Examining Methods and Practices of Source Data Verification in Canadian Critical Care Randomized Controlled Trials

ROXANNE WARD

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Epidemiology and Community Medicine

Faculty of Medicine

University of Ottawa

ABSTRACT

Statement of the Problem: *Source data verification* (SDV) is the process of comparing data collected at the source to data recorded on a Case Report Form, either paper or electronic (1) to ensure that the data are complete, accurate and verifiable. Good Clinical Practice (GCP) Guidelines are vague and lack evidence as to the degree of SDV and whether or not SDV affects study outcomes.

Methods of Investigation: We performed systematic reviews to establish the published evidence-base for methods of SDV and to examine the effect of SDV on study outcomes. We then conducted a national survey of Canadian Critical Care investigators and research coordinators regarding their attitudes and beliefs regarding SDV. We followed by an audit of the completed and in-progress Randomized Controlled Trials (RCTs) of the Canadian Critical Care Trials Group (CCCTG).

Results: Systematic Review of Methods of SDV: The most common reported or recommended frequency of source data verification (10/14 - 71%) was either based on level or risk, or that it be conducted early (i.e. after 1st patient enrolled). The amount of SDV recommended or reported, varied from 5-100%. Systematic Review of Impact of SDV on Study Outcomes: There was no difference in study outcomes for 1 trial and unable to assess in the other. National Survey of Critical Care Investigators and Research Coordinators: Data from the survey found that 95.8% (115/120) of respondents believed that SDV was an important part of Quality Assurance; 73.3% (88/120) felt that academic studies should do more SDV; and 62.5% (75/120) felt that there is insufficient funding available for SDV. Audit of Source Data Verification Practices in CCCTG RCTs: In the national audit of in-progress and completed CCCTG RCTs, 9/15 (60%) included a

plan for SDV and 8/15 (53%) actually conducted SDV. Of the 9 completed published trials, 44% (4/9) conducted SDV.

Conclusion: There is little evidence base for methods and effect of SDV on study outcomes. Based on the results of the systematic review, survey, and audit, more research is needed to support the evidence base for the methods and effect of SDV on study outcomes.

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1.0 INTRODUCTION

1.1 Overall Objectives

The overall objective of this thesis is to establish the evidence-base for source data verification within clinical research.

1.1.2 Primary Objective

To establish the evidence-base for source data verification by conducting a systematic review of the literature with the following specific objectives:

A. To examine published methods of source data verification. Please see section 3.0
B. To examine the effect of source data verification methods on study outcomes. Please see section 4.0

1.1.3 Secondary Objectives

A. To describe current beliefs and practices regarding source data verification of Canadian Critical Care investigators and research coordinators. Please see section 5.0.
B. To describe the current methods for assessing source data verification practices in Canadian critical care research. Please see section 8.0.

These objectives will be met by conducting a systematic review of the literature to examine the methods and effect of source data verification, a national survey, and a retrospective audit of the source data verification practices of members of the Canadian Critical Care Trials Group.

1.2 Source Data and Source Data Verification Defined

According to the International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP)

Guidelines, *source data* is defined as “all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial”(2). *Source data verification* is the process of comparing data collected at the source to data recorded on a Case Report Form, either paper or electronic (1).

2.0 BACKGROUND

2.1 History of International Conference on Harmonisation and ICH GCP

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 for the purpose of improving through harmonisation, the process for developing and registering new medicinal products in Europe, Japan and the United States, in the interest of the consumer and public health (2). Through an informal consensus process involving national regulatory and pharmaceutical industry agencies, topics chosen for harmonisation are reviewed and various guidelines are developed and established. One such guideline, the tripartite ICH harmonized Good Clinical Practice (GCP) Guidelines were finalized in May 1996 and describe the responsibilities and expectations of all participants in the conduct of a clinical trial (2). This document covers various aspects of documenting, reporting, archiving as well as the monitoring (including source data verification) of clinical trials. In September 2001, Health Canada formally adopted ICH GCP Guidelines as part of the Clinical Trials Regulations, Division 5 of the Food and Drugs Act (3). Health Canada implemented a formal inspection program in 2003 with a goal of inspecting 2% of Canadian trial sites per year, determining the extent to which a clinical trial site is following ICH GCP Guidelines.

These guidelines state that clinical trials should be adequately monitored to verify that the rights and safety of participants are protected, that the trial is conducted according to the protocol and to ICH GCP Guidelines, and that the data are accurate, complete and verifiable. On-site monitoring includes source data verification, which is the process of comparing data collected at the source to data recorded on a Case Report Form, either paper or electronic. Source data are contained in source documents (original records or certified copies) (2). There are a number of strategies that help to ensure data integrity, such as logic checks, consistency checks, and range

checks, often referred to as central monitoring techniques. However, ***source data verification has traditionally been considered to be the key method to guarantee that the collected data are accurate, complete and verifiable***.

Data management techniques such as logic, consistency and range checks are able to detect when there are data that fall outside of the expected range of values. An example would be an age of 560 years entered on a Case Report Form where the real age is 56 years. However, these processes will not pick up an incorrect blood pressure of 150/80 entered on a Case Report Form where the real value is 140/80. This difference may appear inconsequential, yet if participants are stratified by blood pressure or eligibility into a clinical trial is based on blood pressure targets, then the subject may be randomized in error. Logic, consistency and range checks are excellent tools for detecting "out-of-the-ordinary" errors. Source data verification can reveal errors that may not be discovered by logic, consistency or range checks and it is source data verification that is the focus of this project.

ICH GCP Guidelines are non-specific as to the extent, nature, and timing of monitoring with source data verification. According to ICH GCP Guidelines, on-site monitoring is generally needed before, during and after the trial, and that statistically controlled sampling for selecting data to be verified may be considered acceptable (2). However, these guidelines are not evidence- based (4) as they were developed by informal consensus, which some consider to be the weakest method of guideline development (4). As well, ICH is financially supported by various national regulatory and industry agencies who were also involved in the development of these guidelines, while representation from investigator-led or academic research was absent. As a result, not only is the evidence-base for the type and amount of on-site monitoring required lacking, but there may be partiality in the focus, development, and use of, ICH GCP Guidelines.

2.2 Source Data Verification: Differences between Industry and Investigator-led Research

Industry sponsored clinical research typically conducts on-site monitoring with source data verification of 100% of data collected. Industry or pharmaceutical companies tend to comply with ICH GCP Guidelines as they require regulatory approval of their products and wish to ensure the safety of novel therapeutics as well as protect their financial investments. However, while investigators of academic research wish to comply with ICH GCP Guidelines, their focus is much different. Investigator-led research does not typically involve the study of novel investigational drugs, but rather trials that compare various approved therapies to current practice. Generally peer-reviewed funding available for investigator led research is considered to be significantly less than for industry sponsored trials. Although both industry and investigator-led research usually employ some quality assurance process in addition to source data verification, to ensure data integrity such as logic, range or consistency checks, source data verification is typically done much less frequently in investigator-led research. Based on anecdotal experience in Canadian randomized controlled trials (RCTs), it is not unusual to find that less than 10% of the data recorded on the Case Report Form has been source document verified in investigator-led research. A United States national survey conducted by the Clinical Trials Transformation Initiative (CTTI) in 2009, found that 31% of academic centres perform monitoring visits as compared to 84% by industry (5).

2.3 Source Data Verification and the Detection of Error

The sources of data error in clinical research include fraud, random and systematic error. While there have been a few highly publicized cases of misconduct involving fraud, this is a relatively rare occurrence in clinical research (6, 7). Therefore, the main sources of error in the data are random and systematic error. Random error occurs by chance and can affect the precision of the data. Investigators can reduce the effect of random error by increasing the sample size,

repeating measurements within a study, or by modifying the study design (8). Systematic error, unlike random error, does not occur by chance, but is introduced by an inaccuracy (such as an observation or measurement) within the system. As such, it can affect the validity of the data, potentially more so than random error, and this effect may be magnified in large studies (9). Methods to avoid the impact of systematic error include randomization and blinding.

Source data verification can help detect both random and systematic error; however, it will not reveal all such errors. For example, if there is an error in the source document, then this error will be repeated in the transcription process. Potential systematic errors that may not be detected by source data verification may be measurements that are made by an improperly calibrated measurement tool. There are other methods that can be used to detect systematic error, such as the use of aggregate statistics (10) that may be as or more effective than source data verification. Such strategies compare distribution of variables across study sites and can detect abnormal trends or patterns in the data. Table 1 below gives examples of common sources of error and the primary detection methods(10).

Table 1: Common sources of error and primary detection methods (10)

	Detection Methods			
Potential Sources of Error	Programmatic Checks	Source Data Verification	Aggregate Statistics	CRF to Database Inspection
Protocol violation		X	X	
Transcription error	X	X		
Data entry error	X	X		
Site equipment error			X	X
Error in reading equipment or printout or inter-rater reliability		X		
Missing data	X	X		
Lost data		X		
Fraud		X	X	

2.4 Limitations of Source Data Verification

Source data verification is conducted to ensure the validity and accuracy of the data. However, on-site monitoring and source data verification are labour intensive, expensive and questions have been raised regarding its cost-effectiveness given the relative infrequency of fraud (7, 11, 12). In a survey conducted by Funning et al, Swedish pharmaceutical companies spend approximately 1/3 of the entire Phase III trial budget on source data verification (13). It is reasonable to expect similar experiences with North American pharmaceutical companies.

Surprisingly, there is little quantitative information available on whether source data verification provides assurances about data integrity and how successful it is in detecting random and systematic error. Unfortunately, few investigators publish or report the results of data audits of their clinical trials. One report of an audit by the National Cancer Institute that was conducted after the discovery of fraud by an investigator, determined that the results of the trial did not change following source data verification (14). Another report of an audit published in 1989 by the European Organization for Research and Treatment of Cancer, found that 97.2% (median) of the data were correct (15). Thus, there remains not only a lack of guidance for investigators regarding how much source data verification is sufficient, but little evidence that this process makes any difference in the outcomes of clinical trials.

2.5 Source Data Verification in Critical Care Research

Research conducted within critical care environments poses special challenges in comparison to research conducted in other health care areas. First and foremost, the patient population is among the most ill and most vulnerable, with the majority of patients being incapable of providing consent to participate in clinical research, because of incapacity due to unconsciousness or sedation, or young age (16, 17). These patients are at greater risk of adverse events simply because of their presenting condition or co-morbidities. Critical care research

protocols are often complex and require the collection of large amounts of data. Two examples of this are a large adult study by Cook et al, looking at the prophylaxis of thromboembolism in Critical Care patients, and a smaller pediatric study, by Choong et al, evaluating the use of vasopressin in pediatric vasodilatory shock (18, 19). For these reasons, thorough oversight of critical care research is imperative.

And so the questions regarding the methods and impact of source data verification have significant relevance within critical care research: does source data verification make a difference in the outcomes of critical care research and how much source data verification should be done? Thus the primary objective of this thesis is to establish the evidence-base for methods of source data verification. It will provide necessary knowledge to inform the next the steps in my research agenda; namely, the development of clearer guidelines for monitoring and source data verification for critical care investigators to remove the current ambiguity that exists within the current ICH GCP Guidelines.

1.0 SYTEMATIC REVIEW – METHODS OF SOURCE DATA VERIFICATION

3.1 Objective

To establish the evidence-base for source data verification by conducting a systematic review of the literature to examine published ***methods*** of source data verification.

3.2 Methods

3.2.1 Data Sources and Search Strategy

We developed an explicit search strategy with the assistance of an information specialist to search the PubMed® (1950 – May 2011), EMBASE® (Ovid) (1980 – July 2011), and Cochrane Central Register of Controlled Trials (CENTRAL®, The Cochrane Library). We attempted to identify all relevant publications, regardless of language, publication status (published, unpublished, in press or in progress), or date of publication. Full details of the search strategy are included in Appendix A. We identified relevant publications by searching the following areas: electronic bibliographic databases for published studies, methodological publications, reports; reference lists of relevant published papers; web sites of clinical trial associations, academic research organizations, or conference proceedings of clinical trial organizations for reports, methods articles, or guidelines on source data verification procedures. We defined guidelines or recommended guidelines as those papers that met either of the following criteria:

a. The publication was referred to as a "Guideline",

b. The main focus of the paper was to provide recommendations on a method(s) of source data verification.

We considered publications to be reports if they provided information on methods of source data verification that had been done.

We searched reference lists of all included citations for any additional relevant published studies, or methodological reports, or guidelines not already assessed for inclusion. We used Web of Science® (ISI Web of Knowledge) (1900 – May 2011) to assist with citation searching.

We conducted hand searching of record titles in specific journals of interest: Clinical Trials, Trials, Applied Clinical Trials, Controlled Clinical Trials, and Drug Information Journal. We used the World Wide Web to search the following clinical trial organizations for potentially suitable records not previously identified: Association of Clinical Research Professionals, Society of Clinical Research Associates, and Drug Information Association. No language restriction was applied during the screening process, but for the purposes of this thesis, we included only English language full-text records for final evaluation.

3.2.2 Study Selection

3.2.3.1 Inclusion Criteria

To meet our inclusion criteria, the primary purpose of the publication was to describe or discuss a method(s) of source data verification.

3.2.3.2 Exclusion Criteria

We excluded animal studies literature or publications that only reported that source data verification was conducted. We excluded non-English language full-text records in the final evaluation.

3.2.3 Outcomes of Interest

Specific outcomes of interest included the following: 1) methods of source data verification (i.e. methods of comparing the source document to the data that is collected using either a paper or electronic record; 2) frequency of source data verification; 3) amount of source data verification;

and 4) other methods used to assess data quality including the role of central monitoring. We defined Central Monitoring as activities that are done centrally to assess the validity and reliability of the data and can include sending copies of source documents to the data coordinating centre. While Statistical Monitoring falls under the umbrella of Central Monitoring, it is more specific in its focus. As such, we defined Statistical Monitoring to include the following activities: comparing data across sites to assess trends with the use of aggregate statistics, observing for out of range, missing or inconsistent data, or conducting statistical analyses.

3.2 4 Record Review and Data Extraction

We utilized two content experts to conduct the search and initial screening. Two experienced Clinical Research Coordinators (Lynda Hoey and Roxanne Ward) independently screened titles and abstracts for relevancy using the search strategy described above (section 3.2.1) (Level 1 screen). Electronic records were reviewed using EndNote©. Potentially eligible records were selected for full-text review. The full-text records were assessed independently by the same two reviewers for appropriateness of inclusion based on the pre-defined inclusion and exclusion criteria (Level 2 screen). Any disagreement between reviewers was resolved by further review and discussion.

We developed a standardized data extraction form to capture pre-defined data items, which the Research Coordinators completed for those papers included. The data extraction form was first piloted on 20 articles independently reviewed by both Research Coordinators to ensure (Appendix B) completeness and feasibility.

In addition to the Outcomes of Interest collected (section 3.2.3), we collected information on the type of publication, year of publication, journal name, primary objective of publication, data collection methods, who performed or should perform source data verification, and information regarding error rates.

As the purpose of the review was to examine methods of source data verification, assessing the methodological quality of the studies or reports was not considered relevant. We report on the types of studies, reports, and guidelines found.

3.2.5 Data Synthesis and Analysis

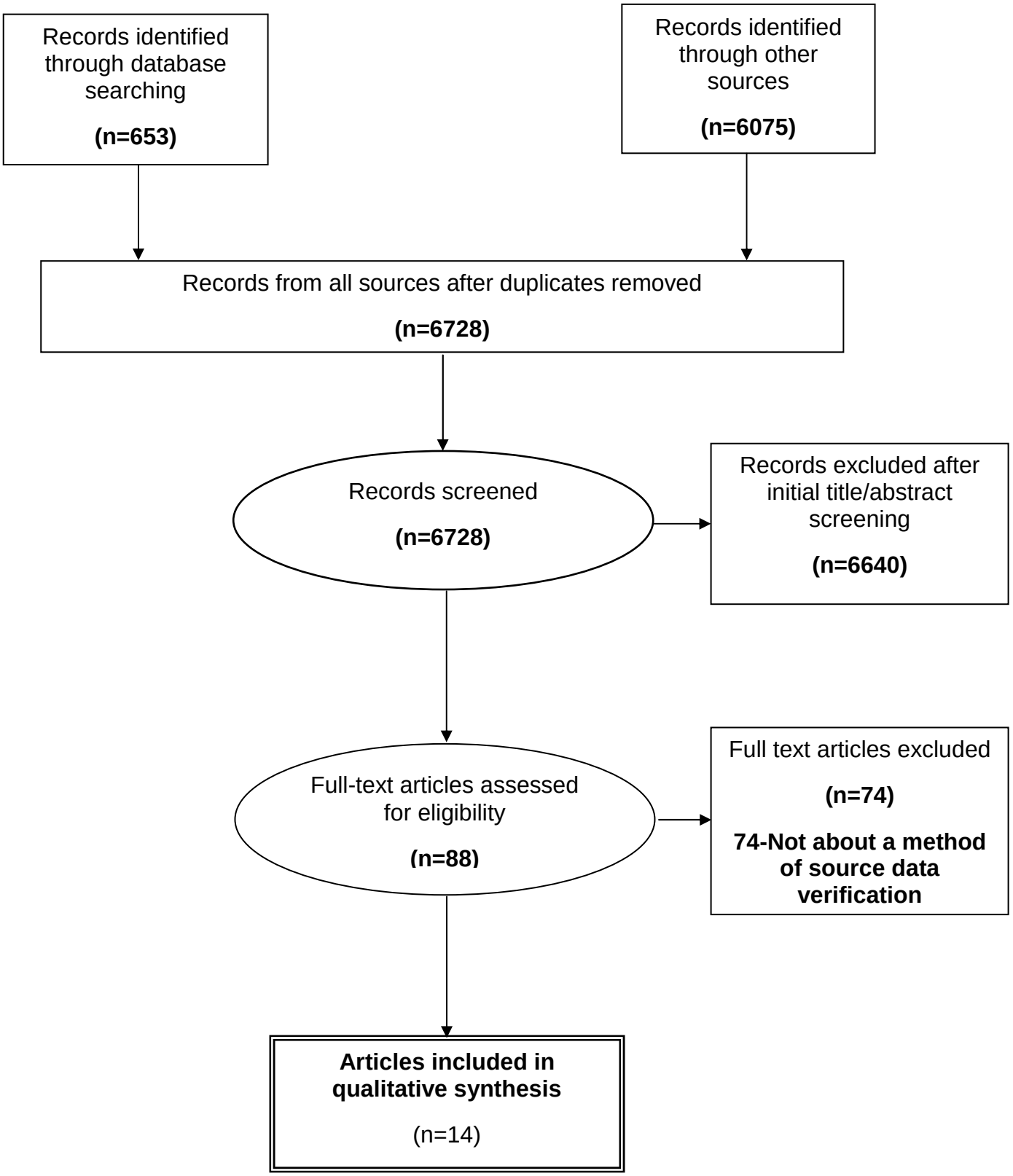
It was not expected that statistical pooling of the results of studies or reports would be feasible given that the majority of the literature would be methodological reports or guidelines, and the number of studies likely small in number. We summarised the information available for each study, methodological publication, guideline, or report in a tabular format which is accompanied by a descriptive commentary in the results section of the review.

3.4 Results

3.4.1 Search Results

We identified 6,728 potentially eligible papers: 653 from electronic databases, 5,954 from hand searching, and 121 from the World Wide Web (Figure 1). After initial screening, we excluded 6,640 articles and retained 88 articles for review of the full publication. After review of the full-text documents, 74 articles were excluded for the following reasons: 1) the full-text article was not available in English (n=4) and 2) were not specifically about a method of source data verification (n=70).

Figure 1: Systematic review of methods of source data verification: Flow diagram



3.4.2 Study Characteristics

The included articles (n=14) were published between 1998 and 2011, with the majority (64%) published within the past five years (Table 2). Seven were considered guidelines or recommendations. The remaining were commentaries - 2, reports - 2, surveys - 2, and a methods paper -1. Seven publications were from the United States, six were from Europe, and one was from India. Six principal authors reported a primary affiliation with the pharmaceutical industry, seven with academic centres, and one had had both academic and pharmaceutical industry affiliations. Of the 14 publications, 10 were categorized as 'recommendations' and the remaining four were 'reports'.

