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Monitoring and auditing protocol adherence, data integrity and ethical conduct of a randomized clinical trial: A case study

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ABSTRACT

Purpose: To categorize, quantify and interpret findings documented in feedback letters of monitoring or auditing visits for an investigator-initiated, peer-review funded multicenter randomized trial testing probiotics for critically ill patients.

Materials & methods: In 37 Canadian centers, monitoring and auditing visits were performed by 3 trained individuals; findings were reported in feedback letters. At trial termination, we performed duplicate content analysis on letters, categorizing observations first into unique findings, followed by 10 pre-determined trial quality management domains. We further classified each observation into a) missing operational records, b) errors in process, and potential threats to c) data integrity, d) patient privacy or e) safety.

Results: Across 37 monitoring or auditing visits, 75 unique findings were categorized into 10 domains. Most frequently, observations were in domains of training documentation (180/566 [32%]) and the informed consent process (133/566 [23%]). Most observations were missing operational records (438/566 [77%]) rather than errors in process (128/566 [23%]). Of 75 findings, 13 (62/566 observations [11%]) posed a potential threat to data integrity, 1 (1/566 observation [0.18%]) to patient privacy, and 9 (49/566 observations [8.7%]) to patient safety.

Conclusions: Monitoring and auditing findings predominantly concerned missing documentation with minimal threats to data integrity, patient privacy or safety.

Trial Registration: PROSPECT (Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial): NCT02462590.

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1. Background

Quality management and oversight of clinical trials are necessary to protect the rights and safety of participants while ensuring that the final trial results are valid and interpretable [1]. Monitoring and auditing are key features of trial quality management, helping to ensure that a trial is being conducted in compliance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP) and applicable regulatory agencies [2].

Historically, monitoring and auditing have been resource-intensive, often involving annual visits to each participating site with verification of either all source data, or a sample. However, a growing evidence base over the last decade has proposed strategies to minimize monitoring intensity, while striking a balance between quality control and expense. New recommended monitoring strategies are 'risk-adapted', which encourages adapting the intensity of on-site monitoring to the trial's risk of noncompliance with GCP guidelines [3]. Risk-adapted monitoring was found to be non-inferior to intensive on-site monitoring strategies in a cluster randomized trial of 213 sites participating in 11 academic trials [4]. Risk-adapted monitoring is supported by the Food and Drug Administration (FDA), [5]. European Medicines Agency, [6]. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, [7]. and Clinical Trials Transformation Initiative [8]. Of note, risk-adapted monitoring based on trial characteristics differs from risk-triggered monitoring whereby visits are undertaken for certain sites if concerns arise (e.g., sending unredacted patient information to the Methods Center) [9,10]. More recently, studies of low intensity monitoring and remote monitoring strategies have also been reported [11,12]. Such adaptations have been acknowledged as necessary during the COVID-19 pandemic due to restricted hospital visitation [13].

With forthcoming modifications to clinical trial regulations in Canada, [14]. and international regulatory support for risk-based sponsor-led trial monitoring, [5,6]. there is a need to re-evaluate the frequency and scope of monitoring visits and build on frameworks which guide the implementation of risk-adapted approaches. To inform these efforts, we report the findings from PROSPECT, an investigator-initiated, peer-review funded randomized trial testing the effect of the probiotic *Lactobacillus rhamnosus* GG compared to placebo in 2650 critically ill adults, which found no effect on ventilator-associated pneumonia (VAP) or other clinically important outcomes [15]. The objective of the current study was to use content analysis to categorize, quantify, and interpret the findings of on-site monitoring or auditing visits associated with this probiotics trial [16,17].

2. Methods

2.1. Trial methods

The trial methods have been previously published [15,16]. In brief, this study took place in the ICU setting in which clinical and technologic monitoring is ongoing in real-time by a highly skilled interprofessional team. Research Coordinators obtained a priori or deferred written informed consent from patients or substitute decision makers for trial enrolment. When notified about eligible patients, study pharmacists used a password-protected randomization system to allocate patients to receive either 1×10^{10} colony forming units of L. *rhamnosus* GG (i-Health, Inc.) or an identical enteral placebo twice daily for up to 60 days or until discharge from the intensive care unit (ICU). Study product was stopped if *Lactobacillus* species was isolated from a sterile site.

Prior to the main trial, 15 centers participated in a pilot trial with feasibility objectives focused on timely recruitment, maximal protocol adherence, minimal contamination, and the estimated incidence of pneumonia [16,17]. During the pilot, case report forms were developed and refined with feedback from participating centers. No monitoring or auditing was undertaken during the pilot phase. After successful completion of the pilot trial, patients were enrolled in the main phase of the trial between October 2013 and March 2019. Participating sites serially engaged over this period. All centers underwent an in-person start-up visit. Each center was provided by the Methods Center with a partially populated regulatory binder and standard operating procedures, with materials also accessible on the trial website.

Research Coordinators abstracted data from hospital charts, entering anonymized data for each patient in the electronic data capture system, iDataFax, housed on a password-protected server run on Red Hat Enterprise Linux. Bilingual Research Coordinators in participating Quebec centers also captured French source documents which were translated into English at the Methods Center to assist with outcome adjudication. Bi-weekly patient recruitment and protocol adherence were tracked per site at the Methods Center.

