Therapeutic Innovation
& Regulatory Science
2014, Vol. 48(6) 671-680
© The Author(s) 2014
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/2168479014554400
tirs.sagepub.com

Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials

Nicole Sheetz, PharmD[1], Brett Wilson, BSP[2], Joanne Benedict, MS[3], Esther Huffman, BS[4], Andy Lawton, ASTAT[5], Mark Travers, PhD[6], Patrick Nadolny, MS[7], Stephen Young, MA[8], Kyle Given, BA[9], and Lawrence Florin, MBA[10]

Abstract

TransCelerate has developed a risk-based monitoring methodology that transforms clinical trial monitoring from a model rooted in source data verification (SDV) to a comprehensive approach leveraging cross-functional risk assessment, technology, and adaptive on-site, off-site, and central monitoring activities to ensure data quality and subject safety. Evidence suggests that monitoring methods that concentrate on what is critical for a study and a site may produce better outcomes than do conventional SDV-driven models. This article assesses the value of SDV in clinical trial monitoring via a literature review, a retrospective analysis of data from clinical trials, and an assessment of major and critical findings from TransCelerate member company internal audits. The results support the hypothesis that generalized SDV has limited value as a quality control measure and reinforce the value of other risk-based monitoring activities.

Keywords

source data verification, source data review, risk-based monitoring, quality control, data integrity

Introduction

The ICH guideline for Good Clinical Practice[1] (GCP) defines clinical trial monitoring as "the act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, [standard operating procedures], GCP, and the applicable regulatory requirement(s)." The guideline advises that monitoring should safeguard patients' well-being and ensure data accuracy and completeness, and it suggests that "there is a need for on-site monitoring before, during and after the trial and the use of central monitoring in conjunction with other procedures may be justified." Although it is not a requirement, sponsors have traditionally relied on high levels of source data verification (SDV) as the primary method of ensuring data quality.

By definition, SDV is the process of ensuring that the data reported for analyses accurately reflect the source data at the clinical trial site.[2] The information collected during a clinical trial is the source data, and it includes original records documenting clinical findings, observations, and any other activities notable within the clinical trial.[3] SDV focuses on identifying transcription errors, or those errors made in entering the source data into the case report forms (CRFs). Historically, SDV has been conducted for the majority of the CRF data; however, SDV of 100% of the data does not guarantee error-free results, and concentration on transcription accuracy does not guarantee data quality.

TransCelerate BioPharma's position paper on risk-based monitoring[4] (RBM) proposes that a shift away from conventional on-site monitoring methods is warranted. The paper

[1] Clinical Development Innovation, Eli Lilly and Company, Indianapolis, IN, USA
[2] Global Development Operations, Bristol-Myers Squibb, Princeton, NJ, USA
[3] Global Product Development, Roche, Genentech, San Francisco, CA, USA
[4] Global Development Operations, Bristol-Myers Squibb, Princeton, NJ, USA
[5] Biometrics and Data Management, Boehringer Ingelheim, Bracknell, UK
[6] Clinical Sciences and Operations, Sanofi, Bridgewater, NJ, USA
[7] Bioinformatics Operations and Systems, Allergan Inc, Irvine, CA, USA
[8] Strategic Consulting Services, Medidata Solutions, Conshohocken, PA, USA
[9] Strategic Consulting Services, Medidata Solutions, Edison, NJ, USA
[10] Consulting Partnerships, Medidata Solutions, Conshohocken, PA, USA

Submitted 08-Aug-2014; accepted 12-Sep-2014

Corresponding Author:
Esther Huffman, Global Development Operations, Bristol-Myers Squibb, Princeton, NJ, USA.
Email: esther.huffman@bms.com

includes an analysis of 9 sample studies demonstrating that only 2.4% of the queries in critical data were driven by SDV, suggesting that SDV has a negligible effect on overall data quality. The paper also introduces the concept of source data review (SDR), a quality assessment of source documentation to ensure adequacy of the documents, ensure protocol compliance, and confirm compliance with ICH GCP. SDR is a quality management method to evaluate critical processes, including those not associated with a data field in the CRF.

On-site monitoring with a primary purpose of SDV is resource intensive, accounting for up to 25% of the total clinical trial cost,[5] and SDV predominantly detects random errors that likely have little impact on the results of clinical trials. Despite this evidence and encouragement from regulators to develop strategic monitoring processes, SDV remains widely engrained in the clinical trial industry as the primary focus of on-site monitoring visits. Perpetuating this model inhibits the industry from focusing on monitoring activities that may yield higher value with respect to subject safety, data integrity, and GCP compliance. The present article explores the effectiveness and value of SDV, corroborating the growing body of evidence that supports replacing SDV with more optimal monitoring activities.

Method

To determine the value of SDV as a quality control mechanism, three investigations were undertaken to evaluate available information: literature review, data analysis, and audit findings review.