Table 2: Characteristics of the 14 publications included in the systematic review

Author / Publication / Year	Author Affiliation: Academic or Industry	Country	Publication Type	Reported or Recommended
Baigent et al. / Clinical Trials - 2008	Academic	UK, USA, Belgium	Guideline[b]	Recommended
Bertoye et al. / Therapie - 2006	Academic	France	Round-table Report	Recommended
Brosteanu et al. / Clinical Trials - 2009	Academic	Germany	Guideline[b]	Recommended
Busch-Heidger et al. / Applied Clinical Trials - 2001	Industry	Germany	Survey	Reported[c]
Hines S. / Applied Clinical Trials - 2011	Industry	USA	Commentary	Recommended
Journot et al. / Contemporary Clinical Trials - 2011	Academic	France	Methods - Validation of risk assessment scale and risk adapted monitoring plan	Recommended
Khosla R. / Indian Journal of Pharmacology - 2000	Academic	India, Germany	Guideline[b]	Recommended
Knatterud et al. / Controlled Clinical Trials - 1998	Academic	USA	Guideline[b]	Recommended
N/A / EMC2 - Accessed May 2011	Industry	USA	Commentary	Reported[c]
Morrison et al. / Clinical Trials 2011	Academic and Industry	USA	Survey	Reported[c]
Schuyl et al. / Drug Information Journal - 1999	Industry	UK	Guideline[b]	Recommended
Tantsyura et al. / Drug Information Journal - 2010	Industry	USA	Report	Recommended
Usher RW / Drug Information Journal - 2010	Industry	USA	Guideline[b]	Recommended
Weiss et al. / Cancer Chemo. Pharmacology - 1998	Academic	USA	Report - Refers to Guideline	Reported[c]

[a]May include, but not limited to eligibility criteria, randomization, primary/secondary endpoints, adverse events, safety data, informed consent
[b]Suggested or recommended guideline
[c]Reported on what was done

3.4.3 Variables for Source Data Verification

3.4.3.1 Publications Categorized as Guidelines or Recommendations

Two of the eight publications that made recommendations regarding methods of source data verification, did not specify which variables should be included for source data verification (20, 21) (Table 3). The remaining six publications recommended conducting source data verification on 'key' or 'critical data' (15, 22-27). Key data included, but was not limited to, eligibility criteria, randomization allocation, primary and secondary endpoints, adverse events, safety data, and informed consent. While key data was not defined the same within studies, the components that were common to all included primary endpoints and eligibility.

One of the eight publications that recommended using key data (28) further stated that the amount and frequency of source data verification of key data would depend upon the risk assessment for the study. The authors recommended assessing the risks associated with a number of factors, including, the type of study, the complexity of the protocol, the vulnerability of the study population, the experience of the study site personnel, the safety of the product/treatment being studied, and what the effect would be on patient safety and/or data safety of potential sources of error (27).

Table 3: Publications – Guidelines or recommendations on methods of source data verification

Author	Variables	Frequency of Source Data Verification (SDV)	Amount of Source Data Verification (SDV)	Central or Statistical Monitoring	Results/ Comments
Baigent et al.	Not stated	Depends on potential for bias arising from errors	Random sample at each site	Central and Statistical monitoring	Intensive on-site monitoring not needed in all trials. Better use of central and statistical monitoring needed
Bertoye et al.	Not stated	Not stated	10-100% depending on level of risk assigned: Risk A, B, C, D	Central monitoring	Modify on-site monitoring according to risk level. Evaluated risk to participant only, not to validity of study results.
Brosteanu et al.	Key data[a]	**Low** - 1X **Intermediate** - 3X per year **High** - 6X per year	**Low** - key data for 20% of subjects **Intermediate** - key data for 20-50% of subjects depending on site factors **High** - 100% SDV for 10% of subjects	Statistical monitoring only	Development of a risk-based assessment tool for non-commercial studies to facilitate the implementation of a QA program. Evaluated risk to participant as well as to validity of study results
Hines S.	Key data[a]	Not stated	Targets key data[a] and uses random sampling methods to select data for SDV using 2 methods: 1. Fixed Field: 100% SDV for 1st 1 - 2 subjects at ea site, then 100% SDV of key data Random: 100% SDV for 1st 1 or 2 subjects at ea site, then random selection of CRF fields, including eligibility criteria and adverse events	Statistical monitoring only	Targeted SDV can be more effective than 100% SDV
Journot et al.	Key data*	Depends on level of risk assessment	Risk A: No SDV Risk B: 10% subjects have 100% SDV Risk C: At least 1 vist/site, 100% SDV on Key data for X subjects	Central and Statistical monitoring	49 Assessors evaluated 200 protocols: 952 assessments to compare Risk Assessment Scale to VAS Evaluated risk to participant, not to validity of study results
Khosla R.	Key data*	Thorough SDV for first few patients at each site, then quick SDV for each remaining pt.	100% SDV of Key data for first X subjects, then reduced SDV OR 100% SDV Key Data for all subjects and 15-25% of non-critical items	Not described	Determine SDV needs early Develop an SOP for SDV
Knatterud et al.	Key data[a]	2X (At beginning and end), 3X if > 3 years	5 - 10%	Central and Statistical Monitoring	SDV only part of QA program. Publications should describe methods to ensure data quality.
Schuyl et al.	Key data[a]	Early and then ongoing	100% of Key data* for all pts, then 25% randomly selected CRF's - non-critical data	Not described	Develop an SOP for SDV
Tantsyura et al.	Key data[a]	Not stated	Mixed Approach: Screening, baseline visit - 100% SDV 100% SDV for Key data	Central monitoring	Provides proposal on how to modify SDV process that does not affect trial integrity
Usher RW	Focus on Key data[a] Depends on Risk Assessment	Depends on risk assessment for study	Depends on Risk Assessment	Statistical monitoring only	Recommends better use of technology and central monitoring to assess data quality and guide need for on-site monitoring

[a]May include, but not limited to eligibility criteria, randomization, primary/secondary endpoints, adverse events, safety data, informed consent
[b]Suggested or recommended guideline

3.4.3.2 Publications Categorized as Reports

Of the four articles that reported on methods of source data verification, one did not specify which variables were considered for source data verification (5) (Table 4). Three articles reported (29-31), using 'key' or 'critical' data for source data verification. As noted in Section 3.4.3.1 above, key data was not defined consistently in all studies. However, the components that were common to all included eligibility, and primary endpoint. Of the three articles that reported conducting source data verification on key data, two articles reported that either all variables or all key data were source data verified (29, 31). Both articles were based on experience in pharmaceutical industry trials.

Table 4: Publications that reported on methods of source data verification

Author/ Publication/ Year	Variables	Frequency of Source Data Verification (SDV)	Amount of Source Data Verification (SDV)	Central or Statistical Monitoring	Results/ Comments
Busch-Heidger et al. Applied Clinical Trials - 2001	All or Key data[a]	After 1 pt enrolled, Mean 8 wks	1. 100% of all items 2. 100% of Key data 3. Pre-determined algorithm	Not described	Decreased SDV appears reasonable, Most agree that SDV done only on Key data
N/A EMC2 - Accessed May 2011	All or Key data[a]	Depends on level of risk	100% of Key data* for 1st 1 to 5 subjects or 100% of first 2 pts screening, randomization and first 2 on-drug visits, or 100/% of all pts inclusion/exclusion criteria, or 100% of all consent forms, then 100% of X% of subjects randomly selected	Not described	Commentary based on industry practices
Morrison et al. Clinical Trials 2011	Not stated	Not stated	31% of Academic centres always conduct monitoring vs 80-89% of CROs/Industry	Central monitoring done always < 33% of time	Significant variation in monitoring practices across US Academic & Industry. Response rate 30%. Encourage use of technology to develop more efficient monitoring techniques
Weiss et al. Cancer Chemo. Pharmacology - 1998	Key data[a]	1X per 3 years	5-40% of CRF's	Central and Statistical monitoring	Improvement in data accuracy noted over time.

[a]May include, but not limited to eligibility criteria, randomization, primary/secondary endpoints, adverse events, safety data, informed consent

3.4.4 Frequency of Source Data Verification

3.4.4.1 Publications Categorized as Guidelines or Recommendations

Three of the ten publications did not include a recommendation on the frequency of source data verification (21, 23, 26) (Table 3). The remaining seven recommended different frequencies of source data verification; three indicated that frequency was dependent on the level of risk (20, 24, 27), and two recommended conducting source data verification early (after the first 1-2 patients were enrolled) but then did not specify the frequency as the trial progressed (1, 25).

The two remaining publications provided more specific recommendations. One recommended that source data verification be conducted twice (once at the beginning and once at the completion of the trial), but three times if the duration of the trial was more than three years (15). Brosteanu et al recommended three levels of source data verification based on a level of risk as determined using a risk assessment tool (22). Low risk studies should have source data verification done once annually; intermediate risk studies should be visited three times per year; and high risk studies should have source data verification conducted six times per year.

3.4.4.2 Publications Categorized as Reports

One of four publications that reported on the frequency of source data verification, the survey by Morrison et al, did not indicate the frequency of source data verification (5) (Table 4). Of the three remaining publications that described the frequency of source data verification, one indicated that it was usually done after the first patient was enrolled and then conducted an average of every 8 weeks thereafter (29); one reported that it was done once every three years (30); and the third reported that it depended on the level of risk (31).

3.4.5 Amount of Source Data Verification

The amount of source data verification was expressed as a percentage of Case Report Forms (CRF) and/or percentage of variables, and varied from 5 to 100%.

3.4.5.1 Publications Categorized as Guidelines or Recommendations

Three of the ten publications recommended varying amounts of source data verification based on level of risk (Table 3). They recommended specific strategies for the amount of source data verification based on defined categories of risk levels and developed risk assessment tools (e.g. low, intermediate and high risk and Risk Level A, B, C, D, with increasing levels of risk from A to D) (21, 22, 32). Each risk level was also associated with specific recommendations regarding the amount and frequency of source data verification. Risk assessment considerations were specific to participant safety (21, 32) or inclusive of both participant safety and data integrity (22). One recommended source data verification frequency be based on concepts of basic risk management but did not specify the amount of source data verification to be done as a result of this assessment .

Complete (100%) source data verification of key data for the first few participants enrolled at each site, followed by either a random selection of variables, or 100% source data verification on a few number of variables was recommended in two publications (23, 25). One of these two further recommended an additional option of 100% source data verification for all participants followed by 15-25% of non-critical variables (25).

Additional recommendations for the amount of source data verification included: a random sample or 5-10% of CRFs at each site (15, 20); 100% source data verification for screening and baseline visits, followed by 100% source data verification of all key data (26);

100% source data verification of key data followed by non-critical variables in 25% randomly selected CRFs (1).

3.4.5.2 Publications Categorized as Reports

Of the three publications that reported on the amount of source data verification; one reported 100% source data verification on key data to 100% of all data (29), one reported 100% source data verification of key data for the first 1 to 5 study participants and then 100% of a number of randomly selected participants (31); and one reported that 5 to 40% of CRFs had source data verification (30) (Table 4). One publication, a survey, did not report on the amount of source data verification conducted (5).

3.4.6 The Role of Central Monitoring

There was no consistent definition of central monitoring in the literature. Central monitoring activities included the receipt and review of copies of source documents, such as lab or radiology reports, at the Data Coordinating Centre with comparison to the data collected on the CRF or entered into a database. Statistical Monitoring was generally described as checking case report forms for completeness, reviewing data for inconsistencies, out-of-range checks, conspicuous data patterns, or the use of more sophisticated statistical methods such as multivariate analysis.

3.4.6.1 Publications Categorized as Guidelines or Recommendations

Two of the ten publications did not provide recommendations on Central or Statistical Monitoring (1, 25) (Table 3). Three publications recommended both central and statistical monitoring (15, 20, 24). Central monitoring only was recommended in two publications (26) (21). Three publications recommended statistical monitoring, only, without central monitoring (22, 23, 27).

3.4.6.2 Publications Categorized as Reports

Two of the three publications did not describe methods of Central or Statistical Monitoring (29, 31). Morrison et al reported that Central Monitoring was always conducted less than 33% of the time (5) (Table 4). Weiss et al reported that Central and Statistical Monitoring was done as part of a Data Quality Assurance guideline of a large US cooperative group (30).

3.5 Discussion

Based on this review, there are few publications that report on actual source data verification procedures and there is significant variation in the amount and frequency of source data verification recommended in the literature. While the amount of source data verification can be expressed either as a percentage of CRFs or variables, recommendations in the literature are inconsistent and are not easily applied. There was no clear and consistent definition of central monitoring or statistical monitoring.

There were no studies found that evaluated a method(s) of source data verification. There were only two surveys that assessed methods of source data verification; one of which included only pharmaceutical companies in Germany (29) and the other, while it included both academic and pharmaceutical agencies, had a very small response rate (5).

Several authors have developed tools to assess risk that can potentially be used to determine the appropriate amount of monitoring and source data verification (21, 22, 24), termed "risk-based monitoring" or "risk-adapted monitoring"(26). These risk assessments are performed to identify potential errors that would critically affect patient safety and/or data quality. Thus, quality assurance measures (including source data verification) are determined based on the level of risk assessed. Examples of factors that could be associated with greater patient risk may include Phase I studies, or studies involving therapies associated with frequent

serious adverse events. Examples of factors that could be associated with greater risk to data validity potentially include a complex protocol design or sites with inexperienced study personnel.

The risk assessment tool developed by Journot et al, is currently being used in a multi-centre, cluster randomized trial in France. The Optimon Study (24), is comparing two monitoring strategies; standard monitoring based on pharmaceutical practices and an 'optimized' or "risk-adapted" monitoring strategy. The primary outcome is the proportion of patients without error on pre-specified key data. A similar trial, the ADAMON Trial (22, 33), is being conducted by Brosteanu et al in Germany, to compare a risk-adapted monitoring strategy to the usual intensive on-site monitoring strategy on the occurrence of a serious or critical violation of GCP Guidelines.

Pharmaceutical industry trial monitoring continues to adopt a conservative interpretation of ICH GCP Guideline's recommendation on the extent and frequency of monitoring and source data verification with 100% on-site source data verification. Interestingly, no article in our review recommended this strategy. In fact, neither the ICH GCP Guidelines nor the FDA mandate 100% source data verification (23). Division 5 of the Health Canada Regulations, Food and Drug Act C.05.010 states that "a clinical trial is conducted in accordance with good clinical practices" and that "systems and procedures that assure the quality of every aspect of the clinical trial are implemented" (3), but does not specify the amount and frequency of source data verification.

The current emphasis on risk-based approaches to source data verification recognizes that 100% source data verification is labour and resource intensive and lacks sufficient evidence of its

effectiveness (12). The establishment of the Clinical Trials Transformation Initiative (CTTI) in 2008 reflects this trend to increase the efficiency of clinical trials within the current regulatory framework (34). CTTI is a public-private partnership involving representatives from the US Food and Drug Administration (FDA), industry, patient and consumer groups, academia, professional societies, investigator groups and other government agencies, and has included monitoring as one of its priority areas of research.

Based on work completed by CTTI, the FDA has recently withdrawn its 1988 guidance on monitoring clinical investigations and has released a Draft document, "Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" (35). In this document, the FDA encourages risk-based monitoring approaches that include the adoption of Centralized Monitoring, recognizing the dependency of this approach on the availability of electronic records and electronic data capture.

This trend towards risk-based approaches to source data verification is seen outside North America as well. The European Medicines Agency (EMA) released its 'Reflection paper on risk based quality management in clinical trials' in August 2011, where it recognizes that the 'current monitoring practices are not proportionate or well adapted to achieving the desired goals and are generally very costly, resulting either in success at an unnecessarily high cost or failure which is also very costly'(36). In October 2011, the Medicines and Healthcare Products Regulatory Agency (MHRA), released a paper entitled "Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products" (37) which incorporates the categories of risk described by Brosteanu et al.

While this trend to adopt risk-based approaches to source data verification in the US, Europe, and the UK may be applauded as a more pragmatic and feasible way to monitor data

quality, these strategies are being implemented without evidence of their ability to ensure the safety of study participants and validity of the data. Our review of the literature highlights the current paucity of research for the methods, the amount and frequency of source data verification, and suggests that national regulating agencies exercise caution before implementing and enforcing guidelines that are not based on evidence.

3.5.1 Strengths and Limitations

Due to the small number and types of publications located in this systematic review, we were only able to provide a qualitative descriptive analysis, which is what was anticipated. However, the very lack of evidence in the literature regarding the methods of source data verification is a strong indication of the need to conduct further research in this area.

3.6 Conclusion

While published guidelines and recommendations on source data verification exist, the literature is inconsistent and lacks sufficient detail to guide investigators. The findings of this systematic review support the need for current research efforts such as The ADAMON and Optimon Studies; studies which will hopefully provide answers to the questions of how much and how often source data verification should be done. Research is needed to develop the evidence base required for robust guidelines.

4.0 SYSTEMATIC REVIEW – EFFECT OF SOURCE DATA VERIFICATION ON STUDY OUTCOMES

4.1 Objective

To establish the evidence-base for source data verification by conducting a systematic review of the literature to examine the ***effect*** of source data verification on study outcomes. Our first systematic review identified current methods, while this review examines the impact of the various methods on study outcomes.

4.2 Methods

4.2.1 Data Sources and Search Strategy

We developed an explicit search strategy with the assistance of an information specialist to search the PubMed® (1950 – May 2011), EMBASE® (Ovid) (1980 – July 2011), and Cochrane Central Register of Controlled Trials (CENTRAL®, The Cochrane Library). On the advice of the information specialist, we used the same search strategy as outlined in section 3.2.1 as we expected that there would be overlap in the two systematic reviews. We recognized that the available literature was likely to be small and so we wanted to ensure that it was a broad search strategy so as not to miss any potential citations.

We attempted to identify all relevant publications, regardless of language, publication status (published, unpublished, in press or in progress), or date of publication. Full details of the search strategy are included in Appendix A. We identified relevant publications by searching the following areas: electronic bibliographic databases for published studies, methodological publications, reports; reference lists of relevant published papers; web sites of clinical trial associations, academic research organizations, or conference proceedings of clinical trial organizations for reports, or methods articles.

We searched reference lists of all included citations for any additional relevant published relevant studies, or methodological reports, or guidelines not already assessed for inclusion. We used Web of Science® (ISI Web of Knowledge) (1900 – May 2011) to assist with citation searching.

We conducted hand searching of record titles in specific journals of interest: Clinical Trials, Trials, Applied Clinical Trials, Controlled Clinical Trials, and Drug Information Journal. We used the World Wide Web to search the following clinical trial organizations for potentially suitable records not previously identified: Association of Clinical Research Professionals, Society of Clinical Research Associates, and Drug Information Association. No language restriction was applied, but for the purposes of this thesis, we included only English language records for final evaluation.

4.2.2 Study Selection

4.2.3.1 Inclusion Criteria

To meet our inclusion criteria, the primary purpose of the publication was to report on, or describe, the effect of source data verification on study outcomes. We defined 'effect' as changes in measures of effect and their uncertainty for primary and secondary outcomes.

4.2.3.2 Exclusion Criteria

We excluded animal studies or publications that only reported that source data verification was conducted or methods of source data verification. We excluded those studies that reported on the effect of quality assurance or quality improvement measures that may have included source data verification, as it would not be possible to determine what the effect of source data verification

alone, would have on study outcomes. We excluded non-English full-text publications in the final evaluation.

4.2. 3 Outcomes of Interest

Specific outcomes of interest included the following: 1) method of source data verification (i.e. methods of comparing the source document to the data that is collected using either a paper or electronic record; 2) frequency of source data verification; 3) amount of source data verification; 4) error rates reported, 5) method of comparison and 6) effect of source data verification on study outcomes.

4.2.4 Record Review and Data Extraction

Please refer to section 3.2.4.

As the purpose of the review was to evaluate the effect of source data verification on study outcomes, assessing the methodological quality of the studies or reports was not considered relevant. We report on the types of studies or reports found.

