be attributed to a change in lead study coordinator, and the subsequent additional reporting of events which were not previously recognized as deviations as shown in Figure 6. Standardized deviation reporting could eliminate these discrepancies and ensure that each site within a trial is consistently reporting events and developing and implementing corrective preventive actions (CAPA) effectively. Industry-wide reporting guidelines for deviations would standardize and quantify protocol deviations and determine the impact of each deviation on the study data and subject safety. Analyses similar to our current quality improvement project at a multi-site level could provide data to create a more proactive, systematic approach in assessing deviations and allow researchers to better understand the impact of protocol deviations on the final data. This could help to more clearly define what would qualify as a protocol deviation versus a violation, major versus minor deviations, and determine the impact of multiple deviations of each type on the study data integrity

CONCLUSION

The effective maintenance and analysis of internal metrics during study execution can lead to early risk mitigation for current and future studies, fulfilling the goals of risk based monitoring: preservation of data integrity, improvement of subject safety, and optimal resource allocation.[4] When conducting clinical trials, an understanding of the frequency and types of adverse events can provide an expectation for trials researching a particular etiology. In this instance, researchers in wound care can expect a larger number of serious adverse events per subject on average for subjects with diabetic foot ulcers, and these events will be more diverse as compared with venous leg ulcer subjects. Additionally, in all studies, protocol compliance can be improved with effective training and retention of research coordinators, effective CAPA implementation and more frequent internal auditing. Close supervision of performance metrics throughout the execution of the study can reduce the total number of protocol deviations and improve the quality and integrity of data obtained.

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