Literature Review

A systematic review of SDV-related literature was conducted by a professional library service within one of the TransCelerate member companies. Information published between 2008 and 2014 in the form of articles, conference proceedings, and regulatory guidance on the following topics was evaluated:

- Definitions of SDV
- Evidence of SDV detecting data quality issues (eg, study outcomes affected by SDV, percentage of errors missed, SDV queries impact on actual database changes)
- Evidence of the impact of SDV (eg, types of errors being identified, rate of detection)
- Evidence of data transcription error rates acceptable to regulators
- Recommendations of how SDV fits with other forms of quality control

Table 1. Criteria for study selection.

No.	Condition	Purpose
1	Include only completed biopharmaceutical studies for which at least 30% of the eCRF data underwent SDV	Unintended bias would be introduced since not all queries, SDV, and data corrections have been processed yet in ongoing studies. Bias against SDV rates may also be introduced when SDV levels are very low.
2	Exclude studies for sponsors where the SDV flag was used for purposes other than SDV	Conclusions related to SDV cannot be drawn in such studies.
3	Include only studies for which the following 3 query types are present: auto-queries, data management queries, and site monitor queries	If any of these 3 types of queries are not being generated in a given study, the study is not representative of a standard data cleaning approach.

eCRF, electronic case report form; SDV, source data verification.

Retrospective Multistudy Data Analysis

Data analysis was undertaken in partnership with Medidata Solutions Inc to explore the impact that SDV has on data quality. The analysis focused on the following two questions:

1. What is the relative contribution of SDV to the total amount of data correction observed across all electronic CRFs (eCRFs)?
2. How many subject events—particularly, adverse events (AEs) and serious AEs (SAEs)—are initially not recorded (ie, missed) by sites and instead added to the eCRF within various periods following on-site monitoring visits?

The source of information used for this analysis was Medidata's Insights metric warehouse, containing operational data from more than 7000 studies contributed from more than 110 sponsor organizations. Filters as described in Table 1 were applied to identify eligible studies.

Additional filters were applied for data inclusion in the analysis. In particular, SDV data correction metrics were compiled only for eCRF data points that had evidence of SDV (ie, data points must have been source data verified at least once). Data points that did not undergo SDV (eg, derived data and data integrated from central labs) were not analyzed. In this analysis, it was not possible to differentiate between corrections driven by SDV and corrections driven by SDR, nor was it possible to differentiate between critical and noncritical data.

The eCRF data were classified into 2 distinct categories:

Visit data: data generated as a result of protocol-prescribed procedures, assessments, study drug

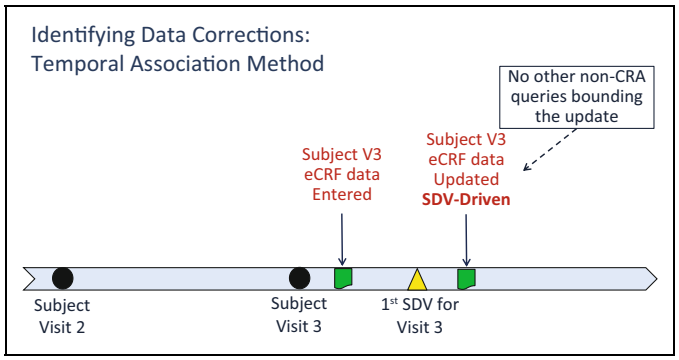

Figure 1. Temporal association method for data corrections. eCRF, electronic case report form; SDV, source data verification.

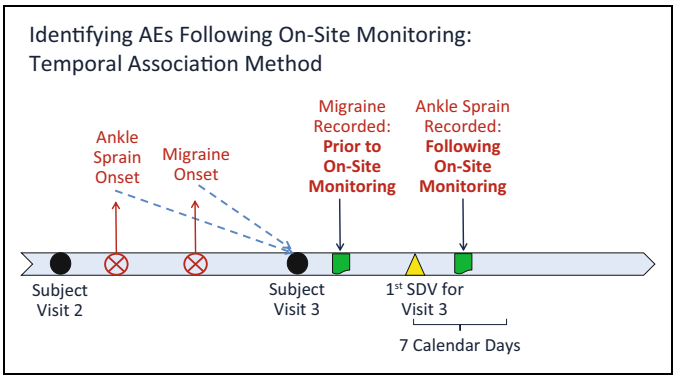

Figure 2. Temporal association method for identifying adverse events. SDV, source data verification.

accounting, and so on and collected as part of a subject's study visit.

Subject event data: events that occur to a subject at any time throughout the course of a trial—for this analysis, AEs and SAEs.

As previously mentioned, TransCelerate's RBM position paper included an evaluation of the percentage of queries that were generated as a result of SDV—particularly those focused on critical data. Some SDV-driven findings, however, are never documented as an electronic data capture (EDC) query by the site monitor. Instead, a common practice is for site monitors to document questions on handwritten notes outside the EDC system. In such cases, the site may perform the necessary corrections directly on the eCRFs without any EDC queries being generated by the site monitor.