4.2.5 Data Synthesis and Analysis

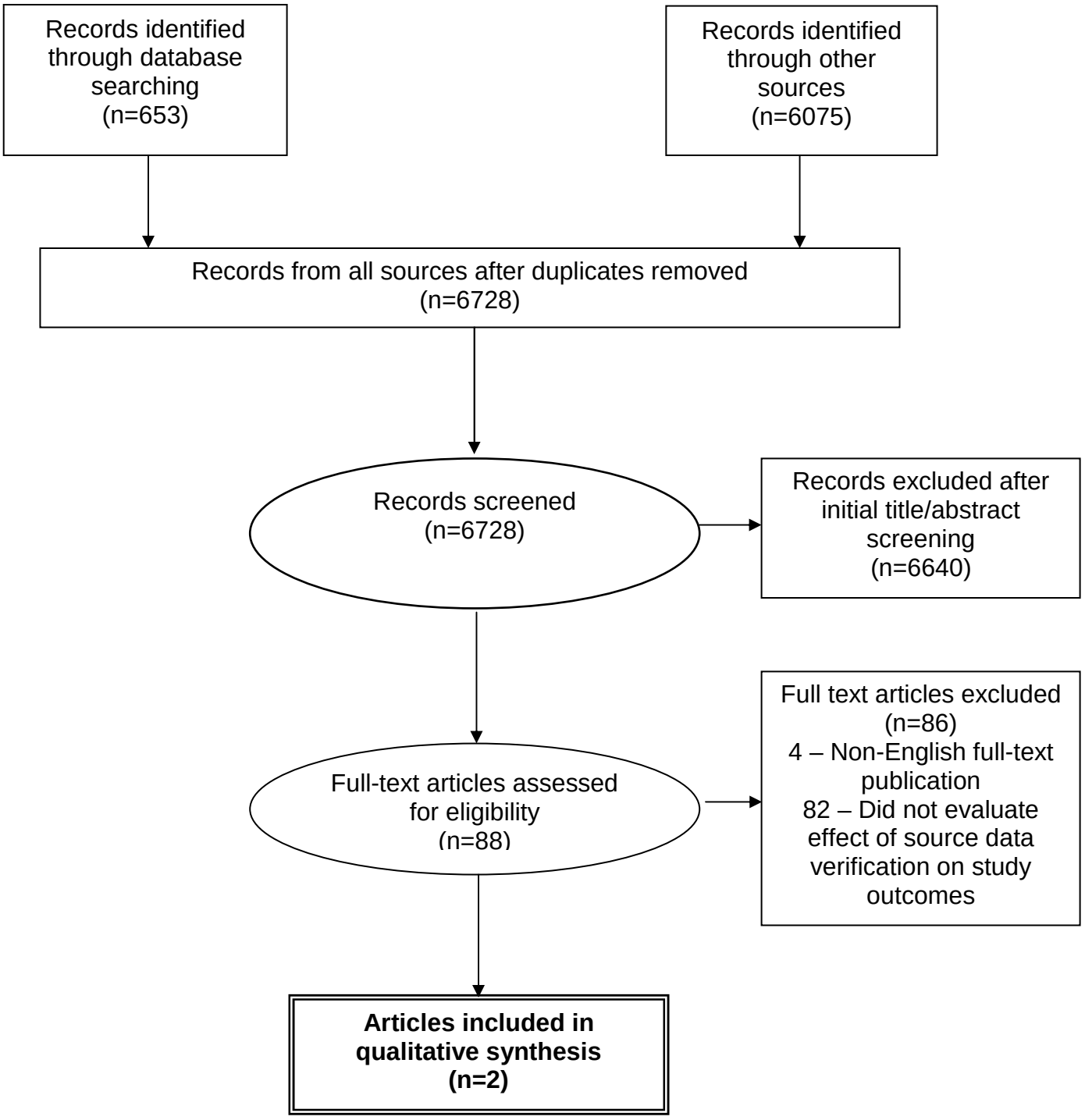
It was not expected that statistical pooling of the results of studies would be feasible given the quality, number, and heterogeneity of studies we expected to identify. We presented the data in a tabular format that summarizes the information available for each study and is accompanied by a descriptive commentary.

4.3 Results

4.3.1 Search Results

We identified 6,728 potentially eligible papers: 653 from electronic databases, 5,954 from hand searching, and 121 from the World Wide Web (Figure 2). After initial screening, we excluded 6,640 articles and retained 88 articles for review of the full publication. Four articles were excluded because they were non-English publications. A further 82 articles were excluded after review of the full document, for a total of 2 included articles that met our eligibility criteria. The reason for exclusion was because the articles did not evaluate the effect of source data verification on study outcomes.

Figure 2: Systematic review of effect of source data verification on study outcomes: Flow diagram



4.3.2 Study Characteristics

The included publications (n=2) were published in 1995 and 2006 (Table 5). The first publication was a report of an American multi-centre national audit (14), involving 89 sites and the author was affiliated with an academic centre. The other publication was a multi-centre randomized trial, involving 135 sites in France that compared two methods of site visits (visited group or non-visited group) (38) and the author was affiliated with an independent clinical research organization.

The primary objective of the national audit (14) was to independently assess sufficient eligibility and outcome data to allow a re-analysis after evidence of fraud had been discovered at one of the sites. The primary objective of the European study (38) was to provide evidence on the impact of on-site initiation visits on submitted data quantity and quality. A secondary outcome was to assess the impact of repeated on-site visits on study outcomes. This study was terminated early in order to redirect monitoring efforts because less than 50% of sites had submitted any data.

Table 5: Characteristics of the two publications included in the systematic review

Author/ Publication-Year	Study Type	Methods	Variables	Frequency of SDV Done	Amount of SDV Done	Results/ Recommendations
Christian et al. NEJM - 1995	RCT	Completed SDV for 7770 items	*Key data	NA	1340/1554 (86.2%) of items	Confirmed adequacy of data for reanalysis of Protocol B-06. Discrepancies were uncommon
Lienard et al. Clinical Trials - 2006	RCT	135 Centres randomized to on-site monitoring or No site visits	Not stated	Initiation, monitoring and close-out	Not stated	Study terminated early because of poor data submission. Unable to evaluate the impact of repeated site-visits on clinical outcomes.

*Key data: May include, but not limited to eligibility criteria, randomization, primary/secondary endpoints, adverse events, safety data, informed consent

4.3.3 Variables for Source Data Verification

Only one publication, the audit, specified which variables were selected for source data verification; eligibility criteria and outcome measures (14).

4.3.4 Frequency of Source Data Verification

As the national audit (14) was conducted at the end of the trial, the frequency of source data verification was not applicable. The European study did not specify the frequency of source data verification.

4.3.5 Amount of Source Data Verification

Eighty-six percent of the patients enrolled in the American study undergoing the national audit had all eligibility and study outcome data source data verified (14). Because the European study was terminated early, the amount of source data verification was not provided (38).

4.3.6 The Role of Central Monitoring

Central monitoring was not assessed in the American study (14). The European study reviewed submitted data for missing values, out of range or inconsistent (38).

4.3.7 Study Results

In the American study that underwent the national audit, less than 1% of the data that was verified by source documents was discrepant (14). There was no difference in the study outcomes between the data before source data verification and after. Because the European study was terminated early, they were only able to assess the effect of site initiation visits on patient recruitment and data quality. They could not evaluate the effect of subsequent site visits and source data verification on study outcomes (38) because most sites had only had one site visit when the study was terminated.

4.4 Discussion

This review of the literature revealed only two publications that aimed to assess the effect of source data verification on study outcomes. The American national audit found that there was no difference in the study outcomes between data that had been source data verified and those data that had not (14). Unfortunately, in the most recent publication (38), the study was terminated early because of problems with obtaining data from sites. Thus, the authors were unable to determine the effect of on-site monitoring on study outcomes.

Along with an interest in a risk-based approach to monitoring, there is greater emphasis on central monitoring as a method of ensuring data quality. Central monitoring is a broad term that can encompass a wide variety of activities, including: sending copies of source documents to the data coordinating centre, generating data queries for missing, out-of-range or inconsistent data, and the use of statistical procedures to assess the data for inconsistent patterns, or non-

randomness. A recent study assessed whether the findings from on-site monitoring of a large international RCT to see if they could have been identified through the use of central monitoring techniques. In their review, the authors reported that over 90% of the findings from on-site monitoring could have been identified by central monitoring.

While these directions are being welcomed by the clinical research community, we are perhaps being premature in adopting yet another monitoring strategy that is not yet proven to have an effect on study outcomes. As this review has demonstrated, there presently is no evidence as to the effect of source data verification on study outcomes. Currently there are two academic initiatives, one in France and one in Germany that are looking at this very question. Both are RCTs that have sites randomized to different monitoring strategies. It is hoped that at the conclusion of these trials, we will have some quantitative evidence that will provide guidance for investigators in developing methods to ensure the safety of study participants and the validity of the data.

4.4.1 Strengths and Limitations

Due to the small number of publications (i.e. 2) discovered in this systematic review, we were only able to provide a qualitative descriptive analysis. However the very fact that there were only two publications located that attempted to assess the effect of source data verification on study outcomes is an important statement regarding the paucity of evidence on this topic.

4.5 Conclusion

Currently, there is no empirical evidence regarding the effect of source data verification on study outcomes. The recent trend towards a risk-based approach to monitoring that includes central monitoring is being welcomed by the three largest regulatory agencies because of the potential to decrease the human and financial burden that is imposed by 100% source data verification. The

current lack of research on the impact of source data verification within clinical trials is leading to the creation of unproven strategies to decrease the financial burden of conducting research while maintaining the data quality. Further evidence is needed in order to provide investigators with appropriate guidance as to the degree of source data verification required to ensure the safety of research participants and the validity of the data.

5.0 JUSTIFICATION FOR A NATIONAL SURVEY

The results of the two systematic reviews indicate the dearth of evidence on the methods of source data verification and its effect on study outcomes. While source data verification is commonly done to ensure data quality, there is little information available on the methods of source data verification and even less on which methods clinical trialists believe will best ensure the safety of study participants and the validity of the data.

A recent survey of US organizations reported that Clinical Research Organizations (CRO's) conduct source data verification more frequently than academic centres, (5); but this survey had a very small response rate, academic organizations were under-represented having contributed only 18% to the overall responses, and the personnel responsible for conducting source data verification, research coordinators were not included. Given the lack of empirical evidence, it is important to first have an understanding of the attitudes and beliefs of academic investigators as well as research coordinators regarding the methods of source data verification and its potential effect on study outcomes.

Using survey methodology, we intend to examine and describe the attitudes and beliefs of Critical Care academic investigators and research coordinators about source data verification in clinical research. The results of this survey provide information on the frequency and amount of source data verification that academic clinical researchers and research coordinators believe should be done as well as what factors should be considered when determining the need for, and amount of source data verification. This will inform the development of future research to determine evidence-based best practices for source data verification.

6.0 NATIONAL SURVEY

6.1 Rationale

It is clear that further research is needed in order to inform the future development of guidelines for source data verification as determined by the two systematic reviews. These would be especially beneficial for academic investigators because of the greater financial and human resource limitations that they face in comparison to the pharmaceutical industry. Before embarking on clinical trials to provide the evidence base for the establishment of guidelines for source data verification, it is necessary to determine the attitudes and beliefs regarding source verification of academic investigators and research coordinators. Having an understanding of what factors are believed to be important to consider when determining the amount and frequency of source data verification will inform the future research agenda.

6.2 Objective

The objective of this survey was to describe the current attitudes and beliefs regarding source data verification within RCTs of Canadian critical care investigators and research coordinators of the Canadian Critical Care Trials Group.

6.3 Methods

Using survey methodology, (39), we conducted a cross-sectional, electronic, self-administered survey of practicing critical care investigators and research coordinators in Canada, who are members of the Canadian Critical Care Trials Group. This is a highly collaborative, multi-disciplinary group who conduct academic as well as industry-sponsored trials. They are well published, having over 100 studies published in a number of prestigious journals, such as The New England Journal of Medicine (NEJM), the Journal of the American Medical Association

(JAMA), the Canadian Medical Association Journal (CMAJ) and many other peer-reviewed journals. As such, members of the CCCTG have extensive trial experience and have a vested interest in determining cost-effective methods to ensure not only the safety of the study participants, but the validity and reliability of the data.

We used research methods based on published evidence to construct, implement and report the results of this survey. We incorporated design and performance elements that have demonstrated a positive effect on response rates (40). Design elements included the use of endorsements from established organizations (Canadian Critical Care Trials Group, University of Ottawa, Ottawa Hospital Research Institute. Performance strategies to improve response rates included the use of a pre-notification letter, and at least four contacts with potential respondents(40). The pre-notification, cover and follow-up letters were structured to emphasize the survey's usefulness and the importance of a response from each individual based on the theory of social exchange. The principles of social exchange are designed to establish trust, to provide rewards and to reduce the costs (real or perceived) associated with participating in the survey (40).

The survey was translated into French and both French and English versions were distributed to critical care investigators and research coordinators within Quebec. This study was approved by the Children's Hospital of Eastern Ontario Research Ethics Board.

6.3.1 Sample

The target population for this survey consisted of practicing critical care investigators and research coordinators working at Canadian academic centres and who were members of the

Canadian Critical Care Trials Group. The names and email addresses were obtained from the membership list of the Canadian Critical Care Trials Group.

6.3.2. Questionnaire Development

Items were first generated by the author and members of the Thesis Committee (D. Fergusson, K. Menon) based on the findings of the two systematic reviews (Sections 3 and 4). They were then vetted at a face-to-face focus group meeting held in June 2011, with six critical care investigators and two critical care research coordinators. During this meeting, participants reviewed the survey objective and contributed to a list of domains that would fulfill this objective. Following this meeting, the same group reduced and revised the domains and response categories using an iterative process that included expert opinion and interactive discussion. The final domains were as follows:

A. General beliefs regarding source data verification

B. Factors believed to determine the amount and frequency of source data verification;

C. The optimal amount and frequency of source data verification;

D. Alternatives to source data verification – Central monitoring, defined as a method of verifying data without being physically at a site. We broke this down further into the following types of central monitoring methods:

    i. Data Checks – Using centrally available data to check for missing values, out of range values, inconsistent or illogical values or protocol deviations,

ii. Statistical Monitoring – Using centrally available data to perform statistical techniques (i.e. descriptive statistics, box and whisker plots, frequency histograms, cross-tabulations, scatterplots, correlation/regression), and

iii. Sending Copies of Source Documents – Having sites copy specific source documents (removing any identifiers) and then sending by fax or electronically to the Coordinating Centre.

E. Workload and costs believed to be associated with source data verification.

F. Need for evidence base of source data verification

Response formats were nominal, ordinal or interval and included responses that acknowledged uncertainty (e.g. Don`t know) or neutrality (e.g. Neutral). The final questionnaire consisted of 22 questions (66 items) that reflected the overall objectives of the survey (Appendix C). The final survey, pre-notification, cover letter and follow-up letters were all translated into French by a certified translator.

6.3.3 Questionnaire Pre-testing and Piloting

We assessed clinical sensibility with eight content experts using 5-point Likert scales (Appendix D) to assess clarity, ability to elicit information pertaining to the objectives of the survey, issues with redundancy, and length of time to complete. After minor revisions, the survey was pilot-tested on four critical care investigators and research coordinators. We evaluated time to completion again, relevance of questions, wording, as well as flow of questions in the survey. Test-retest reliability of individual questions was assessed by having the same 3 research coordinators and 4 investigators complete the identical survey within 2 to 4 weeks.

6.3.4 Implementation Strategy

We used a web-based survey tool, FluidSurveys® to implement the survey. A pre-notification email was first sent to all potential respondents, followed by an invitational email that contained a web link to the web-based survey approximately 10 days later. Non-respondents received two reminder emails at 2 and 4 weeks following the initial survey invitation. All potential respondents who resided in Quebec received both English and French invitations, reminders, and surveys. Individual survey responses remained anonymous. The web-based survey tool automatically generated reminder emails to only non-respondents.

6.3.5 Analyses

Descriptive summaries of responses to each question were prepared for all data and then separately for investigator and research coordinator groups. For categorical questions, frequencies and percentages were tabulated. We collapsed categories, where appropriate to summarize responses in a meaningful manner. For numeric questions, means, medians, standard deviations, interquartile ranges, maximum, and minimum were calculated. We compared responses between investigators and research coordinators using chi-square tests.

6.4 Results

6.4.1 Pre Survey Testing

All investigators and research coordinators who participated in the clinical sensibility testing stated that the survey questions were directed at important issues pertaining to source data verification. There were two crucial or important gaps identified; one concerned the issue of data quality surrounding translational biology; the other concerned the issue that frequently source data was not always available in critical care research and thus creates difficulty in trying

to verify it. There were few survey items that were considered inappropriate or redundant. The majority (88%) stated that the survey was likely or quite likely to describe the beliefs and attitudes of Canadian critical care investigators and research coordinators regarding source data verification. The time to complete the survey was reported to be approximately 15 to 20 minutes for 88% of the respondents. One reported that it took much longer, but was providing feedback at the same time. There were two comments from the content experts that the survey was too long and one was concerned that respondents would need a certain level of expertise and familiarity with source data verification in order to complete the survey.

In assessing for test-retest reliability, there was some variation noted. Of the 66 items, 12 had two or more respondents change their initial response to the opposite category (i.e from agree to disagree, important to not important, or vice versa). Those respondents less familiar with source data verification felt that their responses may have changed when repeating the questionnaire. Based on this feedback, the survey was modified to provide additional detail or information for those respondents who specified that they were less familiar with source data verification.

6.4.2 Respondents

The overall response rate was 46.3% (145/354) (Figure 3). The pre-notification email was sent to 354 potential respondents as identified by the Canadian Critical Care Trials Group Membership list. We subsequently excluded 41 individuals who identified that they were not currently working in Critical Care or for whom the email addresses were not valid. There were a further 18 excluded as the respondent identified that they were neither an investigator nor a research coordinator (9), or the survey was viewed only (9), but no questions were answered,

with a final total of 295 potential respondents. Of these, 189 were Critical Care investigators, and 106 were Critical Care research coordinators. Our final response rate was 43.1% (127/295).

The demographic features of the respondents are summarized in Table 6. The majority of the respondents were female (66.7%), and 47.6% reported that they were Critical Care investigators; the remainder were research coordinators. The majority (65.8%) reported having greater than 6 years experience in critical care research. Most of the respondents worked in adult only (64.1%) intensive care units. The majority of respondents were from Ontario (53%), followed by Quebec (21%) and Alberta (10%).

When asked about their familiarity with source data verification, the majority (69.3%) stated that they knew what source data verification was, had had a site visit for the purposes of source data verification, had been audited, or had conducted source data verification. Of the remaining, 7.1% reported that they had never heard of source data verification and 23.6% stated that they had heard of source data verification, had an understanding or knowledge of it, but had not conducted or performed source data verification.

