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Economic Evaluation alongside the Probiotics to Prevent of Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol

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Abstract

Introduction

Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection in the intensive care unit (ICU). Probiotics are defined as live microorganisms that may confer health benefits when ingested. Prior randomized trials suggest that probiotics may prevent infections such as VAP and *Clostridioides difficile*-associated diarrhea (CDAD). PROSPECT (Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial) is a multicenter, double-blinded, randomized controlled trial comparing the efficacy of the probiotic *Lactobacillus rhamnosus* GG with usual care versus usual care without probiotics in preventing VAP and other clinically important outcomes in critically ill patients admitted to the ICU.

Methods and Analysis

The objective of E-PROSPECT is to determine the incremental cost-effectiveness of probiotics with usual care versus usual care without probiotics in critically ill patients. E-PROSPECT will be performed from the public healthcare payer's perspective over a time horizon from ICU admission to hospital discharge.

We will determine probabilities of in-ICU and in-hospital events from all patients alongside PROSPECT. We will retrieve unit costs for each resource use item using jurisdiction-specific public databases, supplemented by individual site unit costs if such databases are unavailable. Direct costs will include medications, personnel costs, radiology/laboratory testing, operative/non-operative procedures and per-day hospital 'hoteling' costs not otherwise encompassed. The primary outcome is the incremental cost per VAP prevented between groups. Other clinical events such as CDAD, antibiotic-associated diarrhea (AAD), and in-hospital mortality will be included as secondary outcomes. We will perform pre-specified subgroup analyses (medical/surgical/trauma; age; frailty status; antibiotic use; prevalent vs. no prevalent pneumonia) and probabilistic sensitivity analyses, then generate confidence intervals using non-parametric bootstrapping.

Ethics and Dissemination

Study approval was granted by the Hamilton Integrated Research Ethics Board (HIREB) of McMaster University on July 29, 2019. Informed consent was obtained from the patient/substitute decision maker. Findings of this study will be published in peer-reviewed journals.

Article Summary

Article focus

- Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection in the intensive care unit, with high clinical and economic burden to health systems.
- This protocol manuscript outlines the methods for investigating and reporting the cost-effectiveness of the probiotic *Lactobacillus rhamnosus* GG with usual care versus usual care without probiotics for prevention of healthcare-associated infections.

Key messages

- This protocol for an economic evaluation alongside a randomized control trial, provide decision-makers and stake-holders in health policy with information about the cost-effectiveness of an intervention.

Strengths and limitations of this study:

- The strengths of this protocol paper ensure the methods used in the economic evaluation: are transparent; reduce hypothesis-driven bias with an pre-specified *a priori* protocol; utilize trial randomization, reducing bias and confounding according to different baseline characteristics between study groups; collect clinical and economic data concurrently and prospectively, to reduce of data collection and minimize the possible problem of missing data if attempting to collect retrospectively; collection of data from multiple jurisdictions, to allow for capture of variability and enhance the generalizability of our results.

- The limitations of this protocol paper are: a relatively short, non-fixed time-horizon; a primary outcome of incremental cost to avoid a clinical event (cost-effectiveness approach), rather than a cost-utility approach (incremental cost per quality-adjusted life year); as with all efficacy trials, the generalizability and external validity of a health economic evaluation concurrently performed with a randomized control trial may not represent the same treatment effects and costs as in routine clinical practice.

Background

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in the intensive care unit (ICU), resulting in a high burden of illness.[1,2] A 2005 systematic review found a pooled cumulative VAP incidence of 23% (95% confidence interval (CI): 19%–27%) in randomized controlled trials (RCTs) and 10% (95% CI: 7–13%) in observational studies.[2] In addition, VAP is associated with a two-fold attributable risk of dying in the ICU (odds ratio (OR) 2.02, 95% CI: 1.2–3.6), and the cost attributed to VAP ranges from US $10,000 to $13,000 per patient.[2] Thus, VAP prevention is a patient-important safety goal during critical illness.[1,3,4]

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a potential health benefit on the host."[5,6] They are reported to enhance gut barrier function, reduce host pathogenic bacterial load, modify gut microbiota, and modulate the immune system.[7–10] Probiotics studies suggest benefits including reduced incidence of healthcare-associated infections.[11–14] A recent meta-analysis of RCTs suggests that probiotics administered to critically ill mechanically ventilated patients were associated with a 26% lower VAP rate (95% CI: 10–39%) and 20% lower infection rates overall (95% CI: 5–32%).[15] However, these findings arose from 30 small, mostly low quality single-center RCTs (n=18–300, 2972 total patients in the meta-analysis), yielding imprecise estimates and results with uncertain internal and external validity.[15]

Further, probiotics may reduce the incidence of diarrhea, specifically *Clostridioides difficile*-associated diarrhea (CDAD), which can cause serious complications such as pseudomembranous colitis, toxic megacolon, and death.[16] In a recent Cochrane systematic review and meta-analysis of 31 RCTs including 8672 patients who were receiving antibiotics and concurrent probiotics, moderate certainty evidence suggested that probiotics were effective at reducing the burden of CDAD for patients and the healthcare system.[16]

We recently performed a systematic review of economic evaluations examining probiotics in hospitalized patients, evaluating their cost-effectiveness for reducing VAP, CDAD and antibiotic-associated diarrhea (AAD), while also identifying variables that could drive costs.[17] From 721 potentially relevant studies, 7 met the eligibility criteria. Probiotics appear to be either cost-effective or cost-saving in 6 of 7 studies compared to other prophylactic strategies within usual care to prevent healthcare-associated infection in acutely ill hospitalized patients. However, Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluations indicated a high risk of bias and very low quality/certainty of clinical evidence, such that cost-effectiveness evidence on the use of probiotics in adult hospitalized patients was weak. Furthermore, probiotic manufacturers funded 3 of 7 (43%) studies, all of which were reported as either cost-effective or cost-saving.[17] Some probiotic economic evaluations were designed after the results of the trial were published.

Therefore, we have designed this economic evaluation (E-PROSPECT) alongside the multicenter PROSPECT (ClinicalTrials.gov number: NCT01782755), assessing the incremental cost effectiveness ratio (ICER) of probiotics versus usual care for critically ill adult patients.[18–20]

METHODS

Overview of PROSPECT

PROSPECT is a randomized, double-blinded multicenter controlled trial. It used a central system for concealed 1:1 ratio to randomize patients (in variable unspecified block sizes, stratified by center and by medical, surgical or trauma admission status) to either 1×10^{10} colony forming units (CFU) of *L. rhamnosus* GG (iHealth, Inc.) or an identical placebo suspended in tap water administered twice daily via feeding tube in the ICU.[20] PROSPECT has enrolled 2653 critically ill patients between October 2013 and March 2019 throughout 44 ICUs (41 in Canada, 2 in the United States and 1 in Saudi Arabia). Patients, healthcare providers, investigators and research personnel were all blinded to group allocation. Sample size calculation has been previously described.[18–20]

E-PROSPECT design

The primary objective of E-PROSPECT is to estimate the incremental cost per VAP prevented arising from a prevention strategy of using probiotics with usual care (the probiotics arm) versus usual care without probiotics (the usual care arm) during hospitalization. Our secondary analyses of ICERs include healthcare-associated complications (CDAD, AAD) and mortality.[18–20]

Our economic evaluation will be performed from the public healthcare payer's perspective,[21] over the time horizon of the ICU admission to hospital discharge or death (Table 1). Our economic evaluation protocol was developed (Table 1) according to established CHEERS (Consolidated Health Economic Evaluation Reporting Standards) and international cost-effectiveness analysis (CEA) guidelines.[22,23]

Clinical outcomes

Clinical outcomes that will be examined in E-PROSPECT are described with definitions in Supplemental Table 1 that were previously described from PROSPECT [20]. Clinical events such as VAP (primary outcome), CDAD, AAD and hospital mortality (secondary outcomes) will be gleaned from PROSPECT.

