Clinical Trial Learning Curves Affect Outcomes Measurement, Patient Safety, and Trial Success: Contributing Factors and a Potential Solution in Clinical Trial Simulation

Daryl S Spinner,[1] Jeffrey W Walter,[1] Maria Vazquez-Gragg,[1] Tony Bloise,[1] Mark Stafford-Smith,[2] Eric C Faulkner,[1] Jeffrey M Taekman[2]

[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]Duke University Medical Center, Durham, NC, United States

BACKGROUND

- Learning curves are ubiquitous in the acquisition of most cognitive and behavioral tasks.
- Learning curves in performance of clinical procedures have been firmly established in the literature.[1-3]
- Early performance in the learning cycle of a clinical procedure is associated with increased adverse events, increased mortality, and poorer outcomes (Table 1).[1,2,4-16]
- Understanding the learning curve has led to safer and more efficient medical procedures.
- Until recently, there have been minimal attempts to scrutinize clinical research trials for the presence of learning curves.
- If present, learning curves could have profound implications for the development, deployment, and patient enrollment of clinical trials.

Table 1. Learning-Curve-Associated Outcomes Observed in Select Clinical Procedures in the Literature

Clinical Procedure Studied	Trend in Measured Outcomes
Administration of remifentanil analgesic in conjunction with anesthetic using a standardized protocol (during elective surgical procedures)	Reduction in time to eligibility for PACU discharge for surgical outpatients[12] Reduction in adverse events[15]: • Hypoxemia • Severe hypoxemia • Hypoventilation
LVAD implantation[7]	Increase in 30-day survival Increase in 1-year survival
Laparoscopic prostatectomy for prostate cancer[8,13]	Decrease in positive surgical margin in removed tissue
Open prostatectomy for prostate cancer[16]	Decrease in positive surgical margin in removed tissue Decrease in 5-year recurrence of prostate cancer
Colonoscopy[10,11]	Increase in success rate Decrease in time to cecal intubation

LVAD = left ventricular assist device; PACU = postanesthesia care unit.

OBJECTIVE

- To examine the effect of clinical trial learning curves on outcomes measurement, patient safety, and trial success and to suggest a potential solution in clinical trial simulation.

METHODS

- The PubMed database was searched using the search term combinations described in Table 2 to identify the following:
  - Key comparative drug trials exhibiting learning curves
  - Potential impacts of trial learning curves on clinical outcomes
  - Factors contributing to trial learning curve effects
  - Potential solutions to prevent or reduce the impacts of clinical trial learning curves.
- Limits for the search strategy included the following:
  - Publication date: 2000-2010
  - Language: English
  - Research subjects: human patients
  - Study types: clinical trials, randomized controlled trials (RCTs).

Table 2. Results of Literature Search to Identify Drug Trials With Learning Curve Effects

Search #	Text Word/Term	Articles Identified
1	Clinical trial learning curve	323
2	Learning curve	293
3	Enrollment sequence	22
4	Protocol learning curve	17
5	Experience curve	5
6	Enrollment curve	3
Total	**Searches 1 or 2 or 3 or 4 or 5 or 6 (duplicate hits removed)**	**344**

- Inclusion criteria:
  - Comparative drug trials with at least two treatment arms
  - Explicit mention of relationships between outcomes and patient enrollment sequence and other effects attributed to investigator learning curves, such as increased numbers of protocol deviations and documentation queries
- Exclusion criteria:
  - Medical device or procedural trials
  - Single treatment arm trials

RESULTS

Clinical Drug Trials With Learning Curves Identified in the Literature Search

- Three studies on drug RCTs reporting learning curve effects were identified in the literature search (Table 3):
  - ADDRESS: Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis[17]
  - PROWESS: Recombinant Human Factor Activated Protein C Worldwide Evaluation in Severe Sepsis[18]
  - VALIANT: Valsartan in Acute Myocardial Infarction.[19]
- All three trial protocols had a great degree of clinician latitude, with little or no standardization with regard to adjunct/peripheral care (PROWESS and ADDRESS) and/or dosing/dose escalation (VALIANT).