Figure 3: Survey response flow diagram

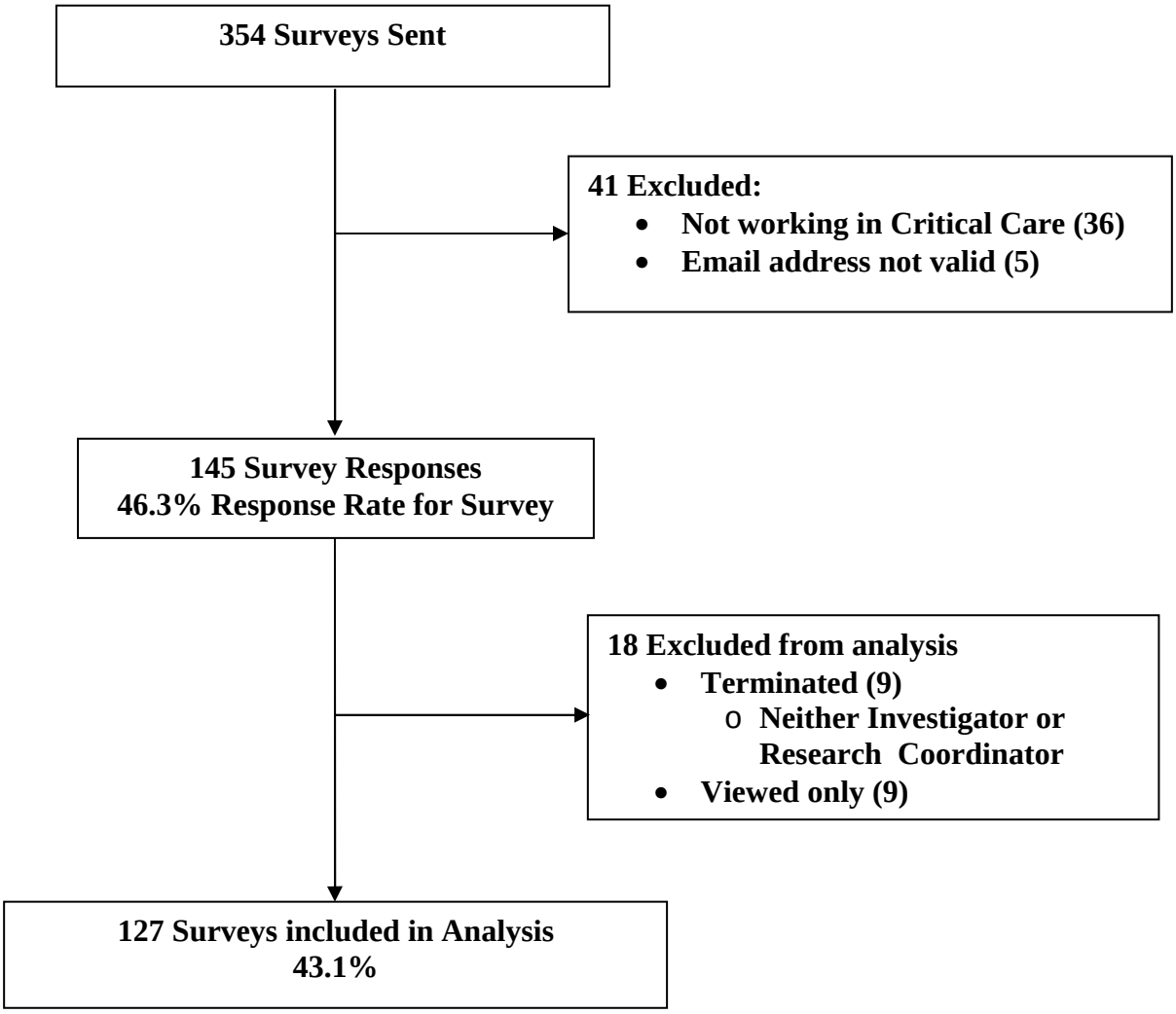


Table 6: Demographics of survey respondents

Demographics	N (%)
Sex (117)	
Male	39 (33%)
Female	78 (67%)
Occupation* (can check > 1)	
Staff Physician	46 (37%)
Trainee/Fellow	0 (0%)
Nurse	33 (26%)
Allied Health	10 (8%)
RC/PM	47 (38%)
RA	4 (3%)
Other	5 (4%)
Experience (117)	
0-1 Years	5 (4%)
2-5 Years	35 (30%)
6-10 Years	26 (22%)
> 10 Years	51 (44%)

6.4.3 Domain – General Beliefs Regarding Source Data Verification

The majority of respondents agreed/strongly agreed that source data verification was an important part of a Quality Assurance program (95.8%), and that the process helped to ensure the validity and reliability of the data (99.2%) (Table 7). Approximately two-thirds (66.7%) disagreed/strongly disagreed with the statement that source data verification should only be conducted when there is greater than minimal risk in an RCT. Over 70% disagreed/strongly disagreed that industry (i.e for-profit pharmaceutical or device companies) should do less source data verification (71.6%), and over 70% agreed/strongly agreed that academic investigators should conduct more source data verification than is done presently (73.3%). Slightly less than two-thirds (62.5%) agreed/strongly agreed that agencies currently provide sufficient funding to perform source data verification.

Table 7: General beliefs regarding source data verification (SDV) by Critical Care investigators and research coordinators

General Beliefs – Source Data Verification (SDV) (N=120)	**Neutral** **N (%)**	**Disagree / Strongly Disagree** **N (%)**	**Agree / Strongly Agree** **N(%)**
SDV important part of QA	3 (2.5%)	2 (1.7%)	115 (95.8%)
Helps ensure data reliability/validity	0 (0.0%)	1 (0.8%)	119 (99.2%)
SDV done only when > min risk	6 (5.0%)	80 (66.7%)	34 (28.3%)
Industry should do less SDV	8 (6.7%)	86 (71.6%)	26 (21.6%)
Academic should do more SDV	7 (5.8%)	25 (20.9%)	88 (73.3%)
Primary objective should be training instead of SDV	16 (13.3%)	57 (47.5%)	47 (39.2%)
Agencies provide sufficient funds for SDV	16 (13.3%)	75 (62.5%)	29 (24.2%)

6.4.4 Domain - Factors believed to determine the amount and frequency of source data verification

The majority (> 75%) stated that the following study design and protocol related factors were considered important or very important in determining the amount and frequency of source data verification (Table 8):

i. Phase of the study (Phase I, II, III, or IV);

ii. An intervention of greater than minimal risk;

iii. The novelty or complexity of the intervention;

iv. An 'off-label' intervention; or,

v. Study participants less than 18 years of age.

Sample size was considered an important or very important factor by 71.7% (small sample size) and 63.7% (large sample size) respectively.

Table 8: Study design and protocol-related factors affecting amount and frequency of SDV

Study Design and Protocol-Related Factors (N=124)	Neutral N (%)	Not / Somewhat Important N (%)	Important / Very Important N (%)
Phase I/II Study	5 (4.0%)	13 (11.3%)	104(78.5%)
Phase II/IV Study	4 (3.2%)	10 (8.1%)	110 (88.7%)
Intervention > Min. Risk	5 (4.0%)	7 (5.6%)	112 (90.4%)
Novelty of Intervention	4 (3.2%)	12 (9.7%)	108 (87.1%)
Off-label	9 (7.3%)	20 (16.1%)	95 (76.6%)
< 18 years	13 (10.5%)	18 (14.5%)	93 (75.0%)
Complex Tx protocol	6 (4.8%)	16 (12.9%)	102 (82.2%)
Small sample size	10 (8.1%)	25 (20.1%)	89 (71.7%)
Large sample size	10 (8.1%)	35 (28.2%)	69 (63.7%)

When asked about data quality and regulatory requirement factors that may affect the amount and frequency of source data verification, the majority (75% or higher) of survey respondents stated that source data verification was an important or very important factor in ensuring the validity and reliability of the data, when conducting Health Canada or FDA trials, or when there is a risk of fraud. Just over two-thirds (67%), felt that the amount of funding available was an important or very important factor when determining the amount and frequency of source data verification (Table 9). Greater than half (57.8%) believed that having a primary outcome of mortality is an important or very important factor when determining the amount and frequency of source data verification.

Table 9: Data quality and regulatory requirement factors affecting the amount and frequency of SDV

Data Quality and Regulatory Requirement Factors	Neutral N (%)	Not / Somewhat Important N (%)	Important / Very Important N (%)
Ensuring reliability/validity (n=122)	1 (0.8%)	3 (2.5%)	118 (96.7%)
HC or FDA Regulated Trials (n=121)	2 (1.7%)	11 (9.9%)	107 (88.4%)
REB Requirements (n=121)	3 (2.5%)	32 (26.5%)	86 (71.1%)
Amt Funding Available (n=121)	5 (4.1%)	35 (28.9%)	81 (67.0%)
Risk of Fraud (n=121)	1 (0.8%)	23 (19.0%)	97 (80.1%)
Method of DC P vs EDC (n=121)	4 (3.3%)	51 (42.1%)	66 (54.6%)
Primary Outcome - Mortality (n=121)	8 (6.6%)	43 (35.5%)	70 (57.8%)
Ability to download data (n=121)	7 (5.8%)	36 (29.7%)	78 (64.5%)

Research-site related factors perceived to be important or very important in determining the amount and frequency of source data verification included those sites with a lack of research experience, a high turnover, or an unexpected number of data queries or serious adverse events (Table 10). Slightly more than half (53.4%) agreed or strongly agreed that sites with poor performance (i.e. having a large number of unanswered data queries) should have more frequent

site visits for the purposes of conducting source data verification. The proximity of the research site to the data coordinating centre was considered not or somewhat important by 65.8% (sites that were far) and 69.2% (sites that were close) respectively. The number of patients enrolled at a site was considered by the majority (76.3%) to be a factor in determining the amount and frequency of source data verification. Sixty-one percent agreed or strongly agreed that a site that has enrolled more participants should have more frequent site visits for source data verification.

Table 10: Research site related factors affecting amount and frequency of SDV

Research Site-related Factors (N=120)	Neutral N (%)	Not / Somewhat Important N (%)	Important / Very Important N (%)
Sites with lack of experience	0 (0.0%)	3 (2.5%)	117 (97.5%)
Sites with high turnover	0 (0.0%)	7 (5.8%)	113 (94.1%)
Unexpected # of data queries	1 (0.8%)	9 (7.5%)	110 (91.7%)
Unexpected # of unanswered data queries	1 (0.8%)	9 (7.5%)	110 (91.7%)
Unexpected # of SAE's	1 (0.8%)	7 (5.8%)	112 (93.4%)
Location - far	6 (5.0%)	79 (65.8%)	35 (29.2%)
Location - close	7 (5.8%)	83 (69.2%)	30 (25.0%)

6.4.5 Domain - The amount and frequency of source data verification that should be done

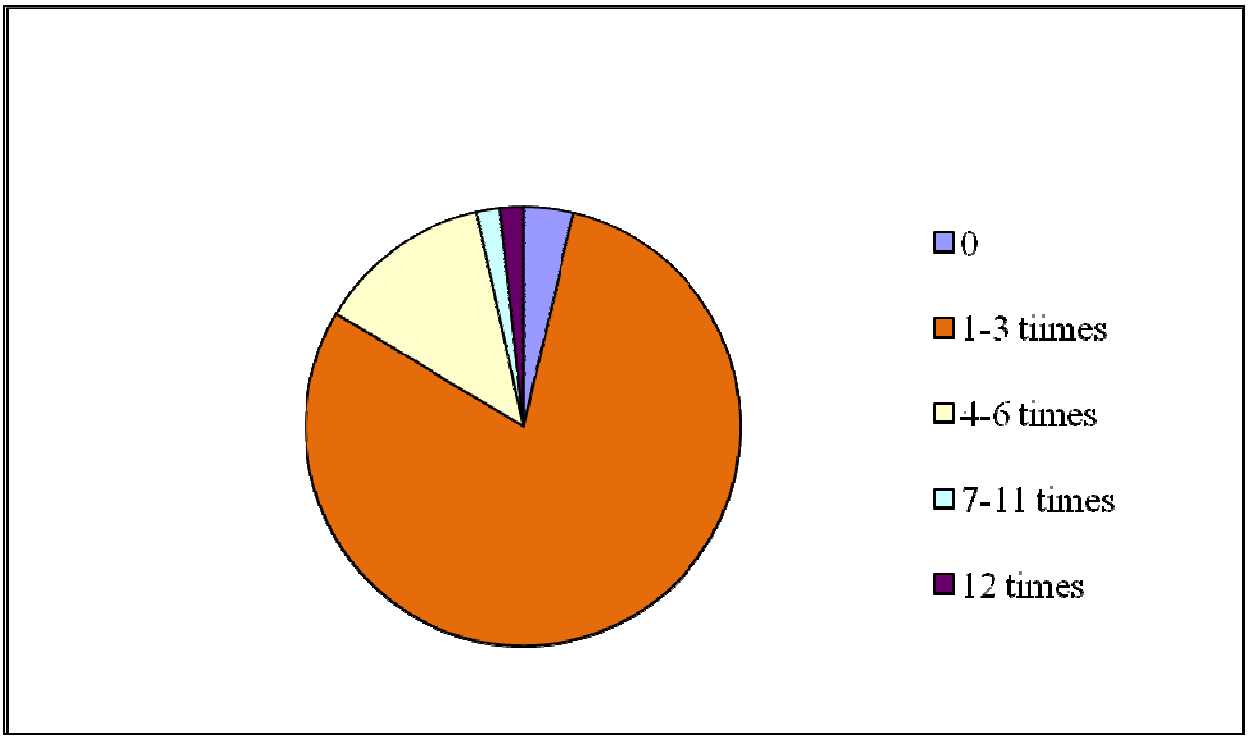
The tables for the amount and frequency of source data verification that should be done are presented in Appendix E. Just over one-third of respondents (35.6%) felt that there should be source data verification done on either a pre-determined amount of CRF's from each site or a random sample of all CRF's from each site . Eleven percent of respondents stated that either the first 1 or 2 CRF's from each site or a random sample of ALL CRF's should have some amount of source data verification.

When asked what percentage of CRF's should have source data verification, the majority of respondents (46.6%) felt that 1 to 20% of CRF's should have some level of source data verification. Less than one-quarter (23.9%) believed that 100% of all variables should be source data verified. Very few (>1%) felt that there should not be any source data verification conducted at all.

Less than fifty percent (44.5%) believed that up to 20% of consent forms or the consent process (48.7%) should be verified by source data. Thirty-four percent believed that all consent forms should be verified using source data. Less than 30% of respondents agreed that 1 to 20% of eligibility criteria (26.7%), primary (20.5%) and secondary trial outcomes (27.8), drug/device accountability (29.1%) and adverse events (27.4%) should have source data verification. Over 50% of respondents agreed that 100% of serious adverse events should have source data verification (53.8%)

When asked to indicate what the best frequency was for site visits for the purpose of conducting source data verification, the majority of respondents stated that site visits should occur 1 to 3 times per year (79.3%) (Figure 4).

Figure 4: Frequency of site visits for source data verification



6.4.6 Domain - Alternatives to source data verification

The majority agreed or strongly agreed that data checks and statistical monitoring (82.2%) helped ensure data validity (Table 11). Less than 50% agreed or strongly agreed that data checks, statistical monitoring and sending source documents are more cost effective than source data verification (47.5%), while 22.9% were unsure. Slightly more than half agreed or strongly agreed that data checks, statistical monitoring and sending source documents are as effective as source data verification (51.7%) or would likely decrease the need for source data verification (54.3%).

Table 11: Alternatives to source data verification

Alternatives to SDV Central Monitoring N=118	Don't Know N (%)	Neutral N (%)	Disagree/Strongly Disagree N (%)	Agree/Strongly Agree N (%)
Data checks help ensure data validity	2 (1.7%)	3 (2.5%)	7 (5.9%)	106 (90%)
Data checks & statistical monitoring help ensure data validity	7 (5.9%)	4 (3.4%)	10 (8.4%)	97 (82.2%)
Data checks, statistical monitoring and sending SD are as effective to ensure data validity as SDV	11 (9.3%)	9 (7.6%)	37 (31.4%)	61 (51.7%)
Data checks, statistical monitoring and sending SD are more cost effective than SDV	27 (22.9%)	6 (5.1%)	29 (24.6%)	56 (47.5%)
Data checks, statistical monitoring and sending SD will likely decrease the ened for SDV	16 (13.6%)	7 (5.9%)	31 (26.3%)	64 (54.2%)
Targeted SDV may be done as result of data checks and statistical monitoring	11 (9.3%)	4 (3.4%)	8 (6.7%)	95 (80.5%)

6.4.7 Domain - Workload and costs believed to be associated with source data verification.

Almost half (45.3%) agreed or strongly agreed that sending source documents is more time-consuming than source data verification, 26.5% disagreed or strongly disagreed, and 28.2% were neutral (Table 12). Less than half agreed or strongly agreed that source data verification was a cost effective way to ensure the reliability and validity of the data (43.6%), and almost a quarter (24.8%) disagreed or strongly disagreed and 31.6% were neutral. The majority (71.0%), agreed or strongly agreed that source data verification was time-consuming for the research coordinator, and disagreed or strongly disagreed (70.1%) that sites were adequately compensated for the work associated with source data verification as part of site visits.

Table 12: Workload and costs associated with source data verification

Workload & Costs Associated with SDV N=117	Neutral N (%)	Disagree / Strongly Disagree N (%)	Agree / Strongly Agree N (%)
Sending source documents (SD) increases my workload more than SDV during SV	33 (28.2%)	31 (26.5%)	53 (45.3%)
SDV is time-consuming for RC during SV	15 (12.8%)	19 (16.2%)	83 (71.0%)
SDV is time-consuming for Site Inv during SV	18 (15.4%)	71 (60.7%)	28 (24.0%)
SDV is cost-effective way to ensure data validity and reliability	37 (31.6%)	29 (24.8%)	51 (43.6%)
Sites are compensated adequately for work associated with SDV as part of SV	27 (23.1%)	82 (70.1%)	8 (7.0%)

6.4.8 Domain – Need for further evidence base of source data verification

More than 80% agreed or strongly agreed that further research is needed on the effect of source data verification on data validity (82.9%), on the cost effectiveness of source data verification (88.0%), and its effect on study outcomes (86.4%) (Table 13). The majority (91.4%) agreed or strongly agreed that it would be important to develop evidence-based guidelines for the amount and frequency of source data verification for academic investigators.

Table 13: Need for further evidence-base and guidelines

Need for Further Evidence-base & Guidelines N=117	Neutral N (%)	Disagree / Strongly Disagree N (%)	Agree / Strongly Agree N (%)
More research needed on effect of SDV on data validity	15 (12.8%)	5 (4.3%)	97 (82.9%)
More research needed on cost effectiveness of SDV in ensuring data validity	11 (9.4%)	3 (2.6%)	103 (88.0%)
More research needed on effect of SDV on study outcomes	9 (7.7%)	7 (6.0%)	101 (86.4%)
Important to develop evidence-based guidelines for amt and freq of SDV for academic Inv	7 (6.0%)	3 (2.6%)	107 (91.4%)

6.4.9 Difference in Responses between Critical Care Investigators and Research Coordinators

There was a statistically significant difference between the attitudes of Critical Care investigators and research coordinators regarding factors that determine the amount and frequency of source data verification. More research coordinators than investigators felt that the novelty of the intervention (p=0.04), a younger population (< 18 years of age) (p=0.002), a complex protocol (p=0.04), and mortality as the primary outcome (p=0.01) were important/very important in determining the amount and frequency of source data verification (Table 14). With regards to academic studies, more research coordinators (52/62 – 83.9%) than investigators (36/58 – 62.1%) agreed/strongly agreed that academic studies should conduct more source data verification than what is currently done (p=0.008). Research coordinators indicated that site visits should be conducted more frequently than investigators (p=0.008) (Table 15).

Research coordinators generally felt that a higher percentage of CRFs and consent forms should be source data verified than investigators ($p<0.001$ and $p=0.001$ respectively) (Table 16). There were statistically significant differences in the beliefs regarding workload associated with source data verification between investigators and research coordinators (Table 17). Specifically, more research coordinators than investigators agreed that source data verification is a cost-effective way to ensure data validity and reliability ($p=0.01$) and that sending source documents increased workload ($p=0.03$). More investigators than research coordinators agreed that source data verification increases the workload for the investigator during a site visit ($p<0.001$). However, more research coordinators than investigators disagreed with the statement that source data verification increases workload during site visits for the research coordinator ($p=0.001$).