Health care resource utilization

Based on our systematic literature review[17] and published evidence[18–20], we identified a list of relevant health care resource items that includes medications, physician/personnel utilization, diagnostic radiology/laboratory testing, and operative/non-operative procedures and per-day hospital 'hoteling' costs not otherwise encompassed. Antimicrobial use in ICU will be defined as days of therapy (DOT), defined daily dose (DDD) of therapy and antimicrobial-free days (AFDs).[24,25] Only systemic antimicrobials will be captured whether prophylactic or therapeutic in intent. Topical creams, eye/ear drops and inhaled antimicrobials will be excluded. We will also document the duration of mechanical ventilation, ICU and hospital length of stay and mortality. The health care resource uses will be collected alongside PROSPECT. For missing resource use data, we will choose appropriate imputation methods according to the type and distribution of the missing data. [26,27].

Unit costs

Unit costs for health care resource items will be identified through jurisdiction-specific (regions/provinces/states which manage health care delivery in their area) public databases (e.g. pharmacy drug formularies, physician billing schedule of benefits, Medicare/Medicaid reimbursement manuals, labour department wages/salaries, manufacturer costs). When there is a small sample or distribution of unit costs (i.e. a provincial jurisdiction may have the same cost for a particular procedure), we will estimate the standard error if possible, or incorporate a ±25% error around the mean unit cost distribution.

For unit costs not represented in public databases, we will obtain site-specific unit costs from the participating PROSPECT sites. We will first conduct a pilot study of unit cost acquisition at a convenience sample of 8 participating centers (Canadian: British Columbia, Alberta, Manitoba, Ontario, Québec, Nova Scotia; US: Minnesota, Missouri; and Saudi Arabia) to request a list of unit costs (Supplemental Table 2). The site investigator or research coordinator will then contact the most appropriate individual in each hospital's accounting, human resources, pharmacy, radiology or laboratory departments to obtain the unit costs. [28] In all cases, costs will be requested (if available). If only charges are known, then we will attempt to convert to costs by the institution's cost-to-charge estimate for that item, where it exists [28].

Direct costs will be presented in the pre-specified cost categories (Supplemental Table 2). Assumptions regarding resource utilization are presented in Supplemental Table 3. We will assess direct unit costs for study product-related resources associated with outcomes of VAP, CDAD, AAD and mortality. If a specific line-item unit cost is not attainable for a specific jurisdiction,[28] we will: 1) ask another site within the same jurisdiction for missing unit costs; 2) derive a cost-ratio from acquired line-items (i.e. drug costs both known in 2 jurisdictions), then using the cost-ratio impute the missing line-item unit costs for the missing jurisdiction (by multiplying the cost-ratio against a known jurisdiction's acquired line-item to impute the line-item unit cost for the missing jurisdiction).

The pilot phase may inform amendments to our protocol. For example, if a unit cost for a particular line-item is deemed to be small and/or has a low clinical incidence rate, then that line-item may be removed from the final analysis. Items without a difference in clinical outcome/resource utilization between intervention and control groups but which contribute substantially to costs may still be retained (even if little to no incremental difference in costs would exist between the two arms) in order to maintain face validity and accurately reflect the magnitude of costs for hospitalization of a critically ill patient. Once the list of line-items has been pared down to those which are deemed to be cost drivers, and clinically relevant while also feasible to obtain, the remaining line-item list will be surveyed across a sampling of individual sites from each representative jurisdiction from PROSPECT.

Unit cost data will be summarized among all sites, and by country, to explore variability across centers and countries and to improve the generalizability of results. Visible outliers will be reconfirmed with individual hospital contacts. Participating sites will be queried to determine if particular costs have changed substantially (for example, by more than 25%), beyond inflationary or deflationary changes, over the course of the study. If there are substantial changes that have occurred over time, we will use the mean unit costs adjusted for inflation over the mean duration of the trial.[28]

Cost analysis

The cost for each resource use item will be calculated by multiplying the natural resource utilization units by the unit cost. The total cost per patient will be the sum of the cost of items utilized from the time of randomization until discharge from hospital or death. All costs will be converted to 2019 United States dollars, accounting for annual inflation. [29–33]

We plan on using international currency conversion, instead of purchase power parity (PPP)-based conversions, because health-specific PPPs are not available for all participating countries, and non-health PPP conversion rates vary substantially over the period of the analysis.[30] Country-specific costs will be considered only in sensitivity analyses.

Incremental costs will be calculated using the difference in mean per patient cost between the two treatment arms. We have developed a costing operations manual outlining this process (Supplemental Appendix 1: E-PROSPECT costing manual). [30]

Base-Case Cost Effectiveness Analyses

Means (standard deviations) or frequency (percentage) will be used to describe effect and cost estimates wherever appropriate. Chi-square tests and two-sample t-test comparisons will be used as appropriate to compare baseline characteristics between the two arms. The primary outcome will be based on the intention-to-treat principle and will form the clinical event estimates for the economic evaluation.

The base case incremental cost-effectiveness ratio (ICER) is the ratio of incremental costs per VAP prevented of probiotics versus usual care during the period of hospitalization (from ICU admission to hospital discharge or death). In secondary analysis we will also calculate ICER using other clinical outcomes (i.e., CDAD, AAD, mortality). If there is dominance in cost effectiveness (i.e. one treatment is better at lower cost than the other treatment), we will present the difference in cost and effect separately, without calculating the ICER for the base case analysis. When there is no difference in clinical outcomes, we will present incremental cost and effects separately, without calculating an ICER for the base case analysis.

Subgroup analyses

As subgroup analyses, we will investigate specific patients who may have differential effects and costs as compared to the entire population, including: diagnostic category (medical, surgical, trauma) [2]; age <65 years, 65-75 years and >75 years [34,35]; frailty status (baseline Clinical Frailty Score $\geq$5 of 9 versus) [36]; patients who received/did not receive antibiotics within 2 days of randomization [20]; prevalent (present at the time of enrollment) vs. no prevalent pneumonia [20].