2.2. Monitoring and auditing methods

We used the following definitions to reflect the bidirectional interest of these visits to identify any errors and prevent future ones [18]. We defined *monitoring* visits as oversight by the study sponsor, reflected in conduct internally by the overall Project Coordinator (NZ) as the Project Lead at the Methods Center, who was trained by one of the auditors. We defined *auditing* visits as oversight by personnel independent of the trial sponsor, reflected in conduct by an individual external to the core Methods Team (AM, AW). Whether a center underwent a monitoring or auditing visit was determined based on scheduling and availability of the monitor or auditor, their proximity to each site, and site convenience. We sometimes scheduled the timing of monitoring or auditing visits for new research staff or following site initiation visits for a different trial led by the Methods Center to reduce travel-related costs. Monitoring and auditing were conducted in-person. We initiated monitoring and auditing visits in southern Ontario, then expanded across Canada. In participating Quebec centers, French documents were translated into English to assist monitors and auditors.

Methods Center staff validated all data centrally, generated queries for participating sites, and checked responses and new data in a multistep process throughout the trial before closing each chart. Built-in database range checks helped to minimize data entry errors (e.g., disallowing entry of implausible ages, laboratory values, and APACHE II scores). In addition, during each visit, the monitor or auditor reviewed all informed consent forms and validated regulatory binders against the trial regulatory binder checklist (Appendix 1). We did not select a fixed proportion of charts at each site to review, due to the staggered start-up of participating sites and the range of patients enrolled across sites. Instead, between 1 and 5 completed patient charts (depending on center experience and number of patients enrolled) were selected for source data verification, prioritizing data integral to trial outcomes, which occurred by checking case report forms against clinical source documentation. Sites were informed about which patient charts and source documents would be reviewed 2–4 weeks in advance of each visit.

At the end of each visit, the site research staff and investigators were provided real-time feedback regarding the findings (status report, implementation progress, and issues needing remediation). Findings were addressed and questions were resolved either immediately following the debriefing session, or after receipt of a structured feedback letter documenting site-specific findings generated by the monitor or auditor, distributed within 2 weeks of each visit. In addition, via periodic newsletters and research meetings throughout the trial, we informally shared common findings from site monitoring and auditing reports with other sites to help avoid similar findings, offering suggestions and solutions.

3. Analysis

We performed qualitative, deductive content analysis to categorize and quantify findings from the structured letters generated following on-site monitoring or auditing visits. Content analysis is a research

1) Good Clinical Practice Compliance
2) Research Ethics Board submissions
3) Investigator Site File
4) Curriculum Vitae & Research Training Records
5) Protocol and SOP Implementation
6) Informed Consent
7) Study Product/Pharmacy/Laboratory
8) Data Collection
9) Safety Reporting
10) Data Security

Fig. 1. Content analysis domains.

method commonly used in psychiatric, gerontological and public health studies, which aims to generate concepts or categories describing a phenomenon of interest [19]. *Deductive* content analysis refers to the operationalization of categories based on previous knowledge [19]. We use the term 'findings' to refer to the items documented by the monitor or auditor which required a site to undertake process modifications or remedial actions. We use the term 'observations' to refer to the total frequency of one finding or across several findings. At trial termination, 1 investigator (MD) reviewed 3 letters and abstracted all findings to grasp the scope of feedback contained therein. Subsequently, in duplicate (MD, NZ), each finding was categorized into only one of the 10 pre-existing GCP-based domains [Fig. 1) developed from an institutional template used to monitor other trials [3]. Thereafter, any discrepancies were collaboratively resolved with input from a third investigator (DJC).

The frequency of each finding across sites was quantified. In duplicate, each observation was interpreted as to whether they were a) missing operational records or b) errors in process (failure to follow the study protocol or standard operating procedures). Findings were identified as werepotential threats to c) data integrity and/or d) patient privacy or e) safety. We considered a threat to patient safety as a risk of harm to individual or future patients (e.g., protocol deviations related to informed consent).

To characterize participating centers and their status at the time of the monitoring or auditing visit, we abstracted the number of patients enrolled at the time of the visit. Using Methods Center files, we recorded whether the site participated in the pilot study, and time from first patient randomized (in the pilot and main trial as applicable) to first monitoring or auditing visit. Following trial initiation, 7 institutions merged, creating 3 sites for the purposes of this report. For these sites, we report site characteristics by individual center and monitoring or auditing visit findings by merged center. We descriptively summarized data using medians and interquartile range (IQR) when appropriate. Building on studies of research conduct in Canadian community hospitals [20,21]. and in consultation with investigators from both types of organizations, we identified academic hospitals and community hospitals and descriptively report site classification.

4. Results

4.1. Site characteristics

We included 41 participating Canadian sites enrolling patients in this multicenter randomized controlled trial, 15 of which participated in the pilot trial. This generated 37 monitoring or auditing reports, as some hospitals merged after the trial was launched. A median (IQR) of 21 (9–44) main trial patients were enrolled per site at the time of monitoring or auditing visits. We report additional individual site characteristics and status at time of monitoring or auditing visits in Table 1.

