Assessment of Protocol Deviations in Clinical Trials for Diabetic Foot and Venous Leg Ulcers at Safety Net Hospital

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INTRODUCTION

Protocol deviations or lack of adherence to study protocol and procedures are dominating Bioresearch Monitoring Program (BIMO) inspection findings, and the top reason for clinical trial enforcement actions by the Food and Drug Administration (FDA). (1) Approximately 30% of all warning letters issued by the FDA during inspections to investigative sites are due to the failure to follow the investigational plan and/or study protocol. (2)

In order to develop proactive risk mitigation strategies and improve the quality and safety aspects, we have performed analysis of risk factors at a single center, safety-net, academic hospital for several recently conducted wound care clinical trials. (3)

OBJECTIVES

- Monitor study protocol compliance and patient safety factors by tracking the rate of deviations;
- Perform systematic retrospective analysis of risk factors such as adverse events and protocol deviations in wound care clinical trials;
- Identify trends in deviations, occurrence and type;
- Compare patterns observed and develop proactive risk mitigation strategies accordingly and improve the quality of trials conducted.

METHODS

- An analysis of 15 recently conducted prospective, randomized wound care clinical trials with 261 subjects enrolled at a tertiary, safety net hospital was performed. These studies had similar objectives, study design, eligibility criteria, and outcomes. The rate of protocol deviations was assessed and compared between two wound types: diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs).
- Adherence to study protocol and compliance with current regulatory requirements were examined based on the rate of protocol deviations. Only subjects deemed fully eligible, randomized to receive study treatment were included. To elucidate the major causes of protocol deviations in wound care studies, each deviation was categorized into one of the pre-defined categories (as shown in Table 1).
- For deviations, cause-effect analysis was performed based on the most common reasons for protocol deviations in these trials.

Study	Duration	Number of Subjects Consented
Study	**Duration**	**Number 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 – January, 2016	24
DFU-2	May, 2014 – April, 2016	30
VLU- 7	March, 2015 – July, 2017	13
VLU-8	September, 2020 – January, 2022	1
DFU-3	February, 2016 – October, 2016	7
DFU -4	May, 2017 – April, 2018	9
DFU-5	March, 2018 – June, 2019	16
DFU-6	March, 2020 – March, 2023	6
VLU-9	October, 2021 – August, 2023	5

RESULTS

- Comparison of protocol deviations (PDV) between the DFU and VLU studies showed nearly a significant downward trend from VLU-1 to VLU-4 with a **12.5-fold** reduction (Figure 1).
- PDV rate increased in studies conducted after VLU-4, but subsequently decreased which was possibly attributed to quality improvement initiatives, implementation of new study personnel training, and more proactive risk assessments.
- The most common deviation for both DFU and VLU was wound infection, both target and non-target wounds. DFU patients had a higher prevalence of gastrointestinal problems and systemic infections.

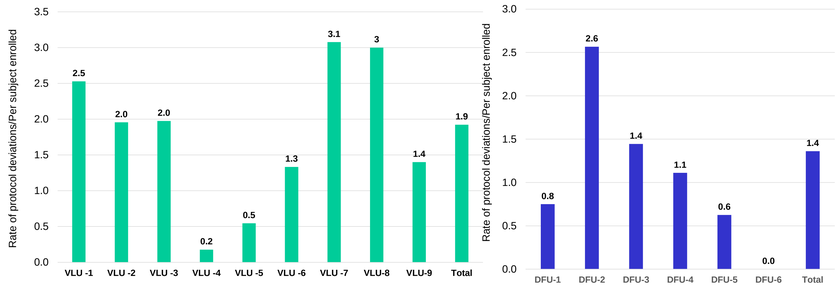

Figure 1. Protocol Deviations per subject for all DFU and VLU studies analyzed.

- An analysis of deviations demonstrated that the most common causes for non-adherance 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 (Figure 2 and Figure 3).
- Closer assessment of the category "*study procedures not performed or performed late*" showed that protocol 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 (Figure 2 and Figure 3).

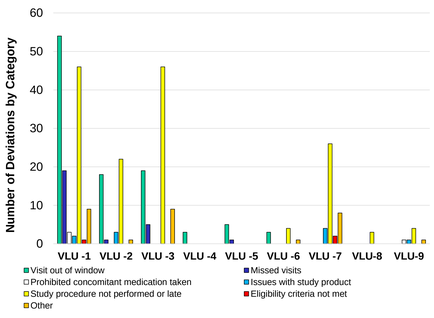

Figure 2. Protocol deviations by category for all VLU studies analyzed.