Uncertainty analyses

Because patient characteristics and costs may differ in different jurisdictions and outside clinical trials settings, and there will be uncertainty associated in the estimation of each group's clinical outcomes and separately in the associated group's costs, we have prospectively planned an uncertainty analysis to explore how ICERs may change with plausible ranges in costs of probiotics.

To test the robustness of our results (and determine the uncertainty associated with cost and effects estimation), we will perform a probabilistic sensitivity analysis of pairs of known costs and effects, using non-parametric bootstrapping techniques to generate 95% confidence intervals. We will perform 1000 bootstrap simulations in the following manner: each simulation will draw the same number of patients per group (as per intention-to-treat), with replacement (for both events and cost) in pairs. For each sample, the difference in event rate and cost was calculated, obtaining 1000 pairs of differences in cost and event rate. [37,38] Cost effectiveness acceptability curves will be used to present the probability of probiotics being cost effective over a wide range of willingness-to-pay thresholds [21].

Scenario analyses will also be performed with variations of estimates of pairs of potentially influential variables (i.e. costs of probiotics, per day cost of care in ICU and hospital wards) across plausible ranges (variation of costs: 50-150%) to explore potential cost differences in higher- and lower-spending health care jurisdictions to determine if different estimates change the overall results.

All analyses will be undertaken using Excel (Microsoft Corp, Redmond Washington, US), and SAS (Cary, North Carolina, US).

Patient and Public Involvement

Patients or the public were not involved in the development of the research question, design, or conduct, or reporting, or dissemination plans of our research. The burden of the intervention was not assessed the patients themselves.

Ethics and Dissemination

Research ethics approval for E-PROSPECT was granted by the Hamilton Integrated Research Ethics Board (HIREB) of McMaster University (project identifier: REB#:15-322). Informed consent was obtained from each participant in PROSPECT, or their substitute decision-maker, in accordance with local REB approvals. We anticipate that a majority of sites participating in E-PROSPECT will consider central HIREB approval as satisfactory to obtain additional non-specific patient-based costing data from their center. All economic data, as with trial data, will be de-identified, maintained in a password-protected and encrypted laptop or desktop, in locked offices. All de-identified datasets, technical appendices and statistical code will be published alongside the economic evaluation. Knowledge translation of the results will be disseminated to patients, public and healthcare providers through peer-review journals.

Discussion

PROSPECT is the largest trial undertaken of probiotic usage for VAP prophylaxis in critically ill patients. Although probiotics have been shown in prior trials to prevent VAP and CDAD, their relative effects, side-effects and cost-effectiveness remain uncertain. PROSPECT will determine whether probiotics reduce the frequency of VAP and other healthcare-associated complications during critical illness.[18–20]

An economic evaluation jointly considers both costs and effects between alternative treatment options. Thus, physicians, administrators and policy-makers can know whether a new treatment provides good value for the healthcare expenditure. E-PROSPECT will answer these questions and address the cost-effectiveness of probiotics for VAP prevention. The literature currently has a paucity of health economic evaluations, illustrating the importance of E-PROSPECT.[39]

Strengths and Limitations

Some aspects of our methodology have potential limitations. First, the time-horizon is relatively short, with no outpatient follow-up (only reporting in-hospital outcomes). Other studies have utilized relative, non-fixed time horizons in health economic evaluations,[40] including those investigating probiotics.[41,42] We will carefully interpret these cost-effectiveness ratios in context from the short time horizon. Second, our primary outcome is the incremental cost to avoid a VAP event and other clinically important outcomes, not the incremental cost per quality-adjusted life year gained in a cost-utility analysis [21]. PROSPECT is not designed to measure long-term outcome or downstream life expectancy (hence no lifetime time horizon). However, if PROSPECT shows a difference in hospital survival due to probiotics, this will be addressed as a secondary outcome. As with all efficacy trials, the generalizability and external validity of a health economic evaluation concurrently performed with an RCT may not represent the same treatment effects and costs as in routine clinical practice.

E-PROSPECT has several advantages.[43] First, we reduce the potential for investigator hypothesis-driven biases by pre-specifying our parameters of analysis (subgroup and sensitivity analysis) for the health economic evaluation prior to unblinding of the trial. Second, trial randomization can reduce bias and confounding according to different baseline characteristics between study groups. Third, the concurrent collection of clinical and economic data can reduce the costs of data collection and minimize the possible problem of missing data if attempting to obtain it retrospectively. Fourth, we have chosen to gather costs from healthcare systems from multiple countries participating in the PROSPECT trial. We anticipate a wide variability in institutional reporting patient-specific cost accounting.[28,40] Although this has the potential to introduce variability in cost estimates, this approach will also likely enhance the generalizability of our results. Finally, timely economic data can be useful to healthcare policy-makers to aid in resource allocation decisions. There are several clinician-researchers that are advocating for the embracing the science of value in healthcare,[44] while others state that cost-effectiveness

analysis should be mandatory in clinical-effectiveness research to aid in clinical guideline development and public healthcare decision policy.[45] By conducting our economic analysis concurrent with the PROSPECT trial, we take advantage of each of these strengths.[28]

Article Summary

In summary, probiotics represent an intervention to consider for VAP prevention. As a randomized trial, PROSPECT will determine the balance of effects, side effects and complications of probiotics for prophylaxis against healthcare-associated infections amongst medical-surgical ICU patients, but leaves unanswered the consequences that probiotic administration would have on the costs of caring for patients with critical illness. E-PROSPECT will complement PROSPECT with a pre-specified prospective economic evaluation.

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Abbreviations

AAD = antibiotic-associated diarrhea;
BCA = bias corrected and accelerated;
CEA = Cost-effectiveness analysis;
CDAD = *Clostridioides* Difficile associated diarrhea;
CHEERS = Consolidated Health Economic Evaluation Reporting Standards
CI = confidence interval;
CIHR = Canadian Institute of Health Research;
CFU = colony-forming unit;
CT = computed tomography;
DOT = days of therapy;
DDD = defined daily dose;
ECMO = extracorporeal membrane oxygenation;
GBP = Great Britain Pound;
ICER = incremental cost-efficacy/effectiveness ratio;
ICU = intensive care unit;
OR = odds ratio;
QALY = quality-adjusted life-year
PCR = polymerase chain reaction;
PPP: purchase power parity
PROSPECT =Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial;
RCT = randomized control trial;
SAE = serious adverse events;
SAS = Statistical analysis software;
US = United States;
V-A = veno-arterial;
V-V = veno-venous;
VAC = vacuum-assisted closure;
VAP = ventilator-associated pneumonia;
WHO = World Health Organization;

Footnotes

Conflicts of interests

The authors declare that they have no competing interests.