To ensure inclusion of data corrections that might be attributed to on-site monitoring activity, a more robust approach was taken in the present analysis. In particular, SDV-related data corrections are included as follows:

1. eCRF data corrections that are temporally associated with an SDV query—that is, corrections that are performed after an SDV query was issued and before it was closed or resolved.
2. Any additional eCRF data corrections that are temporally associated with SDV activity (ie, corrections made within a set period following the date that SDV was performed on CRF data for the same subject visit) and not otherwise associated with any other queries (eg, data management queries). Figure 1 displays this temporal association method.

While this method assesses the impact of SDV corrections made to eCRFs after they are completed, the same method cannot be applied to account for AEs or SAEs that were identified and reported following on-site SDV activity—especially those with no associated EDC query. The approach taken to evaluate the rate of AEs recorded following SDV also uses a temporal association method, focused on AEs that were recorded in the eCRFs only after evidence of SDV for the relevant subject visit data.

- In particular, each AE is associated with a specific subject visit based on a comparison of the AE onset date with each visit date for the subject. Specifically, AEs are associated to the next subject visit following the AE onset date chronologically. The earliest date that SDV was conducted for eCRF data belonging to that subject visit is then identified. Finally, the date that the AE is first recorded into the eCRF is evaluated to determine whether it was recorded on or within no more than 1 or 7 days following the earliest SDV date. Figure 2 displays this temporal association method.
- Additionally, to ensure an appropriate sample for this analysis, studies were included only if they had 10 or more sites with at least 5 AEs per site.

As such, if an AE or SAE was recorded within 7 calendar days following the SDV date, it was considered likely to have been missed upon initial data entry and added to the eCRF after the on-site monitoring of the relevant subject visit occurred.

To summarize the metrics assessed in this investigation, the following definitions were applied:

$$\%\ \text{of total eCRF data correct by SDV} = \frac{\text{total eCRF data points corrected by SDV}}{\text{total eCRF data points entered}}$$

$$\%\ \text{of corrected eCRF data driven by SDV} = \frac{\text{total eCRFdata points corrected by SDV}}{\text{total eCRF data points corrected}}$$

$$\%\ \text{of AEs recorded following SDV} = \frac{\text{total AEs recorded following SDV}}{\text{total AEs recorded}}$$

Table 2. Articles related to SDV definition and general assessment.

Author	Assessment of SDV
Baigent et al[6]	The majority of errors found via SDV are random errors and would not create bias in trial findings, although errors should be minimized for endpoints. Nonrandom errors and errors introduced through falsification of data are better detected through central statistical monitoring.
Tantsyura[7]	SDV is one component of quality management, and it allows for evaluation of conformity of clinical trial data. SDV as a quality management method is in addition to adequate training of investigators and study personnel, data validation procedures and audits.
Duley et al[8]	Verifying parallel documentation within clinical trials, meaning that every data point within a CRF must have a corresponding data point at the investigator's site, does not improve data quality. The CRF in some clinical trials should be the source document, further minimizing the need for SDV.
De[9]	Two myths permeate the argument for traditional monitoring where 100% SDV is foundational: (1) more SDV leads to better quality; (2) SDV is required to comply with regulations. Neither of these myths is supported by data or regulation, and in practice, on-site monitoring inappropriately centers on the completion of SDV activities at the expense of other vitally important on-site monitoring tasks.
European Medicines Agency[10]	Current practices in clinical research are not proportionate to risk. This problem may stem from (1) overinterpretation or misunderstanding of regulatory environment or (2) failure to evolve processes and resistance to new approaches—for example, application of a single model of monitoring for all trials, which is neither appropriate nor effective.

SDV, source data verification.

Audit Findings Review

TransCelerate member companies provided details of recent audits spanning the time frame of 1 January 2012 through 15 May 2014. The member companies identified findings from site and process audits:

> *Critical findings:* deficiencies that adversely affect subject safety and/or data quality and integrity, pose a serious risk to public health or violate applicable legislation, or involve fraud or falsification of records.
>
> *Major findings:* deficiencies that have the potential to adversely affect subject safety and/or data quality and integrity, pose a potential risk to public health or violate applicable legislation, or include a pattern of numerous minor findings.

The member companies then indicated what each deficiency was related to, using standard categories of SDV, SDR, investigator oversight, or other cause, where only a single association could be made. Results were aggregated, blinded, and summarized by a neutral third party.

Results

Literature Review

The body of literature from more than 40 articles related to SDV is summarized here by (1) SDV definition and general assessment, (2) relative effectiveness of SDV as a quality control measure, and (3) evidence of the impact of SDV. No literature was identified as related to the rate of transcription errors that is acceptable to regulators or recommendations of how SDV fits with other forms of quality control.