Clinical Trial Learning Curves Affect Outcomes

- The PROWESS, ADDRESS, and VALIANT trials all exhibited learning curves, potentially affecting different clinical outcomes (Table 4).
- The VALIANT trial exhibited greater numbers of protocol departures (protocol violations or deviations) and documentation inconsistencies (query data) in patients enrolled in the study earlier (Figure 1).[19]
  - Protocol departures were 1.47-fold more common in the 1st versus 30th patient enrolled at a clinical site ($P < 0.0001$) (Figure 1a).
  - Documentation inconsistencies were 2.15-fold more common in the 1st versus 30th patient enrolled at a clinical site ($P < 0.0001$) (Figure 1b).
  - Protocol departures and documentation inconsistencies were significantly more common in clinical sites with lower rates of enrollment ($P < 0.0001$) (Figures 1C and 1D) and with reduced time from start of study to site's first enrollment ($P < 0.001$) (Figures 1E and 1F).
  - There was no reported link between patient enrollment sequence and mortality, but learning curve effects likely increased trial costs associated with query data.

Table 3. Key Characteristics of Clinical Trials Identified in the Search

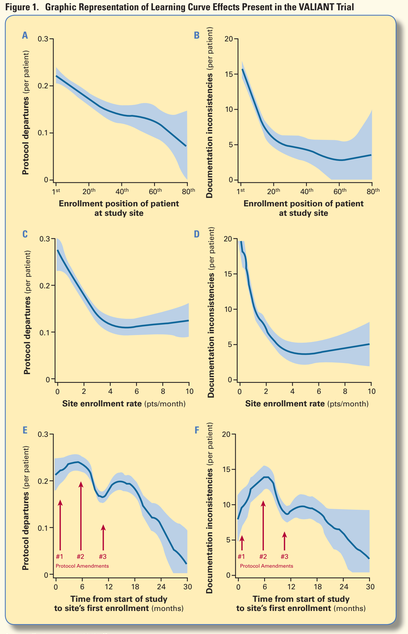
Clinical Trial	Patients, Procedures, and Outcomes Measured	Clinical Sites (Countries)	Site Patient Enrollment
PROWESS (severe sepsis)[17,20]	**Patients:** • DrotAA: 850 • Placebo: 840 **Procedure:** • Intravenous drug infusion for 96 hours **Outcomes:** • 28-day all-cause mortality after the start of infusion	164 (11)	1-4 at 59 sites 5-8 at 33 sites 9-12 at 22 sites > 12 at 50 sites
ADDRESS (severe sepsis)[18,21]	**Patients:** • DrotAA: 1,316 • Placebo: 1,297 **Procedure:** • Intravenous drug infusion for 96 hours **Outcomes:** • 28-day all-cause mortality after the start of infusion	516 (34)	NR
VALIANT (high-risk cardiac disease)[19,22]	**Patients:** • Valsartan: 4,909 • Valsartan + Captopril: 4,885 • Captopril: 4,909 **Procedure:** • Doses of treatment were administered and gradually increased in 4 steps at physician discretion until terminal doses were reached, if possible, by the 3-month visit **Outcomes:** • Mortality • Fatal and nonfatal cardiac events	931 (24)	Mean of 15.8 ± 19.1 per site

DrotAA = drotrecogin alfa activated; NR = not reported.

Table 4. Observed Learning Curves Effects in Clinical Trials Identified in the Search

Clinical Trial	Nature of Learning Curve	Impact on Outcomes
PROWESS (severe sepsis)[17]	Greater numbers of protocol violations in patients enrolled earlier at clinical sites	• Higher mortality rates in patients with protocol violations, favoring placebo group • No treatment benefit for DrotAA observed in patients having a protocol violation • Protocol amendment introduced during the trial resulted in the elucidation of treatment benefit from DrotAA versus placebo in patients treated after the amendment (i.e., reduced mortality more clearly favoring DrotAA) (Placebo vs. DrotAA: Original protocol – 30.3% vs. 28.3%; Amended – 31.3% vs. 22.0%)
ADDRESS (severe sepsis)[18]	Greater mortality and adverse events in patients enrolled earlier at clinical sites	• Higher mortality (and adverse event) rates in patients enrolled earlier at sites, favoring placebo group • Higher mortality in early enrolled patients randomized to DrotAA may have contributed to early trial termination
VALIANT (high-risk cardiac disease)[19,22]	Greater numbers of protocol departures and documentation inconsistencies in patients enrolled earlier at clinical sites	• No reported effect on mortality • Increased trial costs associated with more frequent query data in earlier enrolled patients

Figure 1. Graphic Representation of Learning Curve Effects Present in the VALIANT Trial



Source: Taekman et al., 2010a.[19]

Potential Factors Contributing to Clinical Trial Learning Curve Effects

- Potential contributing factors identified in the learning curve studies on PROWESS, ADDRESS, and VALIANT trials are described in Table 5.
- Other potential contributing factors were not specifically addressed in the learning curve studies on PROWESS, ADDRESS, or VALIANT trials:
  - Inclusion of clinical sites and/or investigators with lack of protocol-specific experience or expertise
  - Inclusion of clinical sites and/or investigators with historically poor clinical trial performance
  - Insufficient evaluation of clinical staff competence prior to inclusion in trial
  - Insufficient clinical protocol walk-through to anticipate issues such as ambiguity and complexity prior to trial onset to prevent need for multiple protocol amendments
  - Complex clinical protocol design.