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Tables

Table 1: Summary of economic evaluation framework

Question:	Is the use of probiotics as compared to standard care without probiotics cost-effective for the prevention of VAP and other clinically important outcomes in critically ill medical-surgical patients in PROSPECT?
Perspective:	Public payer (in-hospital costs)
Setting:	Ventilated ICU patients (44 centers, 3 countries: 41 Canada, 2 USA, 1 Saudi Arabia)
Comparators:	Probiotics (*Lactobacillus rhamnosus* GG) with standard of care versus standard care without probiotics
Time Horizon:	From ICU participant admission to hospital discharge/death (non-fixed time span)
Discount Rate:	No discounting (no long term follow-up over 1 year)
Clinical Outcomes:	VAP, CDAD, AAD, length of stay and mortality (ICU and hospital)
Costs:	Direct medical costs associated with treatment and complications (ICU and ward costs, personnel, medications, laboratory tests, diagnostic testing and procedures/surgeries)
Evaluation:	Primary outcome: Incremental cost-efficacy ratios (ICERs) per in-hospital VAP event avoided Secondary outcomes: ICERs for other clinically important outcomes: (i.) Incremental cost per CDAD avoided (ii.) Incremental cost per AAD avoided (iv.) Incremental cost per death avoided
Currency (price date):	United States Dollars (2019)
Uncertainty:	Non-parametric bootstrapping to produce confidence intervals (probabilistic sensitivity analysis) Cost sampling from various hospitals (stratified by: location) Sensitivity analyses to deal with structural and methodological uncertainty

AAD = antibiotic associated diarrhea; CDAD = *Clostriodiodes difficile* associated diarrhea; ICER = incremental cost-efficacy/effectiveness ratio; ICU = intensive care unit; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAP = ventilator-associated pneumonia;

Supplemental Table 1: Definitions of clinical outcomes

Supplemental Table 2: Healthcare resource utilization and unit costs

Supplemental Table 3: Health economic evaluation assumptions

Supplemental Appendix

Supplemental Appendix 1: E-PROSPECT Costing Manual

BMJ Open

November 26, 2019

Adrian Aldcroft
Editor-in-Chief
BMJ Open Editorial Office
BMA House
Tavistock Square
London, WC1H 9JR, UK

Dear Dr. Aldcroft
Re: Manuscript Title:
Economic Evaluation alongside the Probiotics to Prevent of Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol
Corresponding Author: Vincent Lau
e-mail: vinceissaclau@gmail.com

Thank you for your consideration of acceptance of the enclosed manuscript for publication in BMJ Open.

The objective and approach of our research is to conduct an economic evaluation using a cost-effectiveness analysis alongside the large multi-centered randomized control trial investigating Probiotics to Prevent of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT). We present the pre-specified statistical analysis protocol for that economic evaluation (E-PROSPECT).

BMJ Open is an internationally leading medical journal in the area of protocol publication, and a leader in publication of health economic evaluations and their protocols. PROSPECT is the largest investigation into probiotics and its potential to prevent ventilator-associated pneumonias (VAP) and other healthcare-associated infections (*Clostridioides difficile*-associated diarrhea), and E-PROSPECT is the largest undertaking of economic evaluation of the probiotics into their cost-effectiveness for VAP. Special considerations for this submission are that this protocol is being published *a priori* to the results of PROSPECT being published, to reduce hypothesis-driven bias.

Other related papers by myself and fellow authors are listed below (copies of the previous papers can be submitted upon request):

- Lau VI, Rochwerg B, Xie F, *et al.* Probiotics in hospitalized adult patients: a systematic review of economic evaluations. *Can J Anesth Can Anesth* Published Online First: 12 November 2019. doi:10.1007/s12630-019-01525-2

- Cook DJ, Johnstone J, Marshall JC, *et al.* Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial-PROSPECT: a pilot trial. *Trials* 2016;**17**:377. doi:10.1186/s13063-016-1495-x

- Johnstone J, Meade M, Marshall J, *et al.* Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial-PROSPECT: protocol for a feasibility randomized pilot trial. *Pilot Feasibility Stud* 2015;1:19. doi:10.1186/s40814-015-0013-3

- Johnstone J, Heels-Ansdell D, Thabane L, *et al.* Evaluating probiotics for the prevention of ventilator-associated pneumonia: a randomised placebo-controlled multicentre trial protocol and statistical analysis plan for PROSPECT. *BMJ Open* 2019;**9**:e025228. doi:10.1136/bmjopen-2018-025228

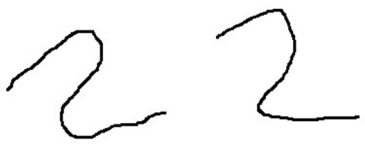
This manuscript has not been submitted or published previously, either in whole or in part, and is not under consideration for publication elsewhere. We have had no reviews of this submission, or previous communication with journal staff (editors/reviewers). All authors attest to the originality of the text, and the originality of any/all supporting tables, images, and supplementary electronic materials as related to this document, except where otherwise indicated that the material has been reproduced with the appropriate permissions. We also hereby affirm that ethical approval for this work was obtained as appropriate to this work.

All authors have made material contributions to this manuscript according to the rules of authorship as explained in the Instructions for Authors. We also accept the terms of reference for manuscript submission and editorial peer review as outlined in the Instructions for Authors. We agree to the terms of any copyright transfer statements which shall be deemed in effect if and when the manuscript is accepted for publication.

Should this manuscript be accepted, we also agree that the editors and the publisher have the right to edit the manuscript and to modify it to comply with the journal's standard punctuation, grammar and sentence structure. We will have the opportunity to review final page proofs, and to insert corrections prior to publication, with the exception of published letters.

Thank you for your consideration of our manuscript. We look forward to further communications in the future.

Sincerely,



Dr. Vincent Lau, on behalf of the authors

Supplemental Table 1: Definitions of clinical outcomes

Clinical Outcome	Definition	Source/Rationale
Ventilator-associated pneumonia (VAP)	The primary outcome is adjudicated VAP. Clinically suspected VAP at participating sites is being centrally adjudicated independently and in duplicate by 2 physicians blinded to allocation and center, informed by the following standardized definition: receiving invasive mechanical ventilation for > 2 days, when there is a new, progressive or persistent radiographic infiltrate on chest radiograph plus any 2 of the following: 1) fever (temperature >38°C) or hypothermia (temperature <36°C); 2) relative leukopenia (<3.0 x 106/L) or leukocytosis (>10 x 106/L); 3) purulent sputum	The American College of Chest Physicians (ACCP) definition did not provide thresholds for leukopenia or leukocytosis. Therefore, the thresholds were obtained from Morrow et al [Morrow] as their VAP definition was also based on the ACCP definition [Grossman]. Any disagreement in adjudication will be resolved through discussion and consensus. Acknowledging that there is no universally accepted gold standard VAP definition [3] , and that in non-immunocompromised patients, routine invasive testing is not associated with improved outcomes [Canadian Critical Care Trials Group], we are also collecting data to allow VAP reporting according to several other definitions [46–49].
Early VAP	Pneumonia arising on day 3, 4 or 5 after the initiation of mechanical ventilation.	We are classifying VAP by early VAP and late VAP, as the etiologic organisms may differ, the antimicrobials prescribed may differ, and the prognosis is often worse for late VAP [50,51]. We will also report a composite outcome of early VAP, late VAP, and post-extubation pneumonia, adjudicated independently and in duplicate by 2 physicians. For the timing of all pneumonia outcomes, we use days rather than hours to inform the classification.
Late VAP	Late VAP is defined as VAP arising on day 6 of mechanical ventilation or later, and including up to 2 days after	