Few publications evaluate on-site monitoring techniques or directly compare multiple monitoring strategies against one another. Table 2 summarizes the body of literature related to general assessment of SDV, and Table 3 summarizes the body of literature related to the relative effectiveness of SDV as a quality control measure. Table 4 summarizes the current body of literature related to evidence of the impact of SDV. Other publications offered definitions, examples, and approaches for both SDV and on-site versus central monitoring, but most failed to offer evidence-based reasoning for selecting one methodology over another.[21]

Retrospective Multistudy Data Analysis

The first results address the relative contribution of SDV to the total amount of data corrections observed across all completed eCRF data. In total, 1168 phase I-IV biopharmaceutical studies across 53 sponsors were included in the analysis. A median of 1.1% of the total eCRF data set was corrected by SDV. Some differences were observed across study phases and therapeutic areas (Table 5); these observations could benefit from further exploration.

Supporting previous findings, this analysis further indicates that only 3.7% of eCRF data was corrected by any data-cleaning method; the next results isolate the rate of those corrections that were driven by SDV. Table 6 displays the percentage of eCRF data that were corrected by SDV, by therapeutic area and by phase of study. The overall median value

Table 3. Articles related to relative effectiveness of SDV.

Authors	Assessment of SDV
Bakobaki[11]	Retrospectively found that 95% of on-site monitoring findings could have been identified through central monitoring strategies.
Duley et al[8]	Questioned conducting randomized trials that include excessive monitoring of data. Noted the lack of clear evidence of the benefits as compared to the costs of various monitoring strategies—in particular, that decreasing monitoring, specifically on-site monitoring, by half is feasible and would not compromise data quality.
Tudur Smith et al[12]	Compared data that had undergone 100% SDV against unverified data, thereby assessing the value of SDV for one clinical trial. The majority of SDV findings were random transcription errors and did not differ systematically across treatment groups or sites. The SDV-found discrepancies had no impact on the main conclusions of the study. SDV-found errors did affect 1 of the secondary analyses, but the authors suggested that other methods of monitoring could have found the errors and would have been sufficient. Noted that data that have undergone SDV is not error free, as indicated through the failure to identify 4 ineligible patients even after 100% SDV was conducted.
US Department of Health and Human Services, Food and Drug Administration[13]	Suggested minimal benefit in conducting 100% SDV and recommended focusing instead on critical data points for a sample of subjects and study visits as an indicator of data accuracy. Noted that SDV of noncritical data may not provide significantly useful information to the sponsor, since errors do not affect the outcome of the trial.

SDV, source data verification.

Table 4. Articles related to evidence of the impact of SDV.

Authors	Assessment of SDV
Neilsen et al[14]	Assessed the benefits and risks of 4 monitoring models by applying each model retrospectively to 30 studies. The models—random SDV, declining SDV, 3-tiered SDV, and mixed (combining the strengths of declining SDV with 3-tiered SDV)—were each analyzed via 3 indicators: percentage critical errors found, percentage noncritical errors found, and percentage saving of forms needed to be screened (resource savings). Determined that each model has a certain amount of risk (the amount of undetected critical and noncritical errors; eg, queries) and benefit (the percentage savings of forms needed to be screened); however, these analyses did not assess the impact on the studies' primary or secondary data analyses, therefore not demonstrating if undetected errors "mattered."
Medidata[15]	Found that, on average, only 3% of the eCRF data entered by sites are updated after their initial entry. The balance (no statistical analysis is available to confirm "singificance") of eCRF data remain unchanged after all data cleaning including SDV is conducted.
Atkinson et al[16]	Suggested that errors in data transcription can be addressed by increasing validation checks; did not mention SDV as a plausible method for detection and correction of errors.
Verhulst et al[17]	Noted error rates of no more than 3.7% in observational studies. Found that errors typically involved dates or transposed numbers; no systematic errors were found.
Carraro and Plebani[18]	Found error rates of 3.2% and 7.2% in imprecise data entry of specific data points.
Funning et al[5]	Reported a widespread misunderstanding that the quality of a clinical trial is dependent on the degree of errors discovered.
Grahnen et al[19]	Illustrated that transcription errors of up to 5% in source data had no significant impact on the outcome of a trial.
Brosteanu et al[20]	Conducted an "extensive literature search with the purpose to identify proposals for monitoring strategies and other quality management measures, as well as their impact on data quality and patient safety" but found a lack of references on this topic. Concluded that "quality management in clinical trials should consist of a package of measures, specifically defined to mitigate the identified risks. Monitoring is part of these measures."

SDV, source data verification.

for this metric is 32.0%, indicating that of the 3.7% corrections made by any method to site-entered eCRF data, approximately one-third are driven by SDV. Some differences were observed across study phases and therapeutic areas (Table 6); these observations could benefit from further exploration. This information is illustrated in Figure 3.