Table 14: Comparison of Investigators and Research Coordinators on factors that determine amount and frequency of SDV

Factors That Determine Amount and Frequency of Source Data Verification	Investigator Important/Very Important N (%)	Research Coordinator Important/Very Important N (%)	p Value
Primary Outcome is Mortality	21 (41.1)	45 (78.1)	< 0.001
Novelty of Intervention	48 (80.0)	60 (93.8)	0.04
Complex protocol	44 (73.3)	58 (90.6)	0.04
Patient population < 18 years	37 (61.7)	56 (87.5)	0.002

Table 15: Comparison of Investigators and Research Coordinators on the frequency of site visits for SDV

Amount of SDV	0%		1 - 3 Times per Yr		4 - 6 Times per Yr		7 - 11 Times per Yr		12 Times per Yr		p Value
	INV N (%)	RC N (%)	INV N (%)	RC N (%)	INV N (%)	RC N (%)	INV N (%)	RC N (%)	INV N (%)	RC N (%)	
Frequency of site visits for purposes of SDV	3 (5.5)	2 (3.3)	50 (90.9)	42 (68.9)	1 (1.8)	14 (23.0)	0 (0)	2 (3.3)	1 (1.8)	1 (1.6)	0.008

Table 16: Comparison of Investigators and Research Coordinators on amount of SDV

Amount of SDV	**0-40%**		**41-80%**		**81-100%**		**p Value**
	INV N (%)	RC N (%)	INV N (%)	RC N (%)	INV N (%)	RC N (%)	
Percentage of CRF`s that should have SDV	49 (87.5)	33 (53.2)	4 (7.1)	10 (16.1)	3 (5.4)	19 (30.6)	< 0.001
Percentage of Consent Forms to have SDV	40 (71.4)	24 (39.3)	1 (1.8)	7 (11.5)	15 (26.8)	30 (49.2)	0.001

Table 17: Comparison of Investigators and Research Coordinators on costs and workload associated with SDV

Costs and Workload	**Investigator**			**Research Coordinator**			**p Value**
	Neutral or Don‘t Know N (%)	**Disagree/ Strongly Disagree N (%)**	**Agree/ Strongly Agree N (%)**	**Neutral or Don‘t Know N (%)**	**Disagree/ Strongly Disagree N (%)**	**Agree/ Strongly Agree N (%)**	
Sending source documents increases workload for Research Coordinator	22 (38.6)	15 (26.3)	20 (35.1)	11 (18.3)	15 (26.7)	33 (55.0)	0.03
SDV is a cost-effective way to ensure data validity	24 (42.1)	16 (28.1)	17 (29.8)	13 (21.7)	13 (21.7)	34 (56.7)	0.01
During a site visit, SDV is very time-consuming for the Site Investigator	12 (21.1)	24 (42.1)	21 (36.8)	6 (10.0)	47 (78.3)	7 (11.7)	< 0.001
During a site visit, SDV is very time-consuming for the Research Coordinator	12 (21.1)	3 (5.3)	42 (73.7)	3 (5.0)	16 (26.7)	41 (68.3)	0.001

6.5 Discussion

In this cross-sectional Canadian survey of critical care investigators and research coordinators, the majority believed that source data verification was an important component of a Quality Assurance program and that it helps to ensure data validity and reliability.

The majority of respondents believed that there were a number of factors that should be considered when determining the amount and frequency of source data verification. Study design or protocol related factors that were considered important were, the phase of the study, whether an intervention posed a greater than minimal risk, or how novel the intervention was. Data quality or regulatory-related factors that were considered important included, ensuring the validity and reliability of the data and the presence of regulation by Health Canada or FDA. Research site-related factors included those sites with lack of experience or that had high turn-over, sites with an unexpected number of data queries or serious adverse events, or sites with high enrolment.

Interestingly, Critical Care investigators and research coordinators had differing opinions as to the importance of some of these factors; namely, the novelty of the intervention, the complexity of the protocol, the age of the study participants (pediatric patients) and mortality as the primary outcome. More research coordinators than investigators agreed that academic studies should conduct more source data verification than is currently done. This finding may be because research coordinators are much more intimately involved in the source data verification process and are direct witnesses to the changes made as a result of source data verification. As well, research coordinators who have had exposure to pharmaceutical industry trials are accustomed to having a much higher percentage of data source data verified. Research coordinators believed more so than investigators, that source data verification is a cost effective

way to ensure data validity and reliability. The differences in opinion regarding workload may be a result of lack of understanding on the part of investigators about what is involved in source data verification or other Quality Assurance activities done to protect data integrity.

Respondents believed that while academic studies should have more source data verification, industry studies should not do less source data verification. Interestingly, more research coordinators than investigators indicated that there should be further source data verification in academic studies than what is currently being done. Generally, respondents felt that public funding agencies do not provide sufficient funding to conduct source data verification. While the majority agreed that all sites should be visited for the purpose of conducting source data verification, it was not clear from the responses whether a pre-determined number of CRF's or a random sample of all CRF's from each site should have source data verification. Critical Care investigators and research coordinators clearly felt that site visits should occur 1 to 3 times per year in order to conduct source data verification, although site visits were perceived to increase the workload for the research coordinator.

It was unclear whether respondents believed that central monitoring was more cost-effective than source data verification or not. While the majority clearly believe that central monitoring ensures data validity, they also believe that source data verification is an important part of Quality Assurance program and aids in the reliability and validity of the data.

Given that source data verification increases research coordinator workload and funding agencies do not typically provide sufficient funding for source data verification, it was somewhat surprising that academic investigators and research coordinators strongly believe that source data verification is an important part of a Quality Assurance program. However, research

coordinators and investigators differed in their judgement as to how cost-effective source data verification is, and its impact on workload. Many in the research community might suggest that the amount of source data verification as interpreted by GCP Guidelines is obstructive in the conduct of academic research because of financial and human resource burdens.

While respondents felt that site visits should occur 1 to 3 times per year regardless of the stage of the study (early versus later on), this was inconsistent with some of the recommendations found in the systematic review (Section 3.0) on methods of source data verification. Although there was no scientific evidence, the current literature supports a recommendation on conducting site visits early to detect problems.

More recent literature reports an emphasis on "risk-based" approaches to source data verification. In a risk-based approach, studies would be assessed for factors that determine a level of risk to the subject or to the validity of the data and the amount and frequency of source data verification would then be determined by this level of risk (22, 24). Some of the factors identified in the literature that affect the level of risk and thus the amount and frequency of source data verification were similar to what critical care investigators reported in the survey, including the phase of the study (III/IV), the amount of potential risk associated with the intervention, the novelty of the intervention and the experience and performance of the research sites.

6.5.1 Strengths and Limitations

There were a number of limitations to this survey. The response rate was less than anticipated (43%) and may affect the validity of our conclusions. There is always a concern that a smaller response rate will introduce non-response bias. The survey was sent to 189 Critical

Care investigators, and 106 Critical Care research coordinators. While the overall response rate was fairly split between investigators and research coordinators, there was a much higher proportion of research coordinators who responded (66/106 – 62.3%) as compared to investigators (60/189 – 31.7%). Thus, there was a much higher non-response rate amongst investigators (129/189 – 68.3%) as compared to research coordinators (60/106 – 37.7%). Research coordinators would generally have more exposure to, and experience with source data verification. When we compared how familiar Critical Care investigators and research coordinators were with source data verification, 83.3% of research coordinators (55/66) indicated that they were very familiar with source data verification, as compared to 53.3% of investigators (32/60). Because of this, the results of our survey may be affected by non-response bias if we consider that Critical Care investigators differ significantly from research coordinators, in their beliefs and attitudes on source data verification which would be influenced by their experience and familiarity with source data verification.

Another factor that may have contributed to a lower response rate is that this was a lengthy survey and some respondents viewed the survey only but did not complete any questions. In addition, there may have been some difficulty with the knowledge level of the topic; not all members of the Canadian Critical Care Trials Group are actively conducting RCTs. Some respondents may not have had much exposure to source data verification and felt inadequately prepared to provide an opinion. Only a few respondents indicated that they had never heard of source data verification, so it may be that those with less familiarity with source data verification did not complete the survey.

We also need to consider that this is a very specific population and the results of this survey may not be applicable to the broader clinical research community because of their

experience and knowledge with critical care clinical research. Furthermore, we did not survey other stakeholders, such as representatives from research ethics boards or Health Canada.

However, the strengths of the survey include scientific rigour utilizing a systematic approach to the development of the survey instrument, pilot and pre-testing. We incorporated evidence-based strategies to enhance response rates that included the use of pre-notification letters, a brief cover letter and multiple reminders, and evidence of endorsement by respected Academic and University establishments. We focused on academic investigators and included research coordinators, both groups that had not been widely canvassed or included in similar topic surveys. There were some interesting differences in opinion between these two groups regarding their beliefs about the impact of source data verification on workload, which have not been explored previously. There were responses from across Canada and equal distribution between critical care investigators and research coordinators.

6.6 Conclusion

Canadian Critical Care investigators and research coordinators believe that source data verification is an important element in Quality Assurance. Other Quality Assurance activities that were considered to help ensure data validity included data checks and statistical monitoring. Sending source documents was felt to be more time-consuming than source data verification, but that source data verification increased workload for the research coordinator. There were some differences in findings between research coordinators and investigators; generally research coordinators felt that more source data verification should be in academic studies and that more CRFs and consent forms should be source verified.

Currently, agencies do not provide sufficient funding to conduct source data verification and it is viewed as contributing considerably to the workload of research coordinators during site

visits. There was variation in opinion about how much source data verification should be done, but the majority thought that the frequency should be 1 to 3 times per year. Overall, it was believed that all sites should have visits for source data verification, but it was not clear how much should be done. The majority of respondents clearly stated that further evidence was needed in order to develop guidelines on source data verification for academic investigators.

7.0 JUSTIFICATION FOR AN AUDIT OF SOURCE DATA VERIFICATION PRACTICES IN CLINICAL TRIALS CONDUCTED BY THE CANADIAN CRITICAL CARE TRIALS GROUP

The results of the survey of Canadian critical care investigators and research coordinators present valuable information on their general beliefs regarding the importance of source data verification and what factors should be considered when determining the amount and frequency of source data verification. In addition, investigators and research coordinators provided us with their opinions as to the amount and frequency of source data verification that should be conducted, alternatives, and the impact of source data verification on workload and costs.

However, surveys may not accurately reflect actual practice and therefore it was felt to be important to document the present practices involving source data verification of critical care investigators. This will enable us to compare the results of the survey to what is actual practice and will guide us in the development of the next steps of the research program. We obtained protocols and related documents of in-progress and completed RCTs through the Canadian Critical Care Trials Group for the purpose of conducting an audit of current source data verification practices of critical care investigators.

8.0 AUDIT OF SOURCE DATA VERIFICATION PRACTICES IN RANDOMIZED CONTROLLED TRIALS CONDUCTED BY THE CANADIAN CRITICAL CARE TRIALS GROUP

8.1 Rationale

The results of the national survey of Critical Care investigators and research coordinators (Section 6.0) indicate that source data verification is considered an important component of the process for ensuring the integrity of clinical data. As surveys may not reflect actual practice, we will review completed and in-progress RCTs of the Canadian Critical Care Trials Group. Using the information from this audit, we will be able to provide a summary of actual source data verification practices within Canadian Critical Care research. We will also gather information on potential factors that may influence the amount and frequency of source data verification, based on information from the systematic reviews and the results of the national survey. Going forward, this information is needed to advance the understanding of Critical Care investigators and research coordinators on the methods source data verification.

8.2 Objective

The objective of this audit was to describe the current methods of source data verification in Canadian Critical Care research.

8.3 Methods

In preparation for this review, this study was presented at several meetings of the Canadian Critical Care Trials Group. The purpose of these presentations was to both inform and request the support of members of the Canadian Critical Care Trials Group in obtaining the documents needed for this review. We included all completed, published and in-progress RCTs by the Canadian Critical Care Trials Group from 1996 onward. We used the list of publications generated by the Canadian Critical Care Trials Group to obtain those RCTs that were completed.

We obtained the list of in-progress RCTs using the minutes from meetings by this same group. Following these presentations, an email was sent to all Canadian Critical Care Trials Group Principal Investigators of in-progress and completed, published RCTs, requesting the following documents be forwarded to the author:

a) Protocol and/or grant submission,

b) Budget requested, including justification,

c) Amount received from funding agency,

d) Which funding agency(ies) provided funding,

e) Case Report Form (CRF), and

f) Data Management Procedures and/or Standard Operating Procedures.

Two follow-up emails were sent to those who had not responded. The published manuscripts for all completed RCTs were obtained by R Ward.

8.3.1 Data Collection and Management

All documents were reviewed by the author (RWard) for details regarding the methods and strategies for source data verification procedures during the conduct of the studies. The protocol was reviewed to determine what methods of source data verification were planned for during the study. For in-progress RCTs, the study procedures, and the protocol were reviewed. A data collection form was created to collect information in a standardized manner and is presented in Appendix G. Information collected was based on findings from the systematic reviews and the survey. It was first piloted on two studies and then modified to include variables that captured source data verification strategies planned for as well as those done.

The following key data were collected for each study:

- Start date,
- Completion date,
- Funding information – funding source, amount of funding requested, amount of funding received for on-site monitoring and source data verification,
- Method of data collection,
- Quality Assurance (QA) methods, defined as 'description of methods used to ensure data integrity (including source data verification and amount and intensity of source data verification)'. This included Standard Operating Procedures (SOPs) and Data Management Plans (DMPs),
- Number of variables for which data was collected,
- Number of variables for which data was reported within the publication and,
- Cost of performing source data verification.

Data was entered into a database (IBM SPSS Version 19). Amount of source data verification was defined as the number and percentage of CRFs that had source data verification for each study. We chose this measure to be consistent with how this measure is generally reported in the literature. Intensity of source data verification was defined as frequency of site visits over the duration of each study. Costs of source data verification were estimated in Canadian dollars, based on information within the documents received, as well as information

from research coordinators who were interviewed by phone for any additional data or needed clarification.

8.3.2 Analyses

Descriptive summaries were used to present the source data verification procedures planned and methods were utilized during the conduct of the study, and ultimately reported. For continuous variables, both means, and medians were calculated with standard deviations and interquartile ranges respectively. For categorical variables, frequencies and percentages were calculated. Using the chi-square test, we planned to conduct the following comparisons:

a) The amount of funding received for monitoring to the cost of source data verification.

b) The number of variables for which data was collected to the number of variables for which data was reported.

c) Using data from the survey of the Canadian Critical Care investigators and research coordinators (See Section 6.0), compare the amount and frequency conducted in Canadian Critical Care RCTs to what Investigators and Research Coordinators believe should be done.

8.4 Results

8.4.1 General Summary of RCTs and Documents Available

There were a total of 21 completed and in-progress RCTs conducted by the Canadian Critical Care Trials Group from 1996 to 2012 (Table 18). Of these, 15 were completed and published (71%), and the remaining six were at various stages of conduct. Of the RCTs that were published, the publication year ranged from 1998 to 2011, and 40% (6/15) were published in the New England Journal of Medicine (NEJM). Slightly less than 40% (8/21) had a single

funding source. The majority of the 21 RCTs included adult study populations (81%). Slightly less than half (47%) were pilot/feasibility studies with sample sizes ranging from 40 to 129. Of the 21 RCTs, the protocol and/or grant application was available for 15 (71%) and the budget justification was provided for 9 RCTs. The majority of the RCTs used a paper CRF as the method of data collection (62%) (13/21). Slightly less than half (43%) had received at least partial funding from industry. For consistency, we focused the analysis on those RCT's that provided either the grant application and/or the study protocol, of which there were 15.

Table 18: General summary of Canadian Critical Care Trials Group RCTs and documents available

Study Acronym	Completed or In Progress	YR of Study Completion	YR of Publication	Journal / Impact Factor	# Sites	Sample Size	Data Collection Method	QA Methods Found in Grant Application &/or Protocol	QA Methods Found in Published Manuscript	QA Methods Found in Budget Justification	QA Methods Found in Data Management Plan &/or SOP's
Protocol Available											
VIP*(18)	Completed	2007	2009	AJRCCM / 10.2	7	69	EDC - Paper	Yes	No	Yes	Yes
SUGAR	Completed	2008	2009	NEJM / 53.5	16 (Canada) 48 (Total)	6104	EDC	No	Yes	Yes	NA
FINESS* (41)	Completed	2006	2008	Can J Anesth / 2.18	4	40	Paper	No	No	N/A	N/A
PROTECT-P*(42)	Completed	2002	2004	J Crit Care / 2.29	16	129	Paper	Yes	No	N/A	No
PROTECT (19)	Completed	2010	2011	NEJM / 53.5	67	3600	Paper	Yes	Yes	Yes	N/A
SLEAP-P* (43)	Completed	2004	2008	Crit Care Med /6.25	3	65	Paper	Yes	No	No	N/A
TRIPICU (44)	Completed	2005	2007	NEJM / 53.5	19	637	Paper	Yes	No	Yes	Yes
PRECISE* (45)	Completed	2009	2011	J Crit Care / 2.29	6	51	Paper	No	No	N/A	N/A
HyP-HIT (46)	Completed	2005	2008	NEJM / 53.5	17	225	Paper	Yes	No	Yes	Yes
ABLE	In Progress	N/A	N/A	N/A	25	2510	EDC	Yes	N/A	Yes	No
REDOXS	Completed	2012	N/A	N/A	35	1200	EDC	Yes	N/A	Yes	Yes
CANTREAT*	In Progress	N/A	N/A	N/A	9	80	EDC	No	N/A	N/A	Yes
HALO*	In Progress	N/A	N/A	N/A	7	70	EDC	Yes	N/A	N/A	N/A
OSCILLATE	In Progress	N/A	N/A	N/A	52	600	Paper	Yes	N/A	N/A	N/A
SLEAP	In Progress	N/A	N/A	N/A	11	410	Paper	No	N/A	Yes	N/A
No Protocol Available											
TRICC	Completed	1997	1999	NEJM / 53.5	22	838	Paper	N/A	No	N/A	N/A
PACS	Completed	N/A	2003	NEJM / 53.5	19	1994	Paper	N/A	No	N/A	N/A
EAEF	Completed	N/A	1999	Crit Care Med	8	120	Paper	N/A	Yes	N/A	N/A
HELIOX	Completed	2003	2005	Pediatrics	4	39	Paper	N/A	No	N/A	N/A
VAP	Completed	2005	2008	Crit Care Med	28	740	EDC	N/A	No	N/A	N/A
SRUGI	Completed	1996	1998	NEJM / 53.5	16	1200	Paper	N/A	Yes	N/A	N/A

8.4.2 Quality Assurance Methods Described and Planned

Quality Assurance methods were described within the grant application and/or protocol for two-thirds (n=10) (Table 19) of the RCTs and found within the budget justification for just over half (53%) (n=8). Specific details of the described Quality Assurance methods are found in Appendix H. Additionally, Quality Assurance methods or activities were described within the Data Management Plan or study specific Standard Operating Procedures for 5 RCTs (33%). Two published RCTs included descriptions of Quality Assurance methods within the actual publication (13%) that were utilized during the conduct of the study; one included a statement that source data verification had been done, and the other referred to the process of sending source documents to the Data Coordinating Centre.

Almost three-quarters (73%) (n=11) described Quality Assurance activities such as visual checking of the data, checking frequencies, out-of range (OOR) and observing for inconsistent data (Tables 18 and 19). Three RCT's included a plan for sending copies of source documents to the Data Coordinating Centre (20%). Nine (60%) of the RCTs included a plan for site visits of 100% of study sites for the purpose of source data verification. Four RCTs (27%) planned to conduct source data verification on 10-20% of CRF's. Two RCTs (13%) described a plan to perform source data verification on the first 1 or 2 CRF's at each site, and one indicated that 25% of CRF's at each site would be source data verified. One RCT described which variables would be source verified (7%).

Table 19: RCTs with protocol available – description of methods of Quality Assurance planned

Specific QA Methods Described N=15	N (%)
Check Frequencies, out-of-range, missing or inconsistent data	11 (73%)
Copies of Source Docs to be sent to DCC	3 (20%)
Site Visits for Monitoring	9 (60%)
Site Visits - All Sites	9 (60%)
% of CRF's to Have SDV Documented	7 (47%)
% of CRF's to Have SDV - 10-20%	4 (27%)
First 1 - 2 CRF's at each Site to Have SDV	2 (13%)
25% of CRF's at each Site to Have SDV	1 (7%)
# or % of Variables to have SDV Specified	1 (7%)

8.4.3 Quality Assurance Methods Conducted

The majority of RCTs (14/15) performed Quality Assurance procedures (Table 20). These processes included checking data frequencies, checking for out-of-range, missing or inconsistent values. Please see Appendix I for specific details on Quality Assurance methods performed. One-third had copies of source documents sent to the Data Coordinating Centre (5/15). Study sites were visited for the purposes of conducting source data verification for eight (53%) RCTs. Five RCTs indicated that all sites had at least one site visit for source data verification. Two RCTs reported that some sites had more than one visit for source data verification. One RCT performed some amount of source data verification on 100% CRFs and one indicated that 1-20% of CRF’s had at least some amount of source data verification.

Table 20: Specific Quality Assurance methods conducted

Specific QA Methods Conducted N=15	N (%)
Check Frequencies, out-of-range, missing or inconsistent data	14 (93%)
Copies of Source Documents sent to Data Coordinating Centre	5 (33%)
Site Visits for Monitoring Done or In-progress	8 (53%)
All Sites Visited at least 1X	5(33%)
100% of CRF's That Had SDV	1 (7%)
1-20% of CRF's That Had SDV	1 (7%)
# or % of Variables With SDV Specified	2 (13%)

8.4.4 CRF Information

All RCTs with protocols (15/15) provided CRFs for review (Table 21). The number of variables collected in the CRFs ranged from 150 to 742 (excluding variables that repeated based on time, i.e. hourly, daily, monthly, etc) with a median of 238. Of the 15 published RCTs with available protocols, 9 had been published. The number of variables reported within these publications ranged from 30 to 181 with a median of 78. Five to 88% of variables collected in the CRF were reported within the published manuscripts. Two-thirds of published RCTs reported less than 50% of the collected variables within the manuscript. We were unable to determine which variables that were published had undergone source data verification. Specific details regarding the CRF from each RCT can be found in Appendix J.