	discontinuation of mechanical ventilation (also relevant for patients with a tracheostomy)	
Post-extubation pneumonia	Pneumonia arising in the ICU following discontinuation of mechanical ventilation (3 or more days after discontinuation), labeled post-extubation pneumonia, to avoid suppressing potentially relevant lung infections that arise in ICU	
Diarrhea	Diarrhea in the ICU: • World Health Organization definition (≥3 loose or watery bowel movements per day • Bristol Stool classification for loose or watery stool (type 6 or 7)	We will record each bowel movement and define diarrhea incorporating 2 metrics [6,52]
Clostridioides difficile–associated diarrhea (CDAD)	Clostridioides difficile in the ICU and prior to discharge from hospital: diarrhea (as previously defined) and laboratory confirmation of C. difficile or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis	Definition from Cohen et al. [53]. Will be adjudicated independently and in duplicate by 2 physicians
Antibiotic-associated diarrhea (AAD)	AAD: diarrhea (as above) defined as following the administration of antibiotics, any day antibiotics are administered or within 1 day after starting any antibiotic	Definition from Thibault et al. [54]
Other healthcare–associated infections	Any infection acquired during the ICU stay, including bloodstream infection, intravascular catheter-related bloodstream infection, intra-abdominal infection, C. difficile infection, urinary tract infection, skin and soft tissue infection, and others.	These individual infections are classified using definitions adapted from the International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit [47], as adapted in prior studies [46]. We will also report a composite outcome of any infections (including pneumonia) acquired during the ICU stay. Secondary infectious outcomes (other than pneumonia and C. difficile) are being centrally adjudicated by 1 physician blinded to allocation and center, based on review of data collected at each participating site.
Serious adverse events (SAE)	Defined as isolation of Lactobacillus spp. in a culture from a sterile site or as the	The rationale for our approach to SAEs [Guidance

	sole or predominant organism cultured from a non-sterile site and results in: 1) persistent or significant disability or incapacity; 2) that is life-threatening, or; 3) that results in death	Document for Industry] accords with our guidelines for academic drug trials in critical care [55]. Any culture obtained by the ICU team and processed by the clinical microbiology laboratory as positive for Lactobacillus spp. is recorded. Any such bacterial sample is sent to a McMaster University research laboratory for strain genotyping to evaluate consistency with the administered L. rhamnosus GG strain

Supplemental Table 2: Healthcare resource utilization and unit costs

Cost Categories	Natural Units	Unit Cost	Total Cost	Source

Study-related drugs
• probiotics *(Lactobacillus rhamnosus GG)*
• antibiotics:
  ○ pipercillin-tazobactam
  ○ ceftriaxone
  ○ ceftazidime
  ○ azithromycin
  ○ vancomycin
  ○ metronidazole
  ○ levofloxacin
  ○ imipenem
  ○ meropenem
  ○ amoxicillin-clavulin
  ○ cefuroxime
  ○ linezolid
  ○ cefazolin
  ○ cloxacillin
  ○ ciprofloxacin
  ○ gentamicin
  ○ trimethoprim-sulfamethoxazole
• steroids
  ○ dexamethasone
  ○ methylprednisone
  ○ hydrocortisone
  ○ prednisone
• stress ulcer prophylaxis
  ○ cimetidine
  ○ ranitidine
  ○ famotidine
  ○ nizatidine
  ○ lansoprazole
  ○ dexlansoprazole
  ○ pantoprazole
  ○ esomeprazole
  ○ omeprazole
  ○ rabeprazole
• laxatives/motility agents
  ○ domperidone
  ○ metoclopramide
  ○ erythromycin
  ○ senna
  ○ dulcolax
  ○ golytely
  ○ glycerin
  ○ lactulose				

○ colace ○ citro-mag ○ PegLyte ○ pancreatic enzymes ○ enema • opiates ○ morphine ○ hydromorphone ○ demerol ○ fentanyl ○ oxycodone ○ percocets				
Laboratory testing • complete blood count • creatinine • arterial blood gas • lactate • albumin • blood cultures • urine cultures • sputum/tracheal aspirate/bronchoalveolar lavage cultures • *C. difficile* polymerase chain reaction (PCR), toxin assays, ELISA, cell culture, LAMP • other aerobic/anaerobic cultures ○ thoracentesis ○ paracentesis				
Personnel (*per diem or hourly wage)* • most responsible physician ○ ICU ○ Hospital • consultation physicians • nursing • pharmacist • respiratory therapist • physical therapist • social work • ICU administrative and/or clerical staffing				
Radiology • portable chest or abdominal radiographs • computerized tomography (CT) scan: chest, abdomen, pelvis, sinusitis, head • MRI: head, chest, joint				

• abdominal ultrasound				

Procedural costs:
• central venous catheter, peripherally inserted central catheter, arterial lines
• chest tube
• naso- or oro-gastric tube
• percutaneous endoscopic gastrostomy (PEG) tube
• tube feed
• fiber
• protein supplement
• ventilator circuit changes
• endotracheal tubes (with or without subglottic suction)
• invasive ventilation (ventilator days)
  ○ heat moisture exchange
  ○ heated humidifier
• non-invasive positive pressure ventilation
• high-flow nasal cannula
• vasopressor/inotropic agents
• VAP prevention bundles
  ○ chlorhexidine usage
  ○ bacterial filters
  ○ oral decontamination
  ○ gut decontamination
  ○ oral antibiotic paste
• colonoscopy (cautery, epinephrine injection)
• echocardiograms (transthoracic/transesophageal)
• bronchoscopy
• thoracostomy
• tracheostomy
• interventional radiology drain
• intermittent hemodialysis
• continuous renal replacement therapy
• fecal management device				

Operative costs • laparotomy (toxic megacolon, bowel perforation) • colectomy • thoracotomy • open abdominal wound (vacuum-assisted closure (VAC) devices)				

• surgeon • surgical assistant • anesthesiology • nursing				
Overhead costs • ICU days • ward days				

CT = computerized tomography; ELISA = enzyme-linked immunosorbent assay; ICU = intensive care unit; LAMP = loop-mediated isothermal amplification; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia;