4.2. Content analysis

We report all domains, findings, frequencies, and summary statistics in Table 2. We documented a total of 566 observations across 19 monitoring and 18 auditing reports, representing 75 unique findings. There was a median (IQR) of 13 (10–20) observations per site and the most frequently observed findings were in 2 of 10 domains related to research training documentation ($n = 7$ findings; $n = 180$ total observations) and the informed consent process (n = 18 findings; $n = 133$ total observations).

Across all 566 observations, most were classified as missing operational records ([438/566 [77%]) rather than errors in process (128/566 [23%]). Of 75 total findings, 13 were classified as potential threats to data integrity, representing 62/566 observations (11%), 1 finding was classified as a potential threat to patient privacy, representing 1/566 observation (0.18%), and 9 findings were classified as potential threats to patient safety, representing 49/566 observations (8.7%). There were no findings in the research training documentation domain which were classified as potential threats to data integrity, patient privacy or safety; however, 2 findings in the informed consent domain ("inclusion/exclusion criteria not signed by site investigator", and "physician confirming eligibility not trained and/or not on the delegation of authority log") were classified as potential threats to both data integrity and patient safety. These 2 findings comprised 27 observations and were identified across 23 sites, 10 of which participated in the pilot study.

In Fig. 2, we summarize the total number of observations across domains and display whether they were categorized as missing operational records or errors in process. In Fig. 3, we display the proportion of total sites with one or more finding in each domain with the median (IQR) number of findings per domain across all sites.

Overall, the median (IQR) observations per site were similar between 34 academic (13.5 [9–19.8]) and 7 community centers (13 [12.5–17]).

5. Discussion

In this content analysis of reports generated from one-time on-site monitoring and auditing visits in a large multicenter randomized controlled trial, findings were concentrated in categories of training documentation and informed consent; however, centers had relatively few observations per site overall. Among the observations reported, missing documentation was more common than errors in protocol implementation or data collection, and relatively few findings posed potential threats to data integrity, privacy or patient safety.

Although a risk-adapted approach to monitoring was not explicitly applied in PROSPECT, our monitoring methods were consistent with those for an intermediate-risk trial, in which the risk of the therapeutic intervention was higher than that of standard medical care using prior classification criteria [3]. This classification proposes a pre-study visit, a study initiation visit, and the frequency of monitoring visits dependent on the site's recruitment and catalogue of monitoring tasks [3]. For each of these academic and community centers, we conducted a study initiation visit and one on-site monitoring or auditing visit over the course of the trial, between October 2013 and March 2019. With existing international recommendations to use a risk-based approach to monitoring, and forthcoming guidance from Health Canada on 'modernization' of trial regulation, [14]. results from this content analysis may inform the development of monitoring plans, start-up visits, staff training, readiness for regulatory monitoring or auditing visits, and ongoing study management in similar future intermediate-risk trials.

Our findings may also be informative for regulatory authorities overseeing randomized trials. The high frequency of protocol deviations related to informed consent forms in PROSPECT is consistent with results of other trials which evaluated findings from monitoring visits [4,11,12,22,23]. Similar to our study, reported informed consent

Table 1
Center Participation in Monitoring and Auditing Visits.

Site	Academic (n=34) or community center (n=7)	Total months of enrollment during trial (n)	Auditing (A) or monitoring (M) visit	Time from first pilot patient to visit (days)	Time from first main trial patient to visit (days)	Total pilot patients enrolled at time of visit (n)	Total main trial patients enrolled at time of visit (n)	Findings classified as missing (n)	Findings classified as errors (n)	Total findings (n)
	Median (Q1–Q3):	24 (17–35)	N/A	1405 (1068–1476)	411 (250–652)	16 (6–31)	21(9–44)	11(8–15)	3(1–5)	13 (10–20)
1	Academic	9	M	N/A	212	N/A	8	10	1	11
2	Community	9	A	N/A	96	N/A	11	14	6	20
3	Community	10	M	N/A	272	N/A	37	10	4	14
4	Community	13	M	N/A	174	N/A	2	9	1	10
5	Academic	15	M	N/A	197	N/A	9	9	1	10
6	Academic	15	M	1068	388	5	28	4	1	5
7	Academic	17		885	536	3	56			
8	Academic	16	M	1935	1126	28	21	8	2	10
9	Academic	18	A	N/A	155	N/A	9	11	1	12
10	Academic	20	M	N/A	407	N/A	12	6	1	7
11	Academic	20	M	N/A	596	N/A	27	4	2	6
12	Academic	20	M	N/A	364	N/A	5	9	0	9
13	Academic	21	M	N/A	637	N/A	13	1	2	3
14	Academic	21	M	N/A	890	N/A	36	14	3	17
15	Community	22	A	N/A	7	N/A	1	10	3	13
16	Academic	23		N/A	861	N/A	62			
17	Academic	17	A	N/A	645	N/A	9	25	12	37
18	Academic	17		N/A	173	N/A	14			
19	Academic	24	A	N/A	252	N/A	17	15	4	19
20	Community	24	A	N/A	331	N/A	41	27	9	36
21	Community	28	M	N/A	161	N/A	11	8	2	10
22	Academic	30	A	N/A	294	N/A	5	7	0	7
23	Academic	30	A	N/A	414	N/A	90	23	10	33
24	Academic	32	A	1405	539	31	34	13	8	21
25	Academic	32	A	N/A	690	N/A	89	20	4	24
26	Academic	32	M	N/A	244	N/A	7	11	3	14
27	Academic	32	M	N/A	258	N/A	20	11	6	17
28	Community	33	A	N/A	440	N/A	41	12	1	13
29	Academic	35	M	N/A	344	N/A	40	10	3	13
30	Academic	35	A	1499	979	37	97	21	8	29
31	Academic	35	M	1722	958	12	22	6	0	6
32	Academic	35	M	N/A	995	N/A	11	6	3	9
33	Academic	13		N/A	306	N/A	3			
34	Academic	37	M	580	123	6	3	8	2	10
35	Academic	38	A	N/A	673	N/A	44	19	1	20
36	Academic	39	A	1469	741	16	55	16	4	20
37	Academic	39	A	1475	74	31	72	16	5	21
38	Academic	40	M	1187	433	16	9	6	1	7
39	Academic	41	A	1476	735	28	55	15	3	18
40	Academic	44	A	1049	576	3	46	12	6	18
41	Academic	45	A	1261	618	56	63	12	5	17