Table 21: Case Report Form (CRF) information of Canadian Critical Care Trials Group RCTs

CRF Information N=15	N (%)
CRF Available	15 (100%)
# of Variables Collected in CRF - Median (Min, Max)	238 (150, 742)
# of Variables Reported in Publication - Median (Min, Max)	76 (30, 181)
Percentage of Variables in CRF Reported in Publications - Mean (Min, Max)	34% (5%, 88%)

8.4.5 Funding Information

Seven of the RCTs had a single funding source (53%); the Canadian Institutes for Health Research (CIHR) (Table 22). The number of funding sources for a single RCT ranged from 1 to a maximum of 8. The total amount awarded for the 15 RCTs was $24,728,644 CAD. Amounts per RCT ranged from a minimum of $82,774 to a maximum of $4,880,347 CAD. The total amount awarded for site visits for the purposes of source data verification was $529,658 CAD, approximately 2% of the total funding awarded. The amount awarded for site visits for the conduct of source data verification, ranged from $14,624 to a maximum of $247,957 CAD.

The amount requested for funding was the same amount awarded for 8 RCTs (53%). For two RCTs, the funding received was less than requested (13%), was more than requested for one RCT (7%), and the information was unavailable for 4 RCTs. The amount received for site visits for source data verification was the same as requested for 8 RCTs (53%) and this information was unavailable for 7 RCTs (47%). Please see Appendix K for specific details regarding funding information for each RCT.

Table 22: Funding information for the Canadian Critical Care Trials Group RCTs

Funding Information N=15	N (%)
Funding Source(s)	
CIHR Only	7 (47%)
PSI as one of the funding partners	4 (27%)
Hospital for Sick Children Foundation	2 (13%)
Heart & Stroke Foundation	2 (13%)
Industry Funding as Partner	3 (20%)
Other Funding Sources	8 (53%)
Amount Funded - Total (Median)	$24,728,644 ($859,595)
Amount Funded Same as Amount Requested	8 (53%)
Amount Funded Less than Amount Requested	2 (13%)
Amount Requested for Site Visits for SDV - Total (Median)	$529,658 ($27,300)
Amount Funded for Site Visits Same as Amount Requested	8 (53%)

8.4.6 Comparison of Source Data Verification Planned For Versus Conducted

Eight RCTs followed the described plan for source data verification at least partially (89%), based information from the protocol and the publication. One RCT did not conduct site visits for the purposes of source data verification, although it was planned for according to the budget justification. A comparison for the other 7 RCT's was not possible for the following reasons:

- The information was unavailable, or
- The RCT was still in progress.

We were unable to compare the amount of funding received for monitoring to the cost of conducting source data verification as this information was available for only two RCTs. One RCT calculated the cost for conducting site visits for source data verification to be $53,500, and had been awarded $67,500. The other RCT had received $27,300; however, costs associated with conducting site visits for source data verification were $37,442.

8.4.7 Comparison of Source Data Verification Conducted in Canadian Critical Care Trials Group RCTs to What Investigators and Research Coordinators Believe Should Be Done

Although we had planned to use chi-square tests to compare the amount and frequency of source data verification conducted in Canadian Critical Care Trials to what investigators and research coordinators believe should be done as reported in the survey in Section 6.0, we describe these comparisons in a qualitative manner because of the limitations in the data. In the recent survey on beliefs and attitudes regarding source data verification (section 6.0), almost 75% of critical care investigators and research coordinators indicated that either a pre-determined number of CRFs or a random sample of all CRFs from each site should have some amount of source data verification (Table 23). In the current review of CCCTG RCTs, of the eight studies that had site visits done or were in progress for the purposes of source data verification, five had conducted site visits for all sites, one RCT visited 6 out of the 7 sites and the information was not available for the remaining two RCTs.

With regards to the number or percentage of CRFs that should have some amount of source data verification, roughly half of the survey participants (47%) stated that source data verification should be done on 1 to 20% of CRFs. Based on the current audit of CCCTG RCTs, the number or percentage of CRFs reported to have been reviewed at sites varied from 10% to 100%.

When asked about the frequency of source data verification, almost 80% of survey respondents reported that site visits should be done 1 to 3 times per year. The frequency reported in the audit of CCCTG RCTs varied from at least once, to 3 times over the duration of the study.

For the 11 RCTs that have provided funding details for the amount requested and received, the amount awarded was the same or more for nine (60%) and was less than requested

for two RCTs (13%). The amount requested for site visits in order to conduct source data verification ranged from 0 to 6% of the total funding request for the 10 RCTs that provided this information (67%). However, the majority of critical care investigators and research coordinators reported in the survey that funding agencies do not currently provide sufficient funding and that sites are not adequately compensated for work associated with source data verification.

Table 23: Comparison of SDV Conducted in CCCTG RCTs to Survey Responses

	Survey	Audit
Amount of Source Data Verification	All Sites should have Site Visits for some amt of SDV	5 of 6 studies had conducted site visits at all sites
Percentage of CRFs to have SDV	1-20%	10 - 100%
Frequency of SDV	1 - 3 times per year	1 - 3 times over duration of study
Funding requested compared to received	Do not receive sufficient funding	Funding received was same as requested for 60%

8.5 Discussion

In this audit of 21 RCTs conducted by the CCCTG, there were 15 RCTs that had a study protocol available. Of these 15, there were nine that had been completed and published (60%). Based on the information available for these 9 RCTs, there was consistency between the survey and the audit of actual practices regarding the number of CRFs to have source data verification and the frequency of site visits for source data verification. Only one completed RCT did not conduct site visits for the purposes of source data verification as was planned for.

Of the nine completed, published RCTs, site visits and source data verification were carried out at least partially, according to the described plan for 44% (4/9). Thus, less than half of the completed RCTs included source data verification. However, in the recent survey of

members of the Canadian Critical Care Trials Group, the majority overwhelmingly indicated that source data verification was an important part of a Quality Assurance program. This attitude was not consistent with the findings of the present audit.

Interestingly, of these five RCTs that did not include any site visits for the purposes of source data verification (56%), four of these were pilot RCTs with the sample size ranging from 40 to 129 study participants. In the recent survey of critical care investigators and research coordinators, the majority indicated that small sample sizes were important/very important in determining the amount and frequency of source data verification. Although there is no research on source data verification conducted specifically within pilot studies, these may be a potential venue to test-out source data verification strategies in order to determine their effectiveness and cost. However, this attitude is not clearly represented in current practice.

Six of the 15 RCTs reported having copies of source documents sent to the data coordinating centre. This was done primarily for the purposes of adjudicating primary, secondary and/or safety outcomes. In the recent survey, there was evidence of ambiguity by critical care investigators and research coordinators regarding the effectiveness of sending source documents to the Data Coordinating Centre and this is reflected in the results of this audit.

Overall, the number of variables collected in the CRF was much greater than the number reported in the published manuscript. While it is recognized that there are often variables that need to be collected in order to assess safety and are not included in the final publication (except perhaps in summary form, or in the appendix), on average only 34% of variables were included in the final publications. The Society for Good Clinical Data Management recommends collecting only that data which will be necessary to answer the study question (47). This recommendation is echoed in a number of publications (12, 15, 48) which focuses quality control

efforts on collecting fewer, but important variables. This problem of collecting potentially extraneous data can contribute to errors, as well increase the cost of a trial because of the work involved in collecting, checking and entering data that may not be used in to answer the question. It can also contribute to the cost of source data verification because of the additional data that will need to be source verified.

In the survey of critical care investigators and research coordinators, the majority of respondents felt that public agencies do not currently provide sufficient funding to conduct source data verification, and that sites are not adequately compensated for the work associated with source data verification. However, for the 11 RCTs where information was available for the amount of funding requested and the amount awarded, only two RCTs received less funding. As well, there was no evidence that funding agencies awarded fewer funds for site visits than what was requested. The amount of funding requested for site visits for the purpose of source data verification ranged from 0 to 6% of the total budget requested. This percentage is far less than what industry or pharmaceutical companies report having to spend on monitoring and source data verification efforts (13, 49). Although the perception of critical care investigators and research coordinators is that funding agencies do not provide sufficient funds to conduct source data verification, this was not apparent in this audit. Perhaps the request for funding for source data verification is not sufficient.

8.5.1 Strengths and Limitations

There are a number of limitations in this review that deserve discussion. The most notable is the amount of missing information which prevents some of the planned analysis, including the comparison of amount of funding received to the actual associated costs of source data verification. It became clear during the collection of data, that this level of detail in financial

record keeping is not usually available. We were specifically interested in the costs associated with site visits for the purposes of source data verification. However, site visits are often conducted for other purposes, such as site initiation or training. In one RCT, most sites had been visited, but none of the site visits were done in order to conduct source data verification.

In addition, this review included only Canadian Critical Care RCTs, the majority of which were adult, and may not reflect the practices of investigators of other areas, such as oncology, those from other countries, or other Critical Care trials.

However, the focus of this review is also its strength, in that it allowed a comparison of the attitudes of critical care investigators based on information from the recent survey, to the actual practice and conduct of source data verification within Canadian Critical Care RCT's. I collected most of the information from documents that had been sent, with additional information obtained by telephone and personal interviews with research coordinators. To my knowledge, this study is the first of its kind to be able to compare attitudes regarding source data verification to actual practice.

8.6 Conclusion

Overall, Critical Care investigators and research coordinators conducted source data verification according to their documented plan. There was consistency in the amount and frequency of source data verification found in the audit and what Critical Care investigators and research coordinators believe should be done from the recent survey. However, while source documentation is considered an important part of a QA program by critical care investigators, this was not necessarily reflected in this review, in that approximately half of the completed RCTs did not include source data verification. We found that the number of variables collected is far more than what is reported in the published manuscript. While members of the Canadian

Critical Care Trials Group believe that funding agencies do not provide sufficient funding for source data verification, they received the amount requested for almost all of the RCTs.

9.0 SUMMARY AND FUTURE DIRECTIONS

My overall objective of this thesis was to establish the evidence base for source data verification in clinical research for the future development of evidence-based guidelines for academic investigators. This objective was carried out by designing and conducting four original research projects: a systematic review of the literature on the methods of source data verification, a systematic review of the literature on the effect of source data verification on study outcomes, a national survey on the attitudes and beliefs of source data verification in critical care research, and an audit of source data verification practices in clinical trials conducted by the Canadian Critical Care Trials Group.

The objective of the first systematic review was to determine the evidence of various methods and strategies of source data verification. Fourteen publications were included, half of which were guidelines or recommendations. There was significant variation in the amount and frequency of source data verification recommended and there were no publications that offered any empiric data for the recommendations made. There is a recent trend to adopt a risk-based approach to determining the amount and frequency of source data verification by a number of regulatory agencies. However the scientific verification is unavailable for this method, pending the results of two large RCTs currently underway in Europe. The conclusion from this systematic review was that any literature on methods of source data verification is inconsistent and there were no sound published studies to support any recommendations made. Further research is needed in order to develop robust, evidence-based guidelines for academic investigators.

The objective of the second systematic review was to investigate the evidence-base for the effect of source data verification methods on study outcomes. Remarkably, only two

publications were identified, one of which had to be terminated early and was not able to provide any results on the effect of source data verification. The other was a report of the source data verification of over 80% of the data of a large national RCT after the discovery of fraud. The authors reported no difference in the study outcomes after conducting source data verification on over 80% of eligibility and outcome variables. The conclusion from this systematic review was that there is no evidence for the effect of source data verification and that further research is needed before adopting yet another untested method of source data verification.

Our national survey on the attitudes and beliefs of critical care investigators and research coordinators assessed attitudes and factors that may determine the amount and frequency of source data verification, and how much source data verification should be done. The questions from the survey were built upon the results of the two systematic reviews and expert opinion. This offered an opportunity to examine the attitudes and beliefs of both investigators and research coordinators.

In our national survey, we found that while there were some differences in opinion between research coordinators and investigators, the majority strongly believe that source data verification is a valuable tool to ensure data validity, but not necessarily a cost-effective one. Survey respondents also felt that agencies do not provide sufficient funding to conduct source data verification. With regards to the frequency of site visits for source data verification, the majority felt that site visits should be conducted 1 to 3 times per year. The amount of source data verification that was thought to be sufficient varied. While all sites should be visited and have some amount of source data verification, it was not clear if there should be a pre-determined number of CRFs from each site, or a random sample of CRFs from each site, that should have source data verification. Respondents strongly supported further research efforts to establish evidence-based guidelines.

Building on the results of the national survey, we conducted an audit of both in-progress and completed clinical trials of the Canadian Critical Care Trials Group. Members of this group participated in our survey discussed in Section 6. An audit in the same groups of survey respondents provided an opportunity to describe the current methods of source data verification employed in Canadian critical care research. The results of our audit revealed minor differences in what had been planned for source data verification and what actually occurred. Although members of the CCCTG indicated in the survey that source data verification is an important and valuable tool to ensure data validity, this was not evident in their current practice; approximately half of the clinical trials audited did not include any source data verification. And while survey respondents felt strongly that agencies do not provide sufficient funding for source data verification, this was not supported by the review. Only two RCT's received less funding than requested. In fact, the maximum amount of funding requested for source data verification was 6% of the total amount requested. This is far less than what is usually spent on source data verification activities by industry or pharmaceutical companies (13, 49).

While source data verification is considered to be the 'gold standard' for ensuring that the data are accurate, complete and verifiable for the past two decades, there is no evidence that source data verification does this (5, 49-51). While industry and pharmaceutical companies have taken a very conservative approach and traditionally conducted 100% source data verification, the amount and frequency of source data verification has not been officially stated by any regulatory body. National regulatory bodies and recent literature support other strategies that pose less financial and human resource burden; however, there remains no scientific support for these strategies.

Based on the findings of the survey and audit, there is an opportunity to improve the understanding of Critical Care investigators and research coordinators on the methods of source

data verification. The systematic reviews and the survey have been presented at The Annual Meetings of the Society for Clinical Trials (Vancouver, 2011 and Miami, 2012 respectively). In addition, these projects and their findings have been presented at meetings of the Canadian Critical Care Trials Group. The systematic review on the methods of source data verification has been submitted to the journal, Clinical Trials, for publication and a decision is pending. We will submit the other three projects for publication, in order to disseminate our findings that establish a firm need for further research.

After discussion with members of the Canadian Critical Care Trials Group and my thesis committee, the next step in this research program will be to investigate the effect of source data verification on study outcomes. This will be done by comparing data that has been source data verified to data that has not been verified within a number of published Critical Care RCTs. In addition, we are in discussion with Critical Care investigators to compare different strategies of source data verification to assess their cost effectiveness using RCTs conducted by members of the Canadian Critical Care Trials Group. These projects will contribute greatly to building the evidence-base for source data verification and will inform the future development of guidelines on source data verification for academic investigators.

10.0 LESSONS LEARNED

The seed that planted the idea for this thesis began in October 2006, when the clinical trial that I was coordinating, was inspected and audited by Health Canada. Much to our surprise, we received a Non-Compliance assessment and one of the reasons given was the insufficient monitoring (which included source data verification) of participating study sites. When asked how much monitoring would be considered 'sufficient', the Inspector could not provide a definitive response. When I began investigating this further, I realized that there little guidance for investigators on the amount and frequency of source data verification. We look to GCP Guidelines to provide guidance on how to ensure that the safety of participants as well as the integrity of the data; however, GCP Guidelines are not supported by empiric evidence. It seemed perplexing to me, that we use such methodological rigour in the conduct of our research, but do not apply this to processes that will help assess and perhaps improve techniques to ensure the quality of the data, such as source data verification.

Although the ideas for my thesis were my own, they were further developed and made possible with the expertise of my mentors, Dean Fergusson and Kusum Menon, as well as members of the Canadian Critical Care Trials Group and the Canadian Critical Care Research Coordinators Group. I was fortunate enough to be able to present this project at a number of meetings of the Canadian Critical Care Trials Group and was able to benefit from their expert advice and mentorship. Without the support of the Canadian Critical Care Trials Group, it would not have been possible to complete this thesis. In addition, I know that their continued support will greatly assist in moving forward with establishing an evidence-base for source data verification.

It has not been an easy process, but if it was easy, then everyone would want to do this. However, the challenge has been worth it. Having been involved in the operational side of clinical research for many years, I have been able to gain a greater appreciation of the methodology that goes into the design and conduct of clinical research. Thankfully, my experience in the epidemiology programme at the University of Ottawa, along with my mentors, provided me with the tools and skills to undertake these projects. I have gained a fresh appreciation for anyone who conducts systematic reviews on a regular basis. Reviewing and keeping track of over 6000 citations was a huge challenge, even for a veteran research coordinator who considers herself to be very organized. Although I anticipated that there would be little evidence for source data verification, it was disheartening to realize that there was even less than anticipated. How do you analyze a systematic review that includes only 2 publications? It was quite a learning curve for me to conduct and analyze both systematic reviews, but I am grateful for the expertise of my mentors, as well as David Moher and Margaret Sampson, who were there to guide me through the process.

My next project was a survey and I naively believed that this could only be easier than the systematic reviews. However, it was an excellent learning opportunity to gain a much better understanding of survey methodology. One of the members of the Canadian Critical Care Trials Group, Karen Burns, had published an excellent guide on conducting medical surveys and this publication was a wonderful resource for me. In addition, I was fortunate to have a number of very experienced members of the Canadian Critical Care Trials Group assist in the development and testing phases of the survey.

In order to reduce costs, I elected to use a new electronic survey tool, “FluidSurveys” and to have participants complete this survey on-line. While the cost of mailing can be prohibitive, there are some advantages that may make a difference to response rates. An on-line survey tool

is less personal and you cannot provide a small token of appreciation, both of which are proven factors that can affect survey response rates.

Creating the email distribution list was a challenge as well; I had to merge different email distribution lists to create one. In addition, when I sent out the pre-notification email, there were a number of emails that bounced back. Then it was a matter of reviewing emails for spelling errors and confirming that participants were indeed members of the Canadian Critical Care Trials Group.

Having presented this project at numerous meetings of the Canadian Critical Care Trials Group, I anticipated that the response rate would be well above 50%. However, it was a somewhat disappointing 43%. As I had enlisted the support of many well-respected and experienced members of the Canadian Critical Trials Group, I expected that everyone would want to participate in my survey! However, I understand and appreciate how many surveys people are being asked to take part in. As well, there are likely many who are not familiar with this topic and perhaps felt that they may not have the experience or knowledge level to contribute. It convinces me even more that there is work to be done regarding educating and disseminating research efforts on source data verification.

Although this is the end of my thesis, I will continue on as I look at the next steps in developing an evidence base for source data verification. While this research will not directly contribute to better outcomes for critically ill patients, it will hopefully provide scientifically proven, cost-effective methods to ensure that the data that we collect in the conduct of Critical Care research is valid and reliable.

11.0 CONCLUSION

Based on the work conducted as part of this thesis and the findings presented, it is my hypothesis that there is no solid evidence for current source data verification methods and, more importantly, their impact on study outcomes. Further research on the value of source data verification is needed and supported by academic investigators who want to ensure the integrity of research data collected, but must often work within the limits of funding and human resources available.