The second key focus of the analysis was to assess the impact of SDV in detecting subject events (AEs and SAEs) not

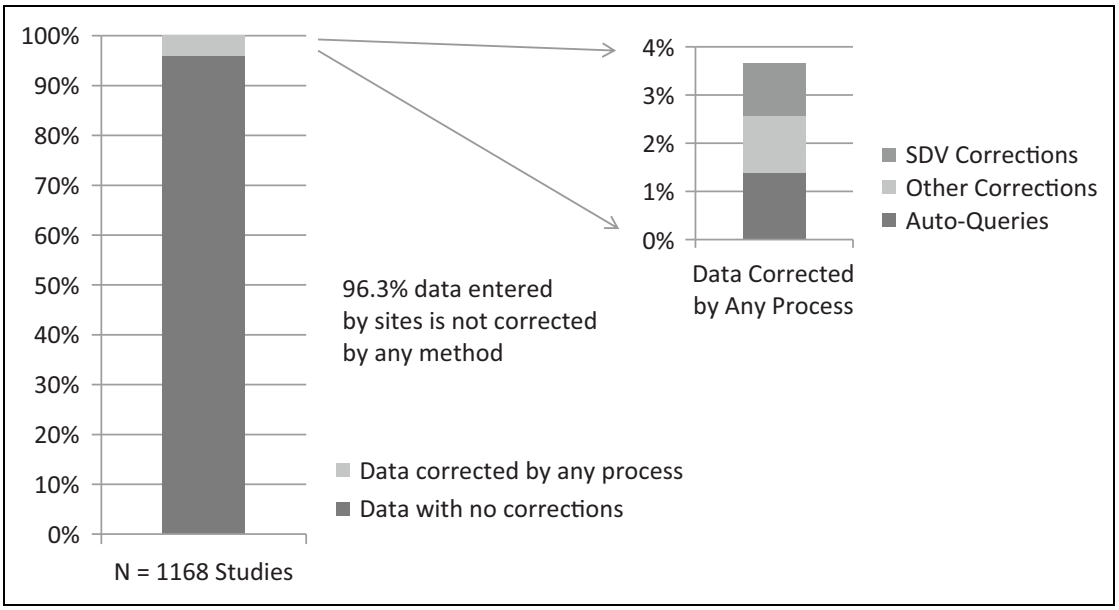

Figure 3. Percentage of electronic case report form corrections attributed to source data verification (SDV) versus other data correction methods.

Table 5. Percentage of the total electronic case report form data set corrected by source data verification.

Therapeutic Area	Sponsors, n	Studies, n	Median, %	Mean, %	SD, %
All	53	1168	1.1	1.6	1.8
Phase 1	30	461	0.9	1.4	1.5
Phase 2	34	269	1.5	2.0	1.8
Phase 3	26	219	1.4	1.8	2.2
Phase 4	13	40	1.2	1.8	1.9
Arthritis, autoimmune diseases	10	49	1.0	1.8	4.2
Cardiovascular	13	59	1.6	1.8	1.2
Central nervous system/ neurology	13	120	1.0	1.2	0.8
Dermatology	9	66	0.8	1.2	1.8
Gastroenterology	8	29	1.6	1.9	1.1
Hematology	6	16	2.2	2.3	1.6
Infectives	13	98	0.9	1.3	1.3
Metabolic disorders, hormone therapies	19	103	1.4	1.5	1.1
Oncology	19	161	2.7	3.2	1.9
Ophthalmology	4	27	1.0	1.6	2.2
Pain/inflammation	8	52	1.1	1.4	1.4
Pharmacokinetic	13	141	0.5	0.7	0.8
Renal disease, urology	5	18	1.1	1.3	1.0
Respiratory	11	69	1.7	1.9	1.4
Other therapeutic areas	15	160	0.5	0.9	1.8

Unless indicated otherwise, each row pertains to all phases.

Table 6. Percentage of corrected electronic case report form data corrected by source data verification.

Therapeutic Area	Sponsors, n	Studies, n	Median, %	Mean, %	SD, %
All	53	1168	32.0	31.9	14.4
Phase 1	30	461	29.8	30.1	15.6
Phase 2	34	269	34.2	34.4	12.0
Phase 3	26	219	34.6	35.1	10.4
Phase 4	13	40	33.7	35.9	15.3
Arthritis, autoimmune diseases	10	49	33.3	34.0	13.7
Cardiovascular	13	59	30.6	31.7	11.4
Central nervous system/ neurology	13	120	32.2	32.2	11.5
Dermatology	9	66	31.2	30.9	13.9
Gastroenterology	8	29	35.3	36.8	12.3
Hematology	6	16	30.0	30.1	11.9
Infectives	13	98	29.5	31.2	14.8
Metabolic disorders, hormone therapies	19	103	33.9	33.6	11.8
Oncology	19	161	43.0	41.3	12.9
Ophthalmology	4	27	32.0	34.9	11.0
Pain/inflammation	8	52	34.8	33.4	15.2
Pharmacokinetic	13	141	21.3	23.9	14.6
Renal disease, urology	5	18	26.3	27.4	14.0
Respiratory	11	69	32.1	31.6	12.9
Other therapeutic areas	15	160	25.6	27.3	15.9

Unless indicated otherwise, each row pertains to all phases.

Table 7. Median percentage of AEs recorded following on-site monitoring.