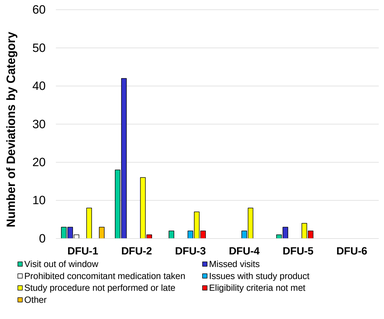

Figure 3. Protocol deviations by category for all DFU studies analyzed.

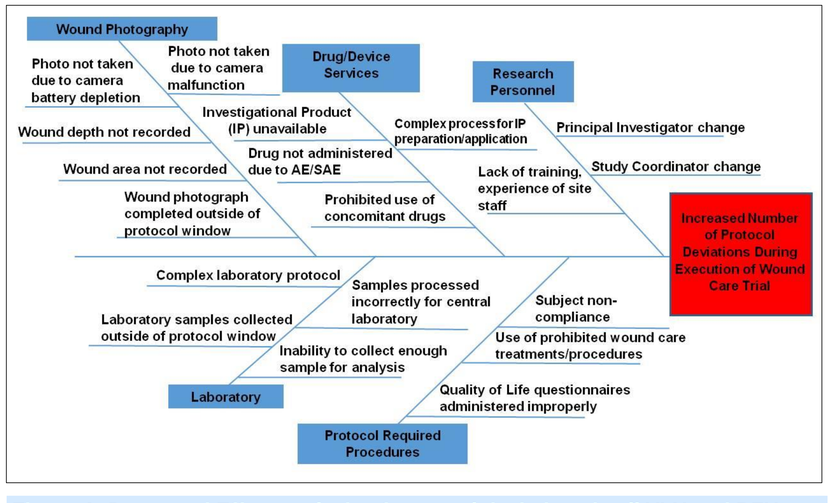

Figure 4. Cause and Effect analysis of protocol deviations in all VLU and DFU studies analyzed.

RESULTS

- Findings revealed that many of the deviations were repetitive and not corrected in a timely manner in earlier conducted studies.
- In the VLU-3 study **27 out of all 79** deviations, which occurred in this study (**34.2%**), were related to a technical issues with the camera, which was used to capture images to determine size of the wounds as a primary outcome measure.
- This issue in turn contributed to the **58.2%** of the "study procedures not performed or performed late" category for the study. Early identification of issues and performance of root-cause analysis can help to prevent reoccurrence, reduce number of deviations and improve data quality and integrity (Figure 4).
- In VLU studies **31.4%** of the deviations were attributed to visits conducted outside of the window allowed by the study protocol; **8.0%** were due to missed visits and **45.2%** were related to the study procedures not being performed or performed late.
- DFU studies had **18.8%** of deviations which were attributed to visits out of window, **37.5%** were due to missed visits and **33.6%** were due to study procedures not being performed or performed late (Figure 2 and Figure 3).
- Number of deviations per active subject throughout the life cycle of each project was examined which provided insight into specific. Trends were noted, frequent changes of research staff and lack of coordinator overlap time for cross training can result in increased amount of protocol deviations (Table 1).

Category of Deviation	VLU Studies	DFU Studies
Study Visit Out of Protocol Window	102	24
Missed Study Visit	26	48
Prohibited Concomitant Medication Used by Subject	3	1
Deviation Related to the Test Article	9	4
Study Procedure Not Performed or Performed Late	147	43
Eligibility Criteria Not Met	3	5
Other	28	3
Total:	325	128

Table 1. Protocol deviations by category for all VLU and DFU studies conducted.

CONCLUSION

- Proactive assessment of key quality and risk indicators, as well as monitoring of safety signals at study implementation can lead to better risk mitigation in clinical trials, and addressing risk- based monitoring requirements (e.g. preserve data integrity, improve patient safety, and aid adequate resource allocation, etc.)
- Deviations and study protocol compliance can be enhanced with implementation of upfront training and better retention of research coordinators as well as more frequent conduct of an internal auditing. Proactive approach and adequate monitoring of key quality, risk and performance metrics throughout the lifecycle of the study can reduce the total number of protocol deviations, improve compliance and quality of conducted research projects.

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