Appendix A: Search strategy for systematic review

Medline and Medline Non-Indexed (OvidSP platform)

1. *quality control/ or *technology, medical/
2. (source or monitoring or scientific misconduct).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui]
3. 1 and 2
4. medical records.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui]
5. 3 and 4
6. 2 and 4
7. (data adj3 monitoring).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui]
8. limit 7 to humans
9. (Abstracting and Indexing as Topic).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui]
10. limit 9 to humans
11. 8 and 10
12. 6 and 10
13. Clinical Trials as Topic/mt [Methods]
14. limit 13 to humans
15. 3 and 14
16. *Clinical Protocols/mt, st, sn [Methods, Standards, Statistics & Numerical Data]
17. limit 16 to humans
18. 3 and 17
19. *Safety Management/mt, og, st, sn [Methods, Organization & Administration, Standards, Statistics & Numerical Data]
20. limit 19 to humans
21. 14 and 20
22. (((crf or case report form$ or data) adj3 monitoring) or source).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui]
23. limit 22 to humans
24. 2 and 4 and 23
25. 8 and 23
26. 1 and 25
27. guidelines.mp. or exp Guideline/ or exp Practice Guideline/
28. 19 and 27

Appendix B: Data extraction form for eligible studies

Reviewer's Initials: _____ Date (dd/mom/yyyy): _____ ID #:_____

SDV – Methods and Impact on Study Outcomes

Data Extraction Form

Title:_____

Author: _____

Journal: _____

Year: _____

1.1 SDV – Category of Review: ☐ Methods ☐ Impact

If Methods -

1.2 Inclusion Criteria (All inclusion criteria should be YES):

YES	NO	
☐	☐	Primary topic about a method of SDV
☐	☐	Publication is one of the following: RCT's, non-RCT's, Observ., Case-control, Cross-sectional, ecological Non-comparative case series, Systematic review, Methodological Report, Guideline, Technical Report, Grey Literature

Exclusion Criteria (All Exclusion Criteria should be NO):

YES	NO	
☐	☐	Non-human literature
☐	☐	Studies that only report on how SDV was performed

If Impact –

1.3 Inclusion Criteria (All inclusion criteria should be YES):

YES	NO	
☐	☐	Primary topic on effect of SDV on study outcomes
☐	☐	Publication is one of the following: RCT's, non-RCT's, Observ., Case-control, Cross-sectional, ecological Non-comparative case series, Systematic review, Methodological Report, Guideline, Technical Report, Grey Literature

Exclusion Criteria (All Exclusion Criteria should be NO):

YES	NO	
☐	☐	Non-human literature

☐ ☐ Studies that only report on how SDV was performed

1.4 Include in final review: ☐ Yes ☐ No

2.0 Type of Publication: ☐ Commentary ☐ Guideline ☐ Research Study
☐ Report ☐ Methods Paper ☐ Conference Proceedings
☐ Book Chapter ☐ Tech. Report ☐ Abstract

2.1 Study Design: ☐ N/A ☐ RCT ☐ Non Randomized CT
☐ Retrosp. Obs. ☐ Prosp. Obs. ☐ Systematic Review
☐ Case Series ☐ Case Control

2.2 Primary Objective or Purpose of Document: ☐ N/A

_____

_____

2.3 Study Date: ☐ N/A _____

2.4 Study Location: ☐ N/A

_____

_____

2.5 Study Population: ☐ N/A _____

2.6 Number of Participants: ☐ N/A _____

2.7 Number of Sites: ☐ N/A _____

3.0 Data Collection Method Used: ☐ N/A

☐ Paper ☐ Electronic ☐ Information not available/unknown

3.1 Data Collection Method Recommended or Discussed: ☐ N/A

☐ Paper ☐ Electronic

3.2a Who performed SDV? (Check all that apply):

☐ N/A

☐ Monitor from CRO ☐ Research Coordinator of Project

☐ Sponsor ☐ Other Research Coordinator

☐ Monitor from Internal QA program ☐ Other: _____

☐ Information not available/unknown

3.2b Who is recommended to perform SDV? (Check all that apply):

☐ N/A

☐ Monitor from CRO
☐ Sponsor
☐ Monitor from Internal QA program
☐ Information not available/unknown
☐ Research Coordinator of Project
☐ Other Research Coordinator
☐ Other: _____

3.3a How was SDV done? (Check all that apply):

☐ N/A
☐ On site (ie. During monitoring visit)
☐ Remotely

*Remotely = source documents sent to coordinating centre and compared to CRF

☐ Information not available/unknown

3.3b What were the recommendations regarding how SDV should be done? (Check all that apply):

☐ N/A
☐ On site (ie. During monitoring visit)
☐ Remotely

*Remotely = source documents sent to coordinating centre and compared to CRF

☐ Information not available/unknown

3.4a How many sites had SDV done?

☐ N/A
☐ All
☐ Other – specify: _____
☐ Information not available/unknown

3.4b How many sites should have SDV done?

☐ N/A
☐ All
☐ Other – specify: _____
☐ Information not available/unknown

3.5a How was SDV performed?:

☐ N/A
☐ Compare paper medical records to paper CRF
☐ Compare electronic medical records to paper CRF

☐ Compare electronic medical records to electronic CRF

☐ Compare paper medical record to electronic CRF

☐ Other – specify:_____

☐ Information not available/unknown

3.5b How should SDV be done?:

☐ N/A

☐ Compare paper medical records to paper CRF

☐ Compare electronic medical records to paper CRF

☐ Compare electronic medical records to electronic CRF

☐ Compare paper medical record to electronic CRF

☐ Other – specify:_____

☐ Information not available/unknown

3.6a Frequency of SDV based on:

☐ N/A

☐ # of patients

☐ Calendar time

☐ Set number of monitoring visits – if yes, how many? _____

☐ Hybrid of above

☐ Other – specify: _____

☐ Information not available/unknown

3.6b What is the recommended frequency of SDV?

☐ N/A

☐ # of patients

☐ Calendar time

☐ Set number of monitoring visits – if yes, how many? _____

☐ Hybrid of above

☐ Other – specify: _____

☐ Information not available/unknown/discussed

3.7a Were variables stated for SDV?

☐ N/A

☐ Yes ☐ No

If yes, what variables were used to do SDV?:

☐ Yes ☐ No All variables

☐ Yes ☐ No Primary Outcome – specify:

☐ Mortality

☐ Other: _____

☐ Yes ☐ No Secondary Outcomes – specify:

_____

_____

☐ Yes ☐ No Safety Outcomes – specify:

_____

_____

☐ Yes ☐ No Other – specify:

_____

_____

3.7b Where there recommendations or discussions regarding what variables should have SDV?

☐ N/A

☐ Yes ☐ No

If yes, what variable were recommended or discussed for SDV?:

☐ Yes ☐ No All variables

☐ Yes ☐ No Primary Outcome – specify:

☐ Mortality

☐ Other: _____

☐ Yes ☐ No Secondary Outcomes – specify:

_____

_____

☐ Yes ☐ No Safety Outcomes – specify:

_____

☐ Yes ☐ No Other – specify:

_____

_____

3.8a Amount of SDV that was performed (as a percentage of CRF's):

☐ N/A

☐ 100% of all CRF's

☐ 75 – 100% of all CRF’s

☐ 50 – 74% of all CRF’s

☐ 25 – 49% of all CRF’s

☐ 20 – 24% of all CRF’s

☐ 10 – 19% of all CRF’s

☐ < 10% of all CRF’s

☐ Not specified/information not available

☐ Other: _____

3.9 Amount of SDV that was performed (as a percentage of variables/items):

☐ N/A

☐ 100% of all variables/items

☐ 75 – 100% of all variables/items

☐ 50 – 74% of all variables/items

☐ 25 – 49% of all variables/items

☐ 20 – 24% of all variables/items

☐ 10 – 19% of all variables/items

☐ < 10% of all variables/items

☐ Not specified/information not available

☐ Other: _____

3.8b Amount of SDV recommended:

☐ N/A

☐ 100% of all CRF’s

☐ 75 – 100% of all CRF’s

☐ 50 – 74% of all CRF’s

☐ 25 – 49% of all CRF’s

☐ 20 – 24% of all CRF’s

☐ 10 – 19% of all CRF’s

☐ < 10% of all CRF’s

☐ Not specified/information not available

☐ Other: _____

4.0 Other methods used to assess data quality (Check all that apply):

☐ N/A

☐ Yes ☐ No Logic/consistency checks – done centrally

☐ Yes ☐ No Range checks – done centrally

☐ Yes ☐ No Missing data checks – done centrally

☐ Yes ☐ No Statistical techniques – specify: _____

☐ Yes ☐ No Other specify:_____

☐ Information not available/unknown

4.1a Were Error Rates Reported?:

☐ N/A

☐ Yes ☐ No

If Yes – Specify the denominator used:

☐ Overall (all variables)

☐ By site

☐ By variable

4.1b Were recommendations made regarding Error Rates?:

☐ N/A

☐ Yes ☐ No

If Yes – Specify the denominator to be used:

☐ Overall (all variables)

☐ By site

☐ By variable

5.0 Were study outcomes compared before and after SDV?: ☐ Yes ☐ No

5.1 Results: ☐ N/A

_____

_____

Review References –

References to be checked: _____

Comments:_____

_____

_____

_____

Appendix C: Final Survey

Current Beliefs Regarding Source Data Verification (SDV)

Source data verification (SDV) is the process of comparing data collected from a source document (i.e., lab results, nursing notes, vitals) to data recorded on a case report form; the source documents or case report form may be either paper or electronic.

The objective of this survey is to describe the current beliefs and attitudes of Canadian Critical Care Investigators and Research Coordinators regarding source data verification, as well as attitudes regarding how to optimize this process. This survey is part of a research program with an ultimate goal of developing context-specific, evidence-based guidelines for source data verification for academic investigators. Our focus for purposes of this survey is randomized controlled trials (RCTs).

- How familiar are you with Source Data Verification (SDV)?
- I know what SDV is and have either had a site visit where SDV was done, been audited, or have conducted SDV.
- I have heard of SDV and know what SDV is, but have not had a site visit where SDV was done and have not conducted SDV.
- I have heard of it and have an understanding of what SDV is, but have never had a site vist where SDV was done or conducted SDV.
- I have heard of it, but am not sure what SDV is.
- I have never heard of SDV.

You have indicated that you may or may not have heard of Source Data Verification and that you have little or no familiarity with it. This section is to give you additional information to assist you as you proceed through the survey.

Source Data Verification (SDV) is the process of comparing the information that is recorded on source documents (such as the patient's medical record) to the data that is recorded on the Case Report Form or Data Collection Form (either paper or electronic).

A Source document refers to the document where information regarding the patient is first recorded. Source document verification usually involves having a trained individual travel to a research site and visually compares data from the patient's medical record to the data recorded on the Case Report Form. It is done to ensure that the data is accurate, complete and verifiable. Pharmaceutical companies usually conduct 80 to 100% source data verification using trained individuals called Monitors. However, academic studies often conduct less than 20% of source data verification because of lack of financial and human resource support.

1. Please choose the statement that best reflects your primary role in research:

- I am a Critical Care Investigator
- I am a Critical Care Research Assistant, Research Coordinator or Project Manager

2. If you chose Critical Care Investigator, please answer the following questions:

- Have you ever incorporated any form of SDV into a trial?
- Yes
- No
- Don't know

- Has your site ever been monitored using any form of SDV?
- Yes
- No
- Don't know

If you chose Critical Care Research Assistant, Research Coordinator or Project Manager, please answer the following questions:

3. Have you ever conducted any form of SDV?

- Yes
- No
- Don't know

4. Have you ever been monitored using any form of SDV?

- Yes
- No
- Don't know

5. Which of the following roles have you had in research?

Check ALL that apply. *For the purposes of this survey "Academic" is defined as Investigator-initiated trials designed and conducted by academic Investigators. "Industry" refers to research that is funded by 'for-profit' companies.

- Principal Investigator of a single-centre RCT
- Site Investigator of a multi-centre RCT
- Principal Investigator of a multi-centre RCT
- Site Investigator of an Industry-funded* RCT
- Principal Investigator of an Industry-funded* RCT
- Site Investigator of an Academic* RCT
- Principal Investigator of an Academic* RCT
- None of the above

- Site Research Coordinator of a single-site RCT
- Site Research Coordinator of a multi-centre RCT
- Lead Research Coordinator or Project Manager of a multi-centre RCT
- Site Research Coordinator of an Industry-funded* RCT
- Lead Research Coordinator or Project Manager of an Industry-funded* RCT
- Site Research Coordinator of an Academic* RCT
- Lead Research Coordinator or Project Manager of an Academic* RCT
- None of the above

6a. Study design and protocol-related factors in determining the amount and frequency of SDV.

Please rate how important you believe the following study design and protocol-related factors are when considering the amount and frequency of SDV to be done in an RCT.

	Very Important	**Important**	**Somewhat Important**	**Not Important**	**Neutral**
Phase* I/II Study	❍	❍	❍	❍	❍
Phase* III/IV Study	❍	❍	❍	❍	❍
Intervention with greater than minimal risk	❍	❍	❍	❍	❍
Novelty of the intervention (i.e. new drug or device)	❍	❍	❍	❍	❍
Off-label intervention	❍	❍	❍	❍	❍
Patient population involving children (< 18 years old)	❍	❍	❍	❍	❍
Complex treatment protocol	❍	❍	❍	❍	❍
Small sample size	❍	❍	❍	❍	❍
Large sample size	❍	❍	❍	❍	❍

*Phase I – First stage of testing in humans. Usually 20 – 100 health volunteers participate to determine the safety, tolerability, pharmacokinetics and pharmacodynamics of a drug.

Phase II – Usually a larger group of patients or volunteers (20 – 300) are given the drug/treatment to continue safety assessments as well as efficacy and dosing requirements.

Phase III – Randomized controlled trials using larger patient groups (300 – 3000, depending on medical condition and population), to determine how effective the drug/treatment is in comparison to the current “gold standard”.

Phase IV – Post-marketing surveillance trials to monitor safety of a marketed drug and to determine any long-term or rare adverse effects.

Please add any comments you may have regarding the above.

6b. Data quality and regulatory requirement-related factors in determining the amount and frequency of SDV.

Please rate how important **you** believe the following data management and regulatory requirement-related factors are when considering the amount and frequency of SDV to be done in an RCT.

Ensuring reliability and validity of data	❍	❍	❍	❍	❍
Health Canada or FDA Regulated trials	❍	❍	❍	❍	❍
Research Ethics Board requirements	❍	❍	❍	❍	❍
Amount of funding available	❍	❍	❍	❍	❍
Risk of fraud	❍	❍	❍	❍	❍
Method of data collection – paper versus electronic data capture	❍	❍	❍	❍	❍
Primary outcome is mortality	❍	❍	❍	❍	❍
Ability to download data directly from health records or lab database into electronic data capture	❍	❍	❍	❍	❍

6c. Research site-related factors in determining the amount and frequency of SDV.

Please rate how important you believe the following research site-related factors are when considering the amount and frequency of SDV to be done in an RCT.

Research sites with lack of experience (Investigator and/or Research Coordinator)	❍	❍	❍	❍	❍
Research sites with high turnover of study personnel	❍	❍	❍	❍	❍
Unexpected number of data queries	❍	❍	❍	❍	❍
Unexpected number of unanswered data queries	❍	❍	❍	❍	❍
Unexpected number of Serious Adverse Events	❍	❍	❍	❍	❍
Geographical location of site (far from Coordinating Center)	❍	❍	❍	❍	❍
Geographical location of site (close proximity to Coordinating Centre)	❍	❍	❍	❍	❍

7. Beliefs regarding the value, amount and frequency of site visits for the purposes of conducting SDV

7A. General Beliefs Regarding SDV

Please rate the level to which you agree or disagree with each of the following statements regarding SDV.

	Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**	**Neutral**
SDV is an important part of a Data Quality Assurance program.	❍	❍	❍	❍	❍
Conducting SDV helps to ensure data reliability and validity.	❍	❍	❍	❍	❍
SDV should be done only in studies where there is greater than minimal risk to the patient.	❍	❍	❍	❍	❍
Industry-funded studies should conduct less SDV than what is currently done*.	❍	❍	❍	❍	❍
Academic studies should conduct more SDV than what is currently done**.	❍	❍	❍	❍	❍
The primary objective of a site visit should be to train study personnel and ensure protocol compliance instead of conducting SDV.	❍	❍	❍	❍	❍
Funding agencies provide sufficient resources to conduct on-site monitoring and SDV.	❍	❍	❍	❍	❍

*Industry funded studies generally conduct 80 – 100% SDV.

**Academic studies generally conduct < 20% SDV.

Please add any comments you may have regarding the above.

7B. How many Case Report Forms (CRF's) should have SDV?

On average, how many CRF's do you believe should have SDV? Please check only one answer.

- The first 1 – 2 CRF's from EACH site should have some amount of SDV.
- The first 1 – 2 CRF's from randomly selected sites ONLY should have some amount of SDV.
- The first 1 – 2 CRF's from targeted sites only should have some amount of SDV.
- A random sample of all CRF's should have some amount of SDV (i.e. may not affect all sites).
- A pre-determined number of CRF's from each site should have some amount of SDV (i.e. SDV will be done on X number of CRF's from each site).
- A random sample of ALL CRF's from EACH site should have SDV.

Please add any comments you may have regarding the above.

7C. What is the proportion of Case Report Forms (CRF's), variables and site that should have SDV?

Please check the percentage of CRF's, variables and site that should have SDV (please check only one for each question).

	0%	**1 to 20%**	**21 to 40%**	**41 to 60%**	**61 to 80%**	**81 to 99%**	**100%**
What % of **CRF's** should have SDV?	❍	❍	❍	❍	❍	❍	❍
What percentage of **variables** should have SDV?	❍	❍	❍	❍	❍	❍	❍
What percentage of sites should have SDV?	❍	❍	❍	❍	❍	❍	❍

Please add any comments you may have regarding the above.

7D. What proportion of each of the following do you believe should have SDV?

When answering each item below, consider the percentage based on all CRF's for an RCT.

	0%	**1 to 20%**	**21 to 40%**	**41 to 80%**	**61 to 80%**	**81 to 99%**	**100%**
Consent Forms	❍	❍	❍	❍	❍	❍	❍
Documentation of Consent Process	❍	❍	❍	❍	❍	❍	❍
Eligibility Criteria	❍	❍	❍	❍	❍	❍	❍
Primary Trial Outcomes	❍	❍	❍	❍	❍	❍	❍
Secondary Trial Outcomes	❍	❍	❍	❍	❍	❍	❍
Drug Accountability/ Device calibration	❍	❍	❍	❍	❍	❍	❍
Serious Adverse Events	❍	❍	❍	❍	❍	❍	❍
Adverse Events	❍	❍	❍	❍	❍	❍	❍

Please add any comments you may have regarding the above.

8A. Frequency of site visits for purposes of SDV.

On average, how many times should a site be visited annually for the purposes of SDV?

Please check only one.

- 0
- 1 – 3 times
- 4 – 6 times (i.e. every 8 – 12 weeks)
- 7 – 11 times (i.e. every 4 – 6 weeks)
- 12 times (i.e. once a month)

8B. Factors affecting the frequency of site visits for purposes of SDV.

Please rate the level to which you agree or disagree with each of the following factors that may affect the frequency of Site Visits for the purposes of SDV.

	Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**	**Neutral**	**Don't Know**
The frequency of Site Visits for SDV would depend on the number of participants enrolled at that site.	❍	❍	❍	❍	❍	
Generally, a site that has enrolled more participants would have more frequent site visits for SDV than a site that has enrolled far fewer participants.	❍	❍	❍	❍	❍	
A site with poor performance (low recruitment, slow to submit CRFs or to respond to data queries) should have more frequent Site Visits for the purposes of conducting SDV than sites with good performance.	❍	❍	❍	❍	❍	

Please add any comments you may have regarding the above.

9. Alternatives to SDV - Central Monitoring

Central Monitoring is a method of verifying data without being physically at a site. It may include any of the following practices:

Data Checks- Using centrally available data to check for missing values, out of range values, inconsistent or illogical values, or protocol deviations,

Statistical Monitoring- Using centrally available data to perform statistical techniques (i.e. descriptive statistics, box and whisker plots, frequency histograms, cross-tabulations, scatterplots, correlation/regression),

Sending Source Documents- Having sites copy specific source documents (eliminating identifiers) and send them by fax or electronically to the Coordinating Centre.

Targeted SDV - The verification of critical trial data, including but not limited to primary and/or secondary study outcomes, and safety data.

Please rate the level to which you agree or disagree with the following statements regarding Central Monitoring.

	Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**	**Neutral**	**Don't Know**
Data checks are useful tools to help ensure data validity.	❍	❍	❍	❍	❍	
Data checks and statistical monitoring done together will help to ensure data validity.	❍	❍	❍	❍	❍	
Data checks, statistical monitoring and sending source documents are as effective in helping to ensure data validity as SDV.	❍	❍	❍	❍	❍	
Data Checks, statistical monitoring and sending source documents are more cost effective than performing SDV.	❍	❍	❍	❍	❍	
Data checks, statistical monitoring and sending source documents will likely decrease the need for SDV.	❍	❍	❍	❍	❍	
Targeted SDV may be done as a result of data checks and statistical monitoring.	❍	❍	❍	❍	❍	

Please add any comments you may have regarding the above.

10. Workload and Costs Associated With SDV

Please rate the level to which you agree or disagree with each of the following statements regarding the workload and costs associated with SDV.

	Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**	**Neutral**
Sending source documents to the coordinating centre (Central Monitoring) increases my workload more than having SDV done during a Site Visit.	❍	❍	❍	❍	❍
During a site visit, SDV is very time-consuming for the Site Research Coordinator/Assistant.	❍	❍	❍	❍	❍
During a site visit, SDV is very time-consuming for the Site Investigator.	❍	❍	❍	❍	❍
SDV is a cost-effective way to ensure data validity and reliability.	❍	❍	❍	❍	❍
Sites are compensated adequately for the work associated with SDV as part of a monitoring visit.	❍	❍	❍	❍	❍

Please add any comments you may have regarding the above.

11. Further Need for Evidence Base of SDV and Development of Guidelines

Please rate the level to which you agree or disagree with each of the following statements regarding the need for further evidence of SDV.

	Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**	**Neutral**
More research should be done on the effect of SDV on data validity.	❍	❍	❍	❍	❍
More research should be done on the cost-effectiveness of SDV in ensuring data validity.	❍	❍	❍	❍	❍
More research should be done on the effect of SDV on study outcomes.	❍	❍	❍	❍	❍
It is important to develop evidence-based guidelines for the amount and frequency of SDV for academic investigators.	❍	❍	❍	❍	❍

12. Please tell us about yourself

12A. I am:

- Male
- Female

12B. What is your occupation?

Please check ALL that apply.

- Staff Physician
- Trainee/Fellow
- Nurse
- Allied Health
- Research Coordinator/Project Manager
- Research Assistant
- Other: _____

12C. How many years have you been involved in critical care research?

- 0 – 1 years
- 2 – 5 years
- 6 – 10 years
- > 10 years

12D. What type(s) of patients are cared for in your ICU(s)? Please check ALL that apply.

- Trauma
- Medical
- Surgical
- Neurosurgical
- Cardiac Surgical
- Pediatric
- Other: _____

13. Please share with us any additional comments you may have regarding SDV.

Thank you for taking the time to complete this survey! If you have any questions, please do not hesitate to contact me at rward@cheo.on.ca

Sincerely,

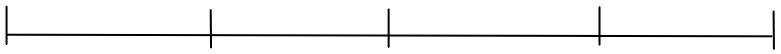
Roxanne Ward
Critical Care Clinical Research Manager
Clinical Research Unit
Children's Hospital of Eastern Ontario Research Institute

Appendix D: Clinical Sensibility Testing Form

Clinical Sensibility Testing Tool

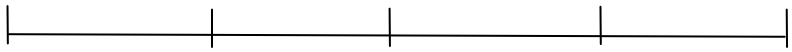
Roxanne Ward requests your assistance in assessing the clinical sensibility of the questionnaire *Current Beliefs Regarding Source Data Verification of Canadian Critical Care Investigators and Research Coordinators* by answering the following questions:

1. To what extent are the questions directed at important issues pertaining to source data verification (Please circle your response).



Small Extent | Limited Extent | Fair Extent | Moderate Extent | Large Extent

2. Are there important issues pertaining to source data verification which have been omitted? (Please circle your response).

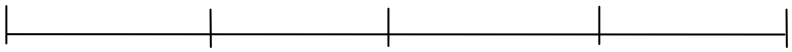


Crucial Gaps | Important Gaps | Minor Gaps | Minimal Gaps | Insignificant Gaps

Please identify any omissions:

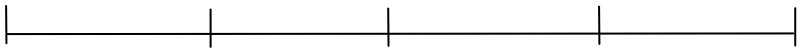
_____

3. To what extent are the response options provided simple and easily understood? (Please circle your response).



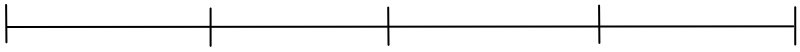
Small Extent | Limited Extent | Fair Extent | Moderate Extent | Large Extent

4. To what extent are questions likely to elicit information pertaining to your familiarity with source data verification?
(Please circle your response).



Small Extent | Limited Extent | Fair Extent | Moderate Extent | Large Extent

5. How many items are inappropriate or redundant?
(Please circle your response).



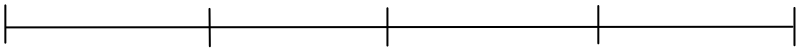
Very Many | Many | Some | A few | Hardly Any

Please identify redundant or inappropriate items:

_____

6. How likely is the questionnaire to elicit information describing the attitudes and beliefs of Canadian critical care investigators and research coordinators regarding source data verification?

   (Please circle your response).



Very Unlikely Unlikely Likely Quite Likely Very Likely

7. How long did it take you to complete the questionnaire? _____ Minutes

Please feel free to provide any other feedback on the back of this form.

Thank you for assisting us with the sensibility testing of our questionnaire!

Appendix E: Survey - Tables on Amount and Frequency of Source Data Verification

How many CRF's should have SDV? N=118	N (%)
The first 1-2 CRFs from EACH site should have some amount of SDV	13 (11.0%)
The first 1-2 CRFs from RANDOMLY selected sites ONLY should have some amount of SDV	3 (2.5%)
The first 1-2 CRFs from targeted sites only should have some amount of SDV	1 (0.8%)
A random sample of all CRFs should have some amount of SDV	13 (11.0%)
A pre-determined # of CRFs from each site should have some amount of SDV	42 (35.6%)
A random sample of ALL CRFs from EACH site should have some amount of SDV	46 (39.0%)

What % of CRFs should have SDV? N=118	N (%)
0%	1 (0.8%)
1 - 20%	55 (46.6%)
21 - 40%	26 (22.0%)
41 - 60%	14 (11.9%)
61 - 80%	11 (9.3%)
81 - 99%	2 (1.7%)
100%	9 (7.6%)

What % of variables should have SDV? N=117	N (%)
0%	1 (0.9%)
1 - 20%	26 (22.2%)
21 - 40%	21 (17.9%)
41 - 60%	24 (20.5%)
61 - 80%	15 (12.8%)
81 - 99%	2 (1.7%)
100%	28 (23.9%)

What % of sites should have SDV? (118)	N (%)
0%	1 (0.8%)
1 - 20%	8 (6.8%)
21 - 40%	5 (4.2%)
41 - 60%	10 (8.5%)
61 - 80%	3 (2.5%)
81 - 99%	4 (3.4%)
100%	87 (73.7%)

What Percentage of Items That Should Have SDV?	0%	1-20%	21-40%	41-60%	61-80%	81-99%	100%
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Consent Forms (n=117)	15 (12.9%)	37 (31.6%)	12 (10.3%)	8 (6.8%)	1 (0.9%)	4 (3.4%)	40 (34.2%)
Consent Process documentation (n=117)	16 (13.7%)	41 (35.0%)	11 (9.4%)	15 (12.8%)	3 (2.6%)	5 (4.3%)	26 (22.2%)
Eligibility Criteria (n=116)	3 (2.6%)	31 (26.7%)	17 (14.7%)	18 (15.5%)	6 (5.2%)	5 (4.3%)	36 (31.0%)
Primary Trial Outcomes (n=117)	1 (0.9%)	24 (20.5%)	18 (15.4%)	23 (19.7%)	7 (6.0%)	6 (5.1%)	38 (32.5%)
Secondary Trial Outcomes (n=115)	2 (1.7%)	32 (27.8%)	27 (23.5%)	16 (13.9%)	11 (9.6%)	8 (7.0%)	19 (16.5%)
Drug/Device Accountability (n=117)	2 (1.7%)	34 (29.1%)	16 (13.7%)	21 (17.9%)	10 (8.5%)	8 (6.8%)	26 (22.2%)
SAEs (n=117)	1 (0.9%)	14 (12.0%)	13 (11.1%)	12 (10.3%)	6 (5.1%)	8 (6.8%)	63 (53.8%)
AE's (n=117)	2 (1.7%)	32 (27.4%)	15 (12.8%)	20 (17.1%)	16 (13.7%)	6 (5.1%)	26 (22.2%)

Appendix F: Survey – Need for Further Evidence-base and Guidelines

Need for Further Evidence-base & Guidelines N=117	Neutral N %	Strongly Disagree N %	Disagree N %	Agree N %	Strongly Agree N %
More research needed on effect of SDV on data validity	15 (12.8%)	1 (0.9%)	4 (3.4%)	60 (51.3%)	37 (31.6%)
More research needed on cost effectiveness of SDV in ensuring data validity	11 (9.4%)	1 (0.9%)	2 (1.7%)	68 (58.1%)	35 (29.9%)
More research needed on effect of SDV on study outcomes	9 (7.7%)	1 (0.9%)	6 (5.1%)	58 (49.6%)	43 (36.8%)
Important to develop evidence-based guidelines for amt and freq of SDV for academic Inv	7 (6.0%)	1 (0.9%)	2 (1.7%)	57 (48.7%)	50 (42.7%)

Appendix G – Data Capture Form for Audit of Canadian Critical Care Trials Group RCTs

Information on Methods of SDV for Completed and In-Progress

CCCTG RCT's

GENERAL INFORMATION

Study Name: _____

_____

Principal Investigator: _____

Study Coordinator (or Contact): _____

Start Date (date funding received):_____

Completion Date (date recruitment finished): _____ NA ☐

Date of Publication: _____ NA ☐

Publication Name: _____ NA ☐

Number of sites: _____

Sample size: _____

Method of Data Collection: _____

METHODS DESCRIBED TO ENSURE DATA INTEGRITY (WHAT THEY SAID THEY WOULD DO)

Grant Application/Protocol:	Yes	☐	No	☐		
Published Manuscript:	Yes	☐	No	☐	NA	☐
Budget Justification:	Yes	☐	No	☐	NA	☐
Data Management Plan	Yes	☐	No	☐	NA	☐
Study Procedures/SOPs	Yes	☐	No	☐	NA	☐

What methods were described to ensure data integrity?

Data Management Plan	Yes	☐	No	☐
Visual check of data	Yes	☐	No	☐
Central Monitoring	Yes	☐	No	☐

If yes, check which processes were described?

Frequency tables ☐

Boxplots ☐

Check for outliers/out of range values ☐

Statistical procedures to look for non-randomness ☐

Copies of source docs sent to DCC ☐

Other: _____

_____

Site Visits/Monitoring Yes ☐ No ☐

If yes to above, provide details of planned site visits/monitoring:

or % of sites to be visited over the duration of the study: _____

or % of CRF's to have SDV over the duration of the study: _____

or % of variables to have SDV over the duration of the study: _____

METHODS USED TO ENSURE DATA INTEGRITY (WHAT THEY DID)

Data Management Plan Yes ☐ No ☐

Visual check of data Yes ☐ No ☐

Central Monitoring Yes ☐ No ☐

If yes, check which processes were conducted?

Frequency tables ☐

Boxplots ☐

Check for outliers/out of range values ☐

Statistical procedures to look for non-randomness ☐

Copies of source docs sent to DCC ☐

Description of process:_____

_____

Other: _____

_____

Site Visits/Monitoring Yes ☐ No ☐

If yes to above, provide details of site visits/monitoring:

or % of sites visited over the duration of the study: _____

or % of CRF's that had SDV over the duration of the study: _____

or % of variables that had SDV over the duration of the study: _____

Information available on error rates/types of errors? Yes ☐ No ☐

If yes to above, describe: _____

_____

_____

CASE REPORT FORM DETAILS

Case Report Form Available: Yes ☐ No ☐

If yes, provide details below:

# of Forms/Sections: _____

# of Variables in CRF: _____

# of variables reported in published manuscript: _____ NA ☐

FUNDING AND COSTS ASSOCIATED WITH SDV

Funding Source: _____

Total Amount Funded: _____

Total Amount Requested: _____

Amount Requested for Site Visits/Monitoring: _____

Amount Received/Allocated for Site Visits/Monitoring based on Funding Received:

_____

Estimated cost of site visits for monitoring: _____ CAD

Details regarding costs associated with site visits: _____

_____

_____

Other comments: _____

_____

_____

_____

Appendix H – Table of Quality Assurance Methods Planned in Canadian Critical Care RCTs

Study Acronym	Central Monitoring Planned	Check Frequencies, Out-of-Range, Missing or Inconsistent Values Described	Statistical Procedures Planned	Copies of Source Documents to be Sent to DCC	Site Visits for Monitoring Planned	#/% of Sites to be Visited	Frequency of Site Visits for SDV	#/% of CRF's to Have SDV	#/% of Variables to Have SDV
VIP	Yes	Yes	No	No	Yes	100%	Min of 3 over study	10% or representative sample	N/A
SUGAR	N/A	N/A	N/A	N/A	Yes	100%	N/A	N/A	N/A
FINESS	No	No	N/A	N/A	No	N/A	N/A	N/A	N/A
PROTECT-P	Yes	N/A	N/A	Yes	No	N/A	N/A	N/A	N/A
PROTECT	Yes	Yes	No	Yes	Yes	100%	1x in YR3	N/A	N/A
SLEAP-P	N/A	Yes	N/A	N/A	No	N/A	N/A	N/A	N/A
TRIPICU	Yes	Yes	No	No	Yes	100%	N/A	10-15%	N/A
PRECISE	Yes	Yes	No	No	No	N/A	N/A	N/A	N/A
HyP-HIT	Yes	Yes	No	No	Yes	100%	N/A	All Run-in Pts, then 10-20%	N/A
ABLE	Yes	Yes	N/A	No	Yes	100%	5X	25% of CRF's at each site	Key Variables
REDOXS	Yes	Yes	No	No	Yes	100%	1x X 3 Yrs	1st & 2nd CRF at each site	N/A
CANTREAT	Yes	Yes	No	No	Yes	100%	1 - 3 X	Representative Sample	N/A
HALO	Yes	N/A	N/A	Yes	No	N/A	N/A	N/A	N/A
OSCILLATE	Yes	Yes	No	NO	N/A	N/A	N/A	N/A	N/A
SLEAP	Yes	Yes	No	No	Yes	100%	N/A	20% of CRF's	N/A

Appendix I – Table of Quality Assurance Methods Performed in Canadian Critical Care RCTs

Study Acronym	Data Management Plan Used	Central Monitoring Done	Checked Frequencies, Out-of-Range, Missing or Inconsistent Values	Conducted Statistical Procedures	Copies of Source Docs sent to DCC	Site Visits for SDV Done/In Progress	# or % of sites visited	Frequency of Site Visits	# or % of CRFs that had SDV	#/% of Variables Verified by Source Data	Was the Original SDV Plan Followed?
VIP	No	Yes	Yes	No	No	Yes	6/7 sites	6/7 sites 2-3 x	71%	N/A	Partially
SUGAR	No	Yes	Yes	No	No	Yes	100%	N/A	100%	Random selection of variables for 10% of forms	Partially
FINESS	No	Yes	Yes	No	No	No	N/A	N/A	N/A	N/A	Yes
PROTECT-P	No	Yes	Yes	No	Yes	No	N/A	N/A	N/A	N/A	Yes
PROTECT	No	Yes	Yes	No	Yes	No	N/A	N/A	N/A	N/A	No
SLEAP-P	No	Yes	Yes	No	No	No	N/A	N/A	N/A	N/A	Yes
TRIPICU	Yes	Yes	Yes	No	N/A	Yes	100%	N/A	N/A	N/A	Yes
PRECISE	No	Yes	Yes	No	No	No	N/A	N/A	N/A	N/A	Yes
HyP-HIT	Yes	Yes	Yes	No	No	Yes	100%	All sites 1X at least	All Run-in Pts, then at least 10% of CRFs at site	N/A	Yes
ABLE	Yes	Yes	Yes	No	Yes	Yes	100%	N/A	N/A	Key Variables	N/A
REDOXS	No	Yes	Yes	No	Yes	Yes	100%	At least 1x, some 2 or 3X	N/A	N/A	N/A
CANTREAT	Yes	Yes	Yes	No	Yes	Yes	N/A	N/A	N/A	N/A	N/A
HALO	N/A	Yes	N/A	No	Yes	N/A	N/A	N/A	N/A	N/A	N/A
OSCILLATE	N/A	Yes	Yes	No	No	N/A	N/A	N/A	N/A	N/A	N/A
SLEAP	N/A	Yes	Yes	No	No	Yes	N/A	N/A	N/A	N/A	N/A

Appendix J – Case Report Form (CRF) Information of Canadian Critical Care Trials Group RCTs

Study Acronym	CRF Available	# Forms/Sections in CRF	# of Variables	# of Variables Reported in Publication	Proportion of Variables Present in Publication
VIP	Yes	24	327	76	23%
SUGAR	Yes	7	279	157	56%
FINESS	Yes	N/A	250	38	38%
PROTECT-P	Yes	16	654	30	5%
PROTECT	Yes	13	184	106	58%
SLEAP-P	Yes	N/A	313	45	14%
TRIPICU	Yes	N/A	206	181	88%
PRECISE	Yes	N/A	225	34	15%
HyP-HIT	Yes	N/A	220	57	26%
ABLE	Yes	N/A	190	N/A	N/A
REDOXS	Yes	18	247	N/A	N/A
CANTREAT	Yes	13	150	N/A	N/A
HALO	Yes	N/A	200	N/A	N/A
OSCILLATE	Yes	N/A	742	N/A	N/A
SLEAP	Yes	N/A	264	N/A	N/A

Appendix K – Funding information for Canadian Critical Care Trials Group RCTs

Study Acronym	Funding Source(s)	No. Of Funding Sources	Amt. Funded (CAD)	Amt. Requested (CAD)	Was the Funding Received the Same as Requested?	Was Funding Received More or Less Than Requested?	Amt. Requested for SV/SDV (CAD)	SDV - % of Budget Requested	Amt. Received for SV/SDV (CAD)	Was Funding Received for Site Visits/SDV More or Less than Requested?
VIP	CIHR, PSI, HSF, CICF, Ferring, Queen's University, Laerdal	8	$ 453,976	$ 720,919	No	Less	$ 27,300	4%	$ 27,300	Same
SUGAR	CIHR	1	$3,037,585	$ 2,965,921	No	More	$ 41,025	1%	$ 41,025	Same
FINESS	Bristol Myers, Squibb, Edwards Life Sciences, Abbott	3	$ 136,545	N/A	N/A	N/A	$ -	0%	$ -	N/A
PROTECT-P	CIHR	1	$ 181,561	$ 181,561	Yes	Same	N/A	N/A	N/A	N/A
PROTECT	CIHR, ANZ College	2	$4,880,347	$ 4,880,347	Yes	Same	$ 37,500	1%	$ 37,500	Same
SLEAP-P	PSI, EW Crann Mem. Trust	2	$ 82,774	$ 82,774	Yes	Same	$ -	0%	$ -	N/A
TRIPICU	CIHR	1	$ 719,358	$ 719,358	Yes	Same	$ 15,000	2%	$ 15,000	Same
PRECISE	CBS, University Fdtn - U of A	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HyP-HIT	CIHR, PSI, HSF, ONF, HSC, CHEO RI	6	$1,591,919	$ 1,591,919	Yes	Same	$ 67,650	4%	$ 67,650	Same
ABLE	CIHR	1	$4,020,188	$ 4,020,188	Yes	Same	$ 247,957	6%	$ 247,957	Same
REDOXS	CIHR	1	$4,742,496	$ 4,798,496	No	Less	$ 78,702	2%	$ 78,702	Same
CANTREAT	PSI, William Spear Foundation, Pfizer	3	$ 385,228	$ 385,228	Yes	Same	$ -	N/A	$ -	N/A
HALO	CIHR, MN HRC	2	$ 200,000	N/A	N/A	N/A	N/A	N/A	N/A	N/A
OSCILLATE	CIHR	1	$3,296,835	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SLEAP	CIHR	1	$ 999,832	$ 999,832	Yes	Same	$ 14,624	1%	$ 14,624	Same

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