Table 5. Potential Factors Contributing to Learning Curves in Clinical Trials Identified in the Search

Potential Contributing Factor	Trials Exhibiting Potential Contributing Factor		
	PROWESS	ADDRESS	VALIANT
Nonspecific inclusion/exclusion criteria	√	√	√
Nonspecific concomitant care	√	√	
Nonspecific dosing parameters			√
Large number of clinical sites compounding the "early patient" effect	√	√	√
Sites with low numbers of patients enrolled	√		√
Sites with slow enrollment			√
Short time to first enrolled patient			√
Protocol amendment during trial	√		√
Multiple site coordinators			√
Site personnel turnover			√

Clinical Procedure/Trial Protocol Simulation as a Solution to Trial Learning Curves

- Clinical protocol simulation is a tool that could potentially flatten clinical research learning curves when used prior to trial enrollment[23,24]:
  - 14 of the 344 studies identified in the search related to clinical simulation.
  - The literature search identified articles related to simulation of endoscopy, laparoscopic methods for surgery, interventional radiology/cardiology, anesthesia, gynecology, epidural administration, and endovascular catheterization.
- Clinical protocol simulation works through the application of human factor strategies such as trial walk-through in a simulated environment and/or iterative user-centered design, and could potentially flatten trial learning curves through improved protocol design and minimization of protocol amendments.
- Clinical research protocol experiences could be simulated in high fidelity (e.g., with a mannequin) or in virtual reality for research personnel to practice trial-specific behaviors (e.g., enrollment, procedure, or cognitive skills).[25,26]
- High fidelity clinical trial protocol simulation:
  - Might mitigate several of the potential contributors to trial learning curves, including suboptimal research personnel performance, personnel turnover/retraining, and suboptimal trial design (potentially minimizing the number and scope of protocol amendments, improving data, and resulting in shorter trials)[25,27]
  - Has been demonstrated to increase study coordinator confidence (an established correlate of competence) in clinical protocol conduct by 49.7% ($P < 0.0001$)[27]
  - Has been used as an evaluative tool in developing clinical research protocols, including protocol walk-through, detailed protocol modification, and development of protocol aids.[25]

Table 6. Potential Uses and Benefits of Clinical Trial Protocol Simulation[23-25]

Potential Uses	Potential Benefits
• Protocol walk-through • Improvement in study design • Improvement in staff training (e.g., prior to enrollment and after site turnover) • Screening of site coordinators and clinical staff	• Reduction in protocol violations and/or deviations • Reduction in documentation queries • Reduction in adverse events • Potential for reduced risk of premature trial failure • Improvement in outcomes data veracity • Improvement in patient safety

CONCLUSIONS

- Clinical trials exhibit a phenomenon consistent with a learning curve that manifests as increased protocol departures and documentation inconsistencies earlier in the enrollment sequence.
- Clinical trial learning curves could potentially affect clinical outcomes measurement and overall trial outcome, and have important safety, ethical, research quality, and economic implications for trial conduct.
- Multiple factors could contribute to trial learning curve effects, including poor protocol design, poor staff and clinical site competence, high turnover, slow enrollment, and large number of clinical sites compounding the "early patient" effect.
- While in some cases post hoc statistical methods may be used to correct for learning curve effects in efficacy endpoint measurement,[3] a high rate of adverse events can cause premature trial termination and/or trial failure.
- Clinical trial learning curves may potentially be addressed prior to the start of trial enrollment through clinical trial simulation, a methodology used as a tool both to improve protocol design and maximize research personnel performance.
- Clinical trial simulation may also be used as a screening tool for study investigators, monitors, and coordinators.
- Clinical trial simulation may be a tool to mitigate trial learning curves, thereby improving the accuracy of outcomes measurement and patient safety, reducing the risk of premature trial termination and/or trial failure, and reducing the ultimate cost of conducting clinical trials.

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REFERENCES

Please see handout for complete reference list.

CONTACT INFORMATION

Daryl S Spinner, PhD, MBA
Senior Associate, Market Access and Outcomes Strategy

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1.919.541.6643
Fax: +1.919.541.1275
E-mail: dspinner@rti.org

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