Therapeutic Area	Studies, n	AEs Recorded Post-SDV, % ≤1 d	≤7 d
All	926	7.5	11.8
Phase 1	358	3.4	9.1
Phase 2	245	9.1	13.6
Phase 3	187	8.9	12.2
Phase 4	34	9.1	12.5
Arthritis, autoimmune diseases	41	9.0	14.5
Cardiovascular	48	9.0	12.9
Central nervous system/neurology	95	8.5	12.0
Dermatology	59	8.5	11.7
Gastroenterology	26	12.3	16.1
Hematology	9	6.1	13.0
Infectives	78	7.2	11.1
Metabolic disorders, hormone therapies	90	8.0	12.4
Oncology	132	7.1	9.9
Ophthalmology	19	12.8	16.7
Pain/inflammation	48	6.2	10.5
Renal disease, urology	15	6.2	11.7
Respiratory	59	10.7	14.7
Other therapeutic areas	94	4.3	11.1

Unless indicated otherwise, each row pertains to all phases. AE, adverse event; SDV, source data verification.

Table 8. Median percentage of SAEs recorded following on-site monitoring.

Therapeutic Area	Studies, n	SAEs Recorded Post-SDV, % ≤1 d	≤7 d
All	380	1.7	3.6
Phase 1	68	0.0	0.0
Phase 2	139	1.7	4.0
Phase 3	157	3.0	4.8
Phase 4	16	0.0	2.3
Arthritis, autoimmune diseases	20	0.0	0.6
Cardiovascular	34	2.7	4.5
Central nervous system/neurology	56	2.3	3.7
Dermatology	21	2.3	6.3
Gastroenterology	12	0.0	2.6
Hematology	3	9.3	9.3
Infectives	25	0.0	3.4
Metabolic disorders, hormone therapies	40	4.1	5.4
Oncology	105	0.0	1.5
Ophthalmology	14	1.8	4.4
Pain/inflammation	22	3.9	8.5
Renal disease, urology	7	1.0	2.9
Respiratory	21	2.8	6.5
Other therapeutic areas	3	0.0	2.7

Unless indicated otherwise, each row pertains to all phases. SAE, serious adverse event; SDV, source data verification.

initially recorded in the eCRF. The percentage of AEs or SAEs that were recorded within 1 or 7 days following on-site monitoring activity are included in the next set of results. The overall industry median values are 7.5% (≤1 day) and 11.8% (≤7 days) for AE data (Table 7). SAEs recorded within the same 1- and 7-day windows (Table 8) yielded overall industry median values of 1.7% (≤1 day) and 3.6% (≤7 days).

Audit Findings

The present survey requested the top 10 categorizations of audit findings that were assessed as major or critical. Eight companies' responses (Table 9) provide insight into the most common types of major or critical findings and indicate the related area for the deficiencies. There were 1376 major or critical findings reported during the 29-month period. In approximately 11% of findings, the deficiency was related to SDV, leaving 89% of findings related to causes other than SDV. Findings related to SDV mostly include inaccuracies in detecting transcription errors or transcription errors in general. Nine of the SDV-related deficiencies were critical findings, accounting for 0.65% of the total.

Discussion

The current body of scientific literature supports shifting the focus away from SDV and employing other methods to monitor clinical trials. None of the published literature identified in this review indicated that reducing SDV is harmful to data quality; instead, current literature consistently supports the conclusion that SDV has a negligible effect on data quality.

The retrospective multistudy data analysis revealed that only 3.7% of eCRF data are corrected following initial entry by site personnel. After removal of the corrections that were driven by auto-queries (1.4%), the remaining percentage of data corrected dropped to 2.3% with only 1.1% of the corrections driven by SDV—including both critical and noncritical data. The remaining portion of data corrections (1.2%) are driven by other data-cleaning methods—including the activities performed by data management, medical, safety, and biostatistics reviewers.

As seen in Tables 5 and 6, slightly more than 1% of the eCRF data analyzed in this investigation were corrected by SDV, and only 32% of the data corrections of any kind are attributable to SDV. Some portion of the SDV-driven data corrections may have been corrected by other downstream data reviews had SDV not been conducted, although a quantitative analysis of this assumption was not possible in this investigation. Additionally, the SDV correction rate seen here applies across all data points in a study and is not limited to the correction of critical data only. Given the very low rate of SDV corrections consistently reported, it is clear that SDV adds little

Table 9. Major or critical findings with assessment of deficiency relationship.

Primary Categories of Audit Findings	No. of Findings	Deficiency Related to . . .			
		SDV	SDR	IO	Other
Clinical supporting documentation (discrepancy)	109	84	12	13	0
Clinical supporting documentation (substantiation)	280	9	229	33	9
Ethics, patients' rights (informed consent)	174	0	71	28	75
Facilities, archiving	2	0	0	2	0
Investigational product (accountability, reconciliation)	82	24	34	17	7
Investigator site personnel (investigator oversight)	123	0	8	108	7
Monitoring practices (conduct)	183	1	36	5	141
Process alignment	1	0	0	0	1
Protocol adherence	252	34	36	153	29
Quality system, standard operating procedures	1	0	0	1	0
Safety (data collection and reporting)	162	5	114	30	13
Sponsor oversight	7	0	0	0	7
Total major, critical audit findings	1376	157	540	390	289
Percentage of audit findings by deficiency type[a]	100.0	11.4	39.2	28.3	21.0

IO, investigator oversight; SDR, source data review; SDV, source data verification.
[a]For example, total SDV findings / total number of findings.

value as a primary quality management process and that SDV of noncritical data is unnecessary.