In this table we present participating centers with a row for each of 41 centers, indicating academic or community center, pilot study participation, total months of enrollment, whether there was a monitoring/auditing visit, time from first pilot and/or main trial patient randomization to visit, number of pilot and/or main trial patients enrolled at time of visit, number of findings classified as missing operational records, number of findings classified as errors in process (failure to follow the study protocol or standard operating procedures), and total number of findings. We report medians, interquartile ranges where appropriate. N/A = not applicable.

violations in the literature include signature or date errors on the form (e.g., improperly signed, not dated or signed by site investigator), amendment issues (e.g., wrong version, failure to reobtain consent following amendments), timing (e.g., form completed after randomization or study data collection) or patient meeting exclusion criteria [4,11,12,22,23]. Although previous studies have demonstrated that risk-based approaches may be sufficient to detect informed consent-related protocol violations when compared with more intensive monitoring, [12]. proactive strategies to reduce informed consent violations may be more fruitful.

Common findings in this trial related to training documentation and missing records highlight the challenges of conducting multiple trials in a single academic or community center with diverse approaches to monitoring or auditing. These approaches are influenced by factors such as whether the trial is investigator-initiated versus industry-initiated, the funding source, sponsor preferences, and perceived risk of the intervention being evaluated. Taking a single-center multi-study view, local guidance and institutional norms could be at variance with expectations from various sponsors or contract research organizations. However, allowing adherence to local guidance during monitoring or auditing may increase efficiencies. Possible enhancements to streamline the monitoring or auditing process include a priori statements embedded in trial protocols acknowledging the role of pre-established local guidance (e.g., declaring that centers will follow their institutionally approved processes for telephone consent). Local SOPs could be submitted in advance to sponsoring organizations for their approval, before a trial starts (e.g., admissible methods to documenting the informed consent process, signing trial-specific physician orders, updating and retaining investigator CVs). This way, institutional guidance documents could be usable across multiple ongoing and future trials. A different tactic would be initiatives to harmonize approaches rather than allow a patchwork of differing local approaches. Perhaps within disciplines at least, a national or provincial SOP could outline key elements of relevance to all trials, which may standardize and simplify the process and increase adherence.

Although monitoring and auditing are typically not conducted for pilot studies whereby objectives are focused on proof of concept or feasibility, intentional incorporation of monitoring or auditing during pilot

Table 2
PROSPECT auditing and monitoring content analysis results.