Supplemental Table 3: Health economic evaluation assumptions

Assumption	Rationale
Prophylactic and therapeutic probiotic administration outside the ICU • If no prophylactic/therapeutic probiotics was used prior to trial enrollment, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will be used for duration of stay in the ICU with no other probiotic co-administration; • If open label probiotics were used in the ICU, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will still be used for duration of stay in the ICU (co-administered); • After the duration of ICU stay (transfer to the ward), we assume that there will be no further probiotic administration	Ward-based/pre-admission ICU prophylactic and therapeutic probiotic administration was not directly measured
Variability in investigations and treatment practice of disease/illness • Based on variability in incidence of disease/illness, we will investigate the incidence of each illness severity, and average resource utilization for a particular illness. • We will utilize the mean costs for a particular illness (we will attempt to directly derive this variability from the case report forms)For patients who undergo multiple investigations, treatment (medications/procedures/surgeries) for a particular disease/illness, we will assume the lowest number of potential interventions to treat the disease/illness, as well as mean resource utilization for such events from PROSPECT	Various clinical diagnoses will have variability in severity, and therefore, variability in the way they are investigated and treated (i.e. *C. difficile* could be investigated/treated with only culture assay, abdominal x-ray and antibiotics to colectomy). Based on prior scoping reviews for VAP/CDAD, there will be variability in the resource utilization of each treatment/test based on illness severity, which may drive differences in resource utilization

Investigations of other infectious outcomes • For those illnesses that are only investigated if positive or indeterminate cultures are detected (i.e. endocarditis), we will assume there is a potential minimum and maximal resource utilization that would be used to investigate/treat a specific diagnosis • Certain assumptions will need to be made for healthcare resource utilization for certain services, investigations, procedures/surgeries, as they may not be explicitly captured in PROSPECT, but can be gleaned indirectly from the case report forms • For example: o central-line blood stream infections would be assumed to warrant a replacement or previous venous or arterial catheters; o broncho-alveolar lavage (BAL) cultures were assumed to have a bronchoscopy procedure to perform them o CDAD was assumed to have an abdominal x-ray (at a minimum) for radiological investigation ▪ At a maximum, a proportion of patients would receive at CT abdo, colonoscopy/flexible sigmoidoscopy, laparotomy, colectomy, fecal transplant, vacuum-assisted closure device o empyema/lung abscess would be assumed to be diagnosed by CT chest, and treated with a chest tube (with a proportion of patients with tissue plasminogen activator into the pleural cavity, or VATS thoracotomy with decortication and irrigation and debridement) o abdominal x-rays can be used to count the number of abdominal drains inserted ▪ a proportion of patients were assumed to receive an abdominal ultrasound, CT abdo, MRI abdo o we will assume that a positive blood culture with specific organisms (known to cause endocarditis) would warrant a transthoracic echocardiogram ± transesophageal echocardiogram; o confirmed endocarditis would be investigated with a transthoracic echocardiogram ± transesophageal echocardiogram o mediastinitis would be assumed to be	There are certain investigations or interventions that would be expected to be associated with various disease state suspicions (and given correct circumstances, we would assume these would be tested/treated in these ways)

diagnosed by CT or MRI chest ▪ at a maximum, they would receive an thoracotomy/sternotomy for an I&D and potential VAC dressing ○ initiation (on the first day) of intermittent hemodialysis or continuous renal replacement therapy would incur a cost of central venous hemodialysis line placement ○ suspected meningitis/encephalitis case would warrant a lumbar puncture ± CT or MRI head; ○ osteomyelitis would warrant a NM scan or MRI; ○ biliary tract infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, ERCP, percutaneous transhepatic cholecystostomy (PTC) tube, cholecysectomy ○ pancreatic infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, MRI abdo, abdominal drain or aspiration ○ typhilitis would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo ○ toxic megacolon would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo ○ urinary tract infection would be assumed to have at a urinalysis and urine culture ○ sinusitis would be assumed to have investigations at baseline ▪ At a maximum, a proportion of patients would receive at CT head ○ septic arthritis would be assumed to have an aspiration culture at a minimum ▪ At a maximum, a proportion of patients would receive an orthopedic surgery for I&D ○ PEG tube insertion would be assumed to be placed when 1st record on the daily data form of PEG tube utilization (Daily Form 4.2 of 3) ○ Tracheostomy insertion would be assumed to be placed when 1st record on the daily	

data form (Daily Form 4.1 of 3 – Mechanical airway in place today)	
Imputation of missing data • For those patients with missing data from a clinical outcomes perspective, multiple imputation methods will be utilized – including generalized estimating equations (GEEs) • For missing unit costs (which are not attainable from public jurisdiction databases or trial site-specific inquiries), we will utilize costing-ratio methodology	We will utilize standard multiple imputation methods to handle missing clinical outcome data, or costing-ratio methodology for missing unit costs

BAL = broncho-alveolar lavage; CDAD = C. Difficile-associated diarrhea; CT = computerized tomography; CXR = chest x-ray; ERCP = endoscopic retrograde cholangio-pancreatography; ICU = intensive care unit; I&D: irrigation & debridement; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia; VATS = video-assisted thorascopic surgery

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4-5
		Present the study question and its relevance for health policy or practice decisions.	Page 4-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, Table1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 5, 8
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not applicable
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable
Estimating resources and costs	13°	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 5-6
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Not applicable

Section/item	Item No	Recommendation	Reported on page No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 5-7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Not applicable
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 6-7
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 5-7
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 5-7
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Page 5-7
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Not applicable
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 7
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Page 7
Other			
Source of funding	23	Describe how the study was funded and the role of	Page 9

Section/item	Item No	Recommendation	Reported on page No
		the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

Economic Evaluation alongside the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Epidemiology, Infectious diseases, Medical management, Research methods, Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, HEALTH ECONOMICS, INFECTIOUS DISEASES, STATISTICS & RESEARCH METHODS, MICROBIOLOGY, PREVENTIVE MEDICINE

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Economic Evaluation alongside the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol

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Key Words: Probiotics, critical care, economics, infection, PROSPECT, cost-effectiveness, ventilator-associated pneumonia

Manuscript Word Count: 3017

Abstract Word Count: 315

Abstract

Introduction

Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection in the intensive care unit (ICU). Probiotics are defined as live microorganisms that may confer health benefits when ingested. Prior randomized trials suggest that probiotics may prevent infections such as VAP and *Clostridioides difficile*-associated diarrhea (CDAD). PROSPECT (Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial) is a multicenter, double-blinded, randomized controlled trial comparing the efficacy of the probiotic *Lactobacillus rhamnosus* GG with usual care versus usual care without probiotics in preventing VAP and other clinically important outcomes in critically ill patients admitted to the ICU.

Methods and Analysis

The objective of E-PROSPECT is to determine the incremental cost effectiveness of *Lactobacillus rhamnosus* GG plus usual care versus usual care without probiotics in critically ill patients. E-PROSPECT will be performed from the public healthcare payer's perspective over a time horizon from ICU admission to hospital discharge.

We will determine probabilities of in-ICU and in-hospital events from all patients alongside PROSPECT. We will retrieve unit costs for each resource use item using jurisdiction-specific public databases, supplemented by individual site unit costs if such databases are unavailable. Direct costs will include medications, personnel costs, radiology/laboratory testing, operative/non-operative procedures and per-day hospital 'hoteling' costs not otherwise encompassed. The primary outcome is the incremental cost per VAP prevented between the two treatment groups. Other clinical events such as CDAD, antibiotic-associated diarrhea (AAD), and in-hospital mortality will be included as secondary outcomes. We will perform pre-specified subgroup analyses (medical/surgical/trauma; age; frailty status; antibiotic use; prevalent vs. no prevalent pneumonia) and probabilistic sensitivity analyses for VAP, then generate confidence intervals using the non-parametric bootstrapping approach.