The negligible impact of SDV on data corrections does not address the impact of SDV on detecting AEs and SAEs that were not initially recorded by the site. There is an essential distinction between visit data and subject event data when the utility of on-site monitoring activities is considered. Protocol-determined visit data are generally expected to be reported for each subject, and it is therefore straightforward to identify and query for missing visit data remotely, without the need to directly review subject source records. Conversely, there is no specific expectation for subject events to occur and thus for such data to be reported. For example, subjects may or may not experience any SAEs during the course of a clinical trial, and there may be differences in the sites' understanding of what events to report. Therefore, a remote review of eCRF data cannot always directly determine whether all relevant AEs or other critical endpoint events have been reported by the site. On-site monitoring methods (eg, SDR, SDV) as well as various remote monitoring methods may be of value in identifying unreported events at some sites.

In the present analysis, a 7-day window was used to identify the rate of AEs most likely to have been identified during on-site monitoring visits. Table 7 indicates that 7.5% of all AEs are recorded in the eCRFs within 1 day following on-site monitoring activities and 11.8% are recorded within 7 days. It is possible then that between 7.5% and 11.8% of the reported AEs are identified by on-site monitoring activities. Table 8 shows that a critical subset of reported events—the SAEs—are recorded in the eCRFs following on-site monitoring at a much lower rate, in the range of 1.7% to 3.6%.

These temporally associated results (recording AEs and SAEs within 1 or 7 days following on-site monitoring) represent a reasonable estimate of the impact of SDV on identifying unrecorded events. In support of the retrospective analysis, results from Medidata Insights indicate that the median cycle time for SDV queries (across 1998 studies) is 3 days—from query open to query resolved; this suggests that a 7-day window plausibly includes the subject events detected during on-site monitoring visits. However, some of the AEs and SAEs entered following on-site monitoring may instead be attributable to other influences:

Data-cleaning processes: Data management and other clinical teams identify unreported AEs during data reviews; for example, when concomitant medications are identified with no associated AEs or when SAEs are reconciled, queries are subsequently issued to the site to add the missing subject event (or events).

AEs identified via laboratory data: There may be a delay in laboratories returning results to the site and an additional delay in investigators assessing significance of any identifying laboratory abnormalities; these factors may result in sites adding AEs later than the subject visit data.

Site delay in entering AEs: Due to the need to collect supplemental or confirmatory information about some events or to time needed for investigator assessment, there may be a delay in sites adding AEs.

It is possible that some AEs identified during on-site monitoring visits are not entered by the site until sometime

after the 7-day window defined in the present analysis. Furthermore, it is fair to assume that some portion of the AEs and SAEs identified via on-site monitoring would have been identified by another data review process if SDV or SDR had not been performed. As a result of these variables, it is clear that some AEs were identified only via on-site SDV or SDR, but this analysis was not able to conclusively determine how many of the late-entered AEs fall into this category.

In the RBM methodology, comprehensive methods can be employed to assess critical variables, such as the use of risk indicators to identify sites that have a lower-than-expected rate of reporting AEs or SAEs. Once a site is identified as an outlier in subject event reporting, additional focus (on- and/or off-site monitoring) can be leveraged to determine if increased monitoring of the site is warranted. For example, to address the identified issue, a site monitor might first conduct SDR to ensure that the process of AE identification and documentation was appropriately followed and then conduct SDV to confirm that the events identified in the source appear on a list of reported events and/or within the EDC system. Additionally, AEs and SAEs are likely to be considered critical data in the risk assessment process for studies and therefore will likely be receiving close attention by multiple monitoring functions, including remote cross-functional reviewers. Any indication of problems or site risks in reporting AEs or SAEs could be mitigated by further increasing monitoring attention as part of the adaptive design of RBM.

Table 9 provides insight to audit data indicating that SDR may be more likely than SDV to identify the errors ultimately noted as audit findings. Less than 1% of the SDV-related audit findings were defined as critical, again suggesting a negligible impact of SDV on overall study quality. Conversely, ineffective SDR was attributed to major/critical findings 3 times more often than SDV; as such, shifting the on-site monitoring focus from SDV to SDR may allow sponsors to better assess the quality of the overall conduct of the study at a site and may result in improved study quality by identifying the issues sooner and preventing them from recurring.

Conclusions

The literature and data analyses conclude that SDV has a negligible impact on data quality. The RBM methodology and evolving technology shift the focus from SDV to more strategic quality management methods. Whereas SDV identifies an insignificant number of transcription errors, other monitoring methods, such as central monitoring or SDR, can instead be used to confirm that the protocol is being followed (improving GCP compliance) and that eligible subjects are enrolled (improving subject safety).