Domain	Findings	Potential Threat to Data Integrity (Y/N)	Potential Patient Harm (or Privacy Safety) (Y/N)	Frequency of Findings			Median (IQR) Findings Per Site
				Missing Operational Records (n)	Error in Process (n)	Total Observation	
1) Good Clinical Practice Compliance	Corrections to source documents obstructing original entry	N	N	0	9	9	0(0–0)
	Patient enrolled prior to fully executed contract	N	N	0	2	2	
	Physician orders not signed and/or dated	N	N	1	0	1	
	Physician not listed on pharmacy orders	N	N	0	1	1	
	Screening log not updated	N	N	1	0	1	
			Total:	**2**	**12**	**14**	
2) Research Ethics Board submissions	Data Monitoring Committee/Data Safety Monitoring Board report not submitted to site REB	N	Y- safety	3	0	3	0(0–0)
			Total:	**3**	**0**	**3**	
3) Investigator Site File	Documentation of staff research protocol training required	N	N	30	4	34	3(2–4)
	Health records storage documentation required	N	N	23	0	23	
	Delegation of Authority Log Staff not updated	N	N	17	0	17	
	Documentation of REB approvals/ submission package /contract / membership / renewals / letters required	N	N	10	1	11	
	Delegation of Authority Log Functions addition or removal Required	N	N	6	3	9	
	Note To File event explanation required	N	N	6	0	6	
	Principal Investigator signature and date on SOP required	N	N	6	0	6	
	Hospital accreditation certificate not documented	N	N	3	0	3	
	Data Safety Monitoring Board Report not documented	N	Y- safety	2	0	2	
	General data management queries not filed in the regulatory binder	N	N	2	0	2	
	Signature required on the Qualified Investigator Undertaking	N	N	1	0	1	
	Signature required on protocol signature page	N	N	1	0	1	
	Patient correspondence not filed in patient specific research Chart	N	N	1	0	1	
	Copy of agreement between site and sponsor required in Binder	N	N	1	0	1	
			Total:	**109**	**8**	**117**	
4) Curriculum Vitae & Research Training Records	GCP training not filed	N	N	30	0	30	5(4–6)
	Health Canada Division 5 training not filed	N	N	32	0	32	
	TCPS 2 training not filed	N	N	30	0	30	
	Privacy Tutorial training not filed	N	N	19	0	19	
	Curriculum Vitae not filed	N	N	31	13	44	
	License, licencing authority registration not filed	N	N	23	0	23	
	Local research training not filed	N	N	2	0	2	
			Total:	**167**	**13**	**180**	
5) Protocol and SOP Implementation	Internal SOPs required for patients discharged from hospital under waived consent without eventual written consent	N	N	2	0	2	0(0–0)
	Site specific SOP required regarding the conduct of clinical research	N	N	1	0	1	
			Total:	**3**	**0**	**3**	
6) Informed Consent	Signature (with date/time) required following patient regaining capacity to consent	N	N	6	21	27	3(1–6)
	Inclusion/exclusion criteria form not signed/dated/time by site investigator	Y	Y-safety	20	5	25	
	Signature (with date/time) required to confirm follow-up for telephone consent (or waived)	N	N	9	5	14	
	Research note from Principal Investigator in Research chart / clinical chart	N	N	11	0	11	
	Patient/SDM signature required on bottom of every page of ICF	N	N	8	2	10	
	Incomplete ICF (missing entire form, missing pages/ boxes / time of consent / not witnessed)	N	N	7	1	8	
	Telephone consent not witnessed	N	N	8	0	8	
	Documentation required when patient does not regain capacity to consent	N	N	5	1	6	
	Documentation required of attempts to contact SDM/Patient for written consent	N	N	4	0	4	
	Incorrect version date of ICF	N	N	0	4	4	

(continued on next page)

Table 2 (*continued*)

Domain	Findings	Potential Threat to Data Integrity (Y/N)	Potential Patient Harm (or Privacy Safety) (Y/N)	Frequency of Findings			Median (IQR) Findings Per Site
				Missing Operational Records (n)	Error in Process (n)	Total Observation	
	ICF not filled out in participants / SDM's own handwriting (printing name, dating, timing)	N	N	0	3	3	
	Original signed ICF not kept in research chart and/or no copy given to participant	N	N	0	3	3	
	Telephone consent script required	N	N	2	0	2	
	Physicians confirming eligibility not trained and/or not on the Delegation of Authority Log	Y	Y- safety	1	1	2	
	Research Coordinator signature required	N	N	2	0	2	
	Principal Investigator sign/date/time consent form (use 24-hour time) required	N	N	0	2	2	
	Principal Investigator signature pre-dated the time of consent	N	N	0	1	1	
	ICF not de-identified	N	N	0	1	1	
			Total:	**83**	**50**	**133**	
7) Study Product/ Pharmacy/ Laboratory	Temperature logs / calibration certificates / maintenance records required	N	N	11	2	13	2(1–4)
	Documentation of pharmacy staff training required	N	N	13	0	13	
	Pharmacy study drug label update required	Y	Y- safety	0	12	12	
	Laboratory license and accreditation expired	N	N	11	0	11	
	Documents required in pharmacy regulatory binder	N	N	10	0	10	
	Note to File event explanation required	N	N	8	0	8	
	Update to Laboratory reference intervals / normal ranges required	N	N	6	0	6	
	Pharmacy order amendment required	N	N	1	5	6	
	Quality assurance capsule added to accountability record arms / quality assurance log	N	N	0	4	4	
	Documentation of returned unused capsules required	Y	N	0	4	4	
	Dispensing records and master drug inventory logs corrections required	Y	N	0	2	2	
	Refrigeration of dispensed study product required	Y	N	0	2	2	
	Study shipment temperature recording device	Y	N	2	0	2	
	Empty study drug blister packs not returned to study coordinator	N	N	1	1	2	
	Thermometer replacement required	N	N	2	0	2	
	Additional study product not ordered	N	N	1	0	1	
	Study product not checked by two pharmacy technicians	N	N	0	1	1	
	Study product on ward post-ICU discharge	N	N	0	1	1	
	Additional research pharmacy staff to assist with PROSPECT trial	N	N	1	0	1	
	Study card not unaccounted for	N	N	1	0	1	
			Total:	**68**	**34**	**102**	
8) Data Collection	APACHE calculation error	Y	N	0	5	5	0(0–0)
	Incorrect enrollment sequence of events (i.e., ICU admit / intubation / screening / enrollment randomization dates and times)	Y	N	0	3	3	
	Patient meets exclusion criteria	Y	Y-safety	0	1	1	
	Culture reporting not fully completed	Y	Y-safety	1	0	1	
			Total:	**1**	**9**	**10**	
9) Safety Reporting	Note of lactobacillus isolate in patient's chart not formally documented	Y	Y-safety	2	0	2	0(0–0)
	Reminders of hand hygiene and wearing gloves when preparing and administering study product required	Y	Y-safety	0	1	1	
			Total:	**2**	**1**	**3**	
10) Data Security	Study documents not stored behind two locks	N	Y-privacy	0	1	1	0(0–0)
			Total:	**0**	**1**	**1**	
			Total # observations:	**438(77%)**	**128 (23%)**	**566**	