Ethics and Dissemination

Study approval for E-PROSPECT was granted by the Hamilton Integrated Research Ethics Board (HIREB) of McMaster University on July 29, 2019. Informed consent was obtained from the patient or substitute decision maker in PROSPECT. The findings of this study will be published in peer-reviewed journals.

Strengths and limitations of this study:

Strengths of this protocol:

- *A priori* study protocol with prospective clinical and economic data collection with representation from international jurisdictions.
- The balance of randomization reduces risk of bias in the cost-effectiveness analysis occurring on patient level.

Limitations of this protocol:

- A relatively short time-horizon.
- Primary outcome of incremental cost to avoid a clinical event (cost-effectiveness approach), rather than a cost-utility approach (incremental cost per quality-adjusted life year).

Background

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in the intensive care unit (ICU), resulting in a high burden of illness.[1,2] A 2005 systematic review found a pooled cumulative VAP incidence of 23% (95% confidence interval (CI): 19%–27%) in randomized controlled trials (RCTs) and 10% (95% CI: 7–13%) in observational studies.[2] In addition, VAP is associated with a two-fold attributable risk of dying in the ICU (odds ratio (OR) 2.02, 95% CI: 1.2–3.6), and the cost attributed to VAP ranges from US $10,000 to $13,000 per patient.[2] Thus, VAP prevention is a patient-important safety goal during critical illness.[1,3,4]

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a potential health benefit on the host."[5,6] They are reported to enhance gut barrier function, reduce host pathogenic bacterial load, modify gut microbiota, and modulate the immune system.[7–10] Probiotics studies suggest benefits including reduced incidence of healthcare-associated infections.[11–14] A recent meta-analysis of RCTs suggests that probiotics administered to critically ill mechanically ventilated patients were associated with a 26% lower VAP rate (95% CI: 10–39%) and 20% lower infection rates overall (95% CI: 5–32%).[15] However, these findings arose from 30 small, mostly low quality single-center RCTs (n=18–300, 2972 total patients in the meta-analysis), yielding imprecise estimates and results with uncertain internal and external validity.[15]

Further, probiotics may reduce the incidence of diarrhea, specifically *Clostridioides difficile*-associated diarrhea (CDAD), which can cause serious complications such as pseudomembranous colitis, toxic megacolon, and death.[16] In a recent Cochrane systematic review and meta-analysis of 31 RCTs including 8672 patients who were receiving antibiotics and concurrent probiotics, moderate certainty evidence suggested that probiotics were effective at reducing the burden of CDAD for patients and the healthcare system.[16]

We recently performed a systematic review of economic evaluations examining probiotics in hospitalized patients, evaluating their cost-effectiveness for reducing VAP, CDAD and antibiotic-associated diarrhea (AAD), while also identifying variables that could drive costs.[17] From 721 potentially relevant studies, 7 met the eligibility criteria. Probiotics appear to be either cost-effective or cost-saving in 6 of 7 studies compared to other prophylactic strategies within usual care to prevent healthcare-associated infection in acutely ill hospitalized patients. However, Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluations indicated a high risk of bias and very low quality/certainty of clinical evidence, such that cost-effectiveness evidence on the use of probiotics in adult hospitalized patients was weak. Furthermore, probiotic manufacturers funded 3 of 7 (43%) studies, all of which were reported as either cost-effective or cost-saving.[17] Some probiotic economic evaluations were designed after the results of the trial were published.

Therefore, we have designed this economic evaluation (E-PROSPECT) alongside the multicenter PROSPECT (ClinicalTrials.gov number: NCT01782755), assessing the incremental cost effectiveness ratio (ICER) of probiotics versus usual care for critically ill adult patients.[18–20]

METHODS

Overview of PROSPECT

PROSPECT is a randomized, double-blinded multicenter controlled trial. It used a central system for concealed 1:1 ratio to randomize patients (in variable unspecified block sizes, stratified by center and by medical, surgical or trauma admission status) to either 1×10^{10} colony forming units (CFU) of *L. rhamnosus* GG (iHealth, Inc.) or an identical placebo suspended in tap water administered twice daily via feeding tube in the ICU.[20] PROSPECT has enrolled 2653 critically ill patients between October 2013 and March 2019 throughout 44 ICUs (41 in Canada, 2 in the United States and 1 in Saudi Arabia). Patients, healthcare providers, investigators and research personnel were all blinded to group allocation. Sample size calculation has been previously described.[18–20]

E-PROSPECT design

The primary objective of E-PROSPECT is to estimate the incremental cost per VAP prevented arising from a prevention strategy of using probiotics with usual care (the probiotics arm) versus usual care without probiotics (the usual care arm) during hospitalization. Our secondary analyses of ICERs include healthcare-associated complications (CDAD, AAD) and mortality.[18–20]

Our economic evaluation will be performed from the public healthcare payer's perspective,[21] over the time horizon of the ICU admission to hospital discharge or death (Table 1). Our economic evaluation protocol was developed (Table 1) according to established CHEERS (Consolidated Health Economic Evaluation Reporting Standards) and international cost-effectiveness analysis (CEA) guidelines.[22,23]

Clinical outcomes

Clinical outcomes that will be examined in E-PROSPECT are described with definitions in Supplemental Table 1 that were previously described from PROSPECT [20]. Clinical events such as VAP (primary outcome), CDAD, AAD and hospital mortality (secondary outcomes) will be gleaned from PROSPECT, with a statistical analysis methodology previously described [20]. For the dichotomous outcomes, we will use time-to-event analyses. Hazard ratios and associated 95% confidential intervals will be estimated using a stratified Cox proportional hazards model. For continuous outcomes, we will report estimates of the difference between intervention and control groups, 95% confidence intervals (CIs) and associated p-values [20].

These dichotomous outcomes with proportions and continuous outcomes with point-estimates (e.g. length of stay, which will be used for calculation of resource utilization) will be used to calculate both incremental costs (resource utilization) and effects. Incremental effects will be defined as the difference in per-patient event rates or the difference in proportion of a clinical event (e.g. VAP) between groups.

Health care resource utilization

Based on our systematic literature review[17] and published evidence[18–20], we identified a list of relevant health care resource items that includes medications, physician/personnel utilization, diagnostic radiology/laboratory testing, and operative/non-operative procedures and per-day hospital 'hoteling' costs not otherwise encompassed. Antimicrobial use in ICU will be defined as days of therapy (DOT), defined daily dose (DDD) of therapy and antimicrobial-free days (AFDs).[24,25] Only systemic antimicrobials will be captured whether prophylactic or therapeutic in intent. Topical creams, eye/ear drops and inhaled antimicrobials will be excluded. We will also document the duration of mechanical ventilation, ICU and hospital length of stay and mortality. The health care resource uses will be collected alongside PROSPECT. For missing resource use data, we will choose appropriate imputation methods according to the type and distribution of the missing data. [26,27] Otherwise, we will utilize an

appropriate “standard dose” for non-titratable medications (e.g. chlorhexidine), and a clinically appropriate “medium dose” for titratable medications (e.g. vasopressors or inotropes).