SDV can still be considered one of many potential quality control methods used to determine whether an acceptable level of accuracy has been achieved in the transcription of critical data. However, the literature review, retrospective data analyses, and audit findings review conducted in this investigation advocate that SDV should no longer be the foremost quality management method employed in clinical trials, as SDV does not meaningfully contribute to overall data quality. Instead, other monitoring methods, such as central monitoring and SDR, should be used to focus on what matters most to the study.

Acknowledgments

The authors gratefully acknowledge the support of TransCelerate BioPharma Inc, a nonprofit organization dedicated to improving the health of people around the world by accelerating and simplifying the research and development of innovative new therapies. The organization's mission is to collaborate across the global biopharmaceutical research and development community to identify, prioritize, design, and facilitate implementation of solutions designed to drive the efficient, effective, and high-quality delivery of new medicines. The authors also gratefully acknowledge the support of Medidata, a leading global provider of cloud-based solutions for clinical research in life sciences. Medidata's mission is to provide innovative clinical research solutions that improve the efficacy, efficiency, and outcomes of clinical trials and, in doing so, safely improve quality of life for patients worldwide.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. ICH harmonised tripartite guideline, guideline for good clinical practice E6(R1). http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. Accessed April 18, 2014.
2. Schuyl ML, Engel T. A review of the source document verification process in clinical trials. *Drug Information Journal*. 1999; 33:789-797.
3. International Federations of Pharmaceutical Manufacturers and Associations. Clinical trials portal. http://clinical-trials.ifpma.org/clinicaltrials/en/tips/#s-link.
4. TransCelerate BioPharma Inc. Position paper: risk-based monitoring methodology. http://www.transceleratebiopharmainc.com/wp-content/uploads/2013/10/TransCelerate-RBM-Position-Paper-FINAL-30MAY2013.pdf. Published 2013.
5. Funning S, Grahnen A, Eriksson K, Kettis-Linblad A. Quality Assurance within the scope of good clinical practice (GCP): what

is the cost of GCP-related activities? A survey within the Swedish Association of Pharmaceutical Industry (LIF)'s members. *Qual Assur J*. 2009;12:3-7.
6. Baigent C, Harrell FE, Buyse M, et al. Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clin Trials*. 2008;5:49-55.
7. Tantsyura V, Grimes I, Mitchel J, et al. Risk-based source data verification approaches: pros and cons. *Drug Information Journal*. 2010;44:745-756.
8. Duley L, Antman K, Arena J, et al. Specific barriers to the conduct of randomized trials. *Clin Trials*. 2008;5:40-48.
9. De S. Hybrid approaches to clinical trial monitoring: practical alternatives to 100% source data verification. *Perspect Clin Res*. 2011;2(3):100-104.
10. European Medicines Agency, Science Medicinces Health. *Reflection Paper on Risk Based Quality Management in Clinical Trials*. London, England: European Medicines Agency; 2013. Publication EMA/269011/2013.
11. Bakobaki J, Rauchenberger M, Joffe N, McCormack S, Stenning S, Meredith S. The potential for central monitoring techniques to replace on-site monitoring: findings from an international multicentre clinical trial. *Clin Trials*. 2012;9:257-264.
12. Tudur Smith C, Stocken DD, Dunn J, et al. The value of source data verification in a cancer clinical trial. *PLoS ONE*. 2012;7(12):e51623.
13. US Department of Health and Human Services, Food and Drug Administration. *Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring*. Washington, DC: US Department of Health and Human Services; 2013. OMB control 0910-0733.
14. Neilsen E, Hyder D, Deng C. A data-driven approach to risk-based source data verification. *Therapeutic Innovation & Regulatory Science*. 2014;48:173-180.
15. Medidata Solutions. Industry metric indicates low ROI with full source document verification. http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDetail.jsp?id=767452. Published April 2012.
16. Atkinson I. Accuracy of data transfer: double data entry and estimating levels of error. *J Clin Nurs*. 2012;21:2730-2735.
17. Verhulst K, Artiles-Carloni L, Beck M, et al. Source document verification in the Mucopolysaccharidosis Type I Registry. *Pharmacoepidemiol Drug Saf*. 2012;21:749-752.
18. Carraro P, Plebani M. Post-analytical errors with portable glucose meters in the hospital setting. *Clin Chim Acta*. 2009;404:65-67.
19. Grahnen A, Karlsson K, Bragazzi F. Impact of transcription errors on the outcome of a clinical trial. *Clinical Pharmacology & Therapeutics*. 2007;81(1):S21.
20. Brosteanu O, Houben P, Ihrig, et al. Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials. *Clin Trials*. 2009;6:585-596.
21. Toth-Allen J. *Building Quality Into Clinical Trials: An FDA Perspective*. Washington, DC: US Food and Drug Administration; 2012.