In this table we present each of the 10 domains, and all findings within each domain from 19 monitoring and 18 auditing reports. We categorized findings as errors or missing, and report whether findings posed a risk to patient safety or privacy, or a threat to data integrity. IQR = interquartile range; REB = research ethics board; SOP = standard operating procedure; GCP = good clinical practice; TCPS = Tri-Council Policy Statement; ICF = informed consent form; SDM = substitute decision maker; ICU = intensive care unit; APACHE II = Acute Physiologic Assessment & Chronic Health Evaluation II.

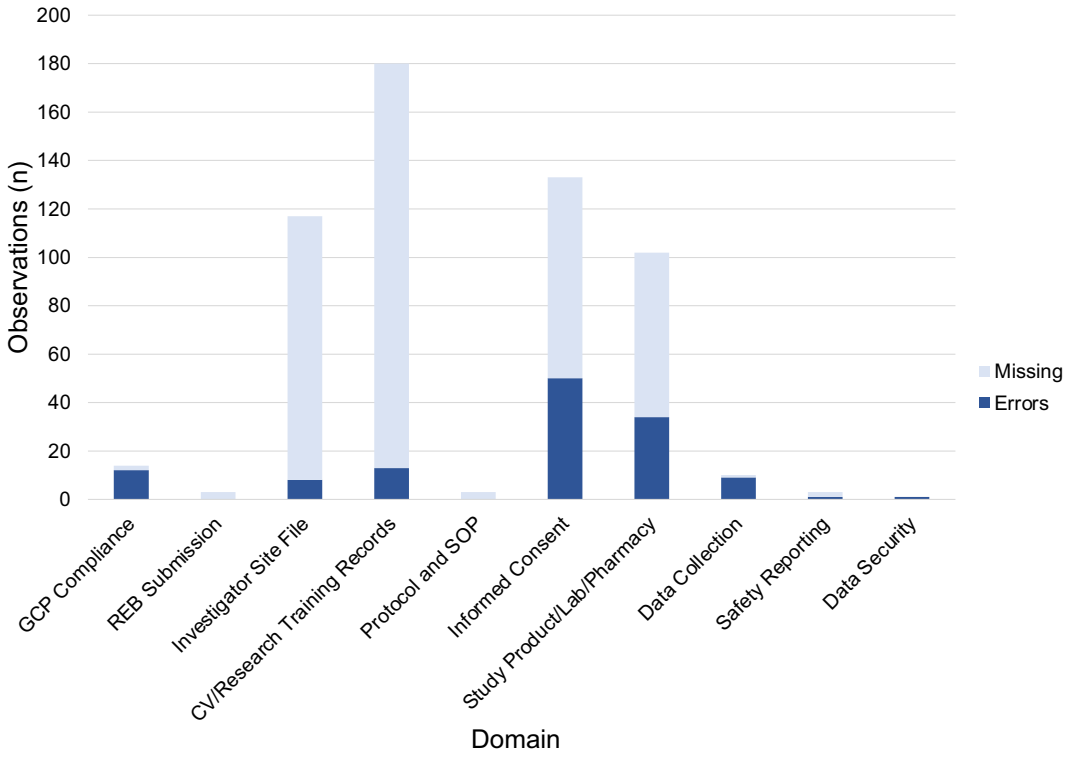

Fig. 2. Total number of observations by domain; observations categorized as missing or error.

trial phases may proactively identify processes to enhance the conduct of larger future trials. The pilot trial preceding PROSPECT was not monitored or audited, but did involve several strategies to optimize protocol implementation [17]. An emphasis on pre-emptive review of processes to optimize research methods may shift the focus from correcting errors that have already occurred toward enhancing future implementation. As suggested in a commentary, site monitoring should perhaps instead be referred to as 'site mentoring', whereby on-site visits can be used as an opportunity for training, supporting study staff, ensuring sites have adequate access to resources, and checking adherence to study protocol [24]. Although risk-adapted monitoring is an effective way to monitor clinical trials while efficiently using resources, based on individual trial characteristics, less intensive on-site monitoring requires more extensive preparation in terms of appropriate risk-assessment, site education, built-in quality assurance checks, and optimized central monitoring.

Developing a risk-adapted monitoring plan and making sites aware of such plans in advance may streamline monitoring and auditing processes while a trial is in progress. Indeed, if the scope and yield of monitoring is planned and documented in protocols following broad community consultation, this could ensure feasibility, affordability, and face validity of the process to all stakeholders, judging whether the monitoring proposal fits with the risk. Whether auditors (considered more external to a trial than monitors per our definition), are more suitable for this exercise is uncertain; ensuring the costs of monitoring and auditing are admissible by granting agencies would help to enable independent individuals to engage in this activity. Remote monitoring which emerged during the COVID-19 pandemic out of necessity, may remain more common as the pandemic abates. It has the additional advantage of minimizing the carbon footprint of research, including the costs of travel. Developing tools and optimal methods to facilitate remote yet rigorous approaches for off-site monitoring or auditing is a priority for current and future trials.

One approach to reduce administrative burden could involve each research group creating an e-binder for investigator CVs, required regulatory training and licenses for review, maintained on a rolling basis with downloadable content as needed. Such approaches may liberate time to focus on other aspects of the research process crucial to trial integrity, which could be particularly helpful for smaller institutions and departments with less research staff. Additional strategies at the institutional level include centralized common document repository for laboratory licenses, normal and reference ranges, accreditation certificates and the like, which can be accessed by investigators, research personnel, monitors and auditors at that institution.

While we did not plan to conduct a formal cost-benefit analysis when developing methods for this study, we used invoices and administrative records to generate cost estimates for these visits. We added the travel costs, preparatory time for all stakeholders, and on-site time of the monitor or auditor and research personnel at each site. The estimated total monitoring or auditing personnel costs were $21,739.78 and travel costs were $30,752.96, for a total cost of $52,492.74, or on average, $1418.73/site. These costs may be lower than other similar exercises due to economies of scale outlined in the methods section. Budgeting for trial monitoring and auditing requires consideration of trial factors (e.g., baseline risk of the population, inherent risk of the intervention, risk of protocol deviation, sample size, regulatory requirements), participating site factors (e.g., number of sites, research experience, site proximity, estimated new site participation) and other issues.

5.1. Strengths and limitations

The monitoring and auditing visits occurred over 4 years for this investigator-initiated peer-review trial by an established research consortium. Our approach to trial integrity was also complemented by many pre-trial discussions, site visits, staff training, a pilot trial in 15 centers, comprehensive data validation at the Methods Center, ongoing communication strategies, and central statistical monitoring to periodically review the entire dataset. We categorized and interpreted findings in duplicate according to their relevance as directly important to data integrity, patient privacy or safety, or neither, showing the most

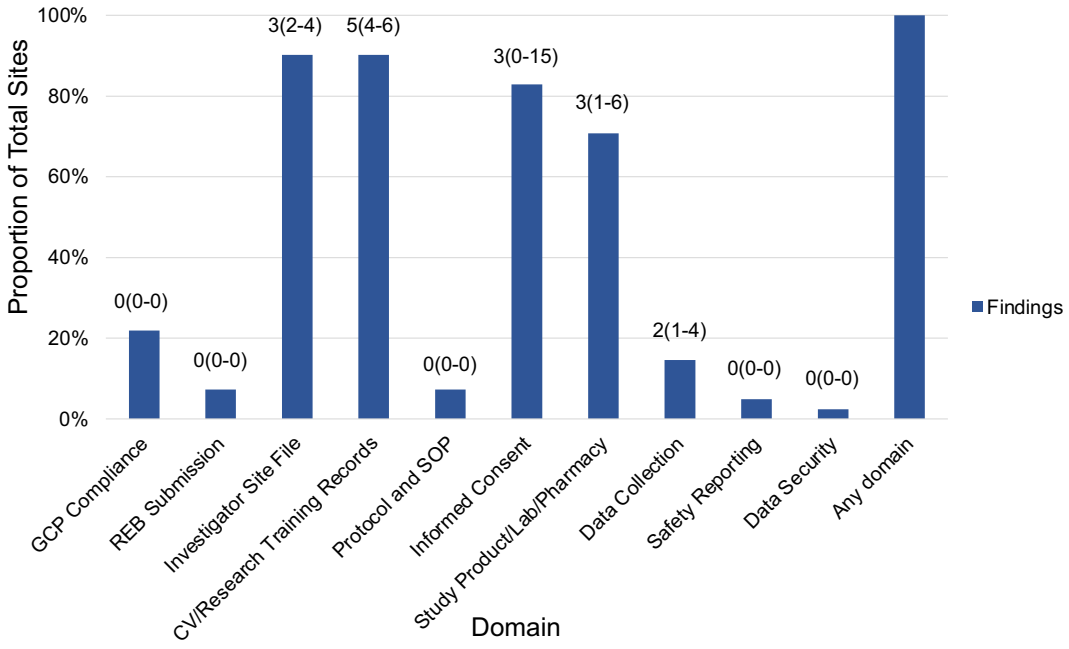

Fig. 3. Proportion of sites with one or more findings in each domain, median (interquartile range) number of site findings per domain reported above each bar.

common problems within each domain, but also the nature and implications of each problem. Our findings are of relevance to investigators, sponsors, Research Coordinators, regulatory agencies, and ethics boards, highlighting the need for improved organization, coordination, and efficiencies. Our content analysis included participating Canadian academic and community hospitals in 6 provinces.

Our analysis is limited in that we did not examine the association between the frequency of observations, or category of findings, and the participation in the pilot trial, number of patients enrolled, or whether the findings were identified during a monitoring or an auditing visit. In this study, and according to others reporting on this issue, [25]. missing training documentation may not necessarily reflect training that was not undertaken, but rather non-documentation of training that was undertaken. None of the observations in this study were directly associated with a pre-defined or unexpected trial-related adverse event based on chart review or case report forms received; however, this was not formally adjudicated. We did not evaluate the monitoring or auditing process on trial performance metrics longitudinally; however, a systematic review of 6 studies reporting on-site monitoring results suggested a positive relationship with recruitment rates and protocol adherence [26]. International centers in PROSPECT were not included in this report. Some of the observations we classified as a threat to patient safety were specifically related to probiotics, and may not apply to other studies (especially industry-initiated), or to hospital wards or other research settings. Findings may be different if conducted by a regulatory authority.

6. Conclusions

For centers participating in a multicenter randomized probiotics trial, findings during monitoring and auditing visits almost exclusively concerned research documentation procedures rather than research practices directly, and posed minimal potential threats to data integrity, patient privacy or safety. With existing international recommendations to use a risk-based approach to monitoring, and given forthcoming guidance from Health Canada, results from this study may inform start-up visits, staff training, and regulatory monitoring or auditing visits in the future.

Funding

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Access to data and data analysis

D Cook and N Zytaruk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding/support

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Role of the funder/sponsor

The funders and sponsors had no role in the design and conduct of the study, including data collection, management, oversight, analysis or interpretation, preparation, review or approval of the manuscript, or decision to submit the manuscript for publication.

Declaration of Competing Interest

Dr. F D'Aragon is a recipient of a Research Career Award from the Fonds de la recherche du Québec-Santé. Dr. S English holds a National New Investigator award from the Heart and Stroke Foundation. Dr. D Cook holds a Canada Research Chair in Knowledge Translation in Critical Care.

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Appendix 1. PROSPECT regulatory binder index completion checklist

SECTION	DOCUMENT	✓ When Filed
1. **Study Protocol**	• Site Investigator Signature page of Protocol	
	• Amendment (when applicable)	
	• Site Investigator Signature page of Protocol Amendments (when applicable)	
2. **Product Information**	• Update (when applicable)	
3. **REB# [Insert REB #]**	• List of REB Membership	
Application/Approval	• REB application and approval letter(s)	
Amendments	• Approval of amendments to the research documents (when applicable)	
Annual Renewal	• Annual Renewal Application and approval letter(s)	
	• Notification to REB of serious adverse events and other safety information (DMC) (when applicable)	
	• Health Canada approval letter(s) and No Objection Letters	
	• Clinical Trial Site Information (CTSI) Form and documentation that CTSI Form sent to Health Canada prior enrolment	
	• Qualified Investigator Undertaking (QIU) (for file only not to be sent to Health Canada)	
	• REB notification of study closure (when applicable)	
4. **Informed Consent Forms**	• Approved Informed Consent Form(s) and all other revised Informed Consent Forms	
5. **Serious Adverse Events (SAE), Serious Adverse Drug Reaction (SADR) and other Safety Information**	• SAE, SADR and other safety information	
	• Instructions (if not included in the protocol) and all correspondence related to SAEs and SADRs	
	• DMC Interim Analyses Reports (when applicable)	
6. **Clinical Trial Material Documentation and Pharmacy Material**	• Shipment and return documents.	
	• Dispensing/accountability records	
Shipment/dispensing	• Refrigerator temperature logs or documentation confirming available for download or printout (Pharmacy and ICU)	
	• Instructions for handling trial related material (if not included in the protocol)	
	• Correspondence with pharmacy *if applicable	
	• PROSPECT dispensing, delivery and administration accountability log	
7. **Laboratory Documentation**	• Local laboratory certification/accreditation and laboratory reference ranges (relevant labs only)	
8. **Meetings/Training**	• Meeting agenda(s)	
	• Training log(s)	
	• Conference Call Agendas	
	• In-service material (abstract handout)	
	• Study updates	
9. **SOPs**	• SOPs applicable to the study	
	• Local approved Informed Consent SOP(s) * templates provided	
	• Local Health Records Retention SOP	
10. **Case Report Forms, Data Collection and Data Entry**	• Case Report Forms and any previous amended versions	
	• iDatafax Manual for secure web-based entry	
	• PROSPECT Website Login Information	
	• Database drop-down lists: Antimicrobials, Organisms & Coenrolment	
11. **Screening Log(s) Enrolment Log(s)**	• Completed screening log(s) and enrolment log(s) must be stored in the file at study completion	
12. **Delegation of Authority**	• Signed Delegation of Authority Form	
13. **Curriculum Vitae and Clinical Trial Agreement(s)**	• Signed/dated curriculum vitae	
	• Professional practice license for the investigator, co-investigator, study coordinator and other research staff (as applicable)	
	• ICH, GCP and Division 5 Training Certificate (update required every 2 years)	
	• Signed clinical trial agreement	
	• ***Copy of the budget/invoices and payments received should be kept in a separate binder***	
14. **General Correspondence**	• Monitoring visits (if applicable)	
	• Study termination notification from the methods centre (if applicable)	
	• Data management correspondence	
15. **Other Optional Study Aids (provided by Methods Centre)**	• Physician order template (if applicable)	
	• Clinical Note for PROSPECT Patient Chart	
	• PROSPECT Bristol 7 day/weekend Stool Classification Worksheet	
	• Daily Data Collection Worksheet	

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