Unit costs

Unit costs for health care resource items will be identified through jurisdiction-specific (regions/provinces/states which manage health care delivery in their area) public databases (e.g. pharmacy drug formularies, physician billing schedule of benefits, Medicare/Medicaid reimbursement manuals, labour department wages/salaries, manufacturer costs). When there is a small sample or distribution of unit costs (i.e. a provincial jurisdiction may have the same cost for a particular procedure), we will estimate the standard error if possible, or incorporate a ±25% error around the mean unit cost distribution.

For unit costs not represented in public databases, we will obtain site-specific unit costs from the participating PROSPECT sites. We will first conduct a pilot study of unit cost acquisition at a convenience sample of 8 participating centers (Canadian: British Columbia, Alberta, Manitoba, Ontario, Québec, Nova Scotia; US: Minnesota, Missouri; and Saudi Arabia) to request a list of unit costs (Supplemental Table 2: E-PROSPECT unit cost data extraction table). The site investigator or research coordinator will then contact the most appropriate individual in each hospital’s accounting, human resources, pharmacy, radiology or laboratory departments to obtain the unit costs. [28] In all cases, costs will be requested (if available). If only charges are known, then we will attempt to convert to costs by the institution’s cost-to-charge estimate for that item, where it exists [28].

Direct costs will be presented in the pre-specified cost categories (Supplemental Table 2). Assumptions regarding resource utilization are presented in Supplemental Table 3. We will assess direct unit costs for study product-related resources associated with outcomes of VAP, CDAD, AAD and mortality. If a specific line-item unit cost is not attainable for a specific jurisdiction,[28] we will: 1) ask another site within the same jurisdiction for missing unit costs; 2) derive a cost-ratio from acquired line-items (i.e. drug costs both known in 2 jurisdictions), then using the cost-ratio impute the missing line-item unit costs for the missing jurisdiction (by multiplying the cost-ratio against a known jurisdiction’s acquired line-item to impute the line-item unit cost for the missing jurisdiction). 3) If line-item unit costs are still missing after multiple imputation (with missing variables), a mean unit cost approach will be utilized for the remaining jurisdictions which did report unit costs.

The pilot phase may inform amendments to our protocol. For example, if a unit cost for a particular line-item is deemed to be small and/or has a low clinical incidence rate, then that line-item may be removed from the final analysis. Items without a difference in clinical outcome/resource utilization between intervention and control groups but which contribute substantially to costs may still be retained (even if little to no incremental difference in costs would exist between the two arms) in order to maintain face validity and accurately reflect the magnitude of costs for hospitalization of a critically ill patient. Once the list of line-items has been pared down to those which are deemed to be cost drivers, and clinically relevant while also feasible to obtain, the remaining line-item list will be surveyed across a sampling of individual sites from each representative jurisdiction from PROSPECT.

Unit cost data will be summarized among all sites, and by country, to explore variability across centers and countries and to improve the generalizability of results. Visible outliers will be reconfirmed with individual hospital contacts. Participating sites will be queried to determine if particular costs have changed substantially (for example, by more than 25%), beyond inflationary or deflationary changes, over the course of the study. If there are substantial changes that have occurred over time, we will use the mean unit costs adjusted for inflation over the mean duration of the trial.[28]

Cost analysis

The cost for each resource use item will be calculated by multiplying the natural resource utilization units by the unit cost. The total cost per patient will be the sum of the cost of items utilized from the time of randomization until discharge from hospital or death. The incremental mean cost will be estimated by calculating the difference in the total per patient costs between the two groups. All costs will be converted to 2019 United States dollars, accounting for annual inflation. [29–33]

We plan on using international currency conversion, instead of purchase power parity (PPP)-based conversions, because health-specific PPPs are not available for all participating countries, and non-health PPP conversion rates vary substantially over the period of the analysis.[30] Country-specific costs will be considered only in sensitivity analyses.

Incremental costs will be calculated using the difference in mean per patient cost between the two treatment arms. We have developed a costing operations manual outlining this process (Supplemental Table 4: E-PROSPECT costing manual). [30]

Base-Case Cost Effectiveness Analyses

Means (standard deviations) or frequency (percentage) will be used to describe effect and cost estimates wherever appropriate. Chi-square tests and two-sample t-test comparisons will be used as appropriate to compare baseline characteristics between the two arms. The primary outcome will be based on the intention-to-treat principle and will form the clinical event estimates for the economic evaluation. Regression analyses may be performed if there is residual confounding, based on previously described methodology [20].

The base case incremental cost-effectiveness ratio (ICER) is the ratio of incremental costs per VAP prevented of probiotics versus usual care during the period of hospitalization (from ICU admission to hospital discharge or death). The incremental mean costs will be estimated from all patients in both groups based on multiplying the resource unit cost by resource utilization as described above. The incremental mean effects will be derived from PROSPECT, where incremental effects were defined as the difference in per-patient event rates or the difference in proportion of a clinical event (e.g. VAP) between groups [28, 40]. In secondary analysis we will also calculate ICER using other clinical outcomes (i.e., CDAD, AAD, mortality). If there is dominance in cost effectiveness (i.e. one treatment is better at lower cost than the other treatment), we will present the difference in cost and effect separately, without calculating the ICER for the base case analysis. When there is no difference in clinical outcomes, we will present incremental cost and effects separately, without calculating an ICER for the base case analysis.

Subgroup analyses

As subgroup analyses, we will investigate specific patients who may have differential effects and costs as compared to the entire population, including: diagnostic category (medical, surgical, trauma) [2]; age <65 years, 65-75 years and >75 years [34,35]; frailty status (baseline Clinical Frailty Score $\geq$5 of 9 versus) [36]; patients who received/did not receive antibiotics within 2 days of randomization [20]; prevalent (present at the time of enrollment) vs. no prevalent pneumonia [20].

Uncertainty analyses

Because patient characteristics and costs may differ in different jurisdictions and outside clinical trials settings, and there will be uncertainty associated in the estimation of each group's clinical outcomes and separately in the associated group's costs, we have prospectively planned an uncertainty analysis to explore how ICERs may change with plausible ranges in costs of probiotics.

To test the robustness of our results (and determine the uncertainty associated with cost and effects estimation), we will perform a probabilistic sensitivity analysis of pairs of known costs and effects, using non-parametric bootstrapping techniques to generate 95% confidence

intervals. We will perform 1000 bootstrap simulations in the following manner: each simulation will draw the same number of patients per group (as per intention-to-treat), with replacement (for both events and cost) in pairs. For each sample, the difference in event rate and cost was calculated, obtaining 1000 pairs of differences in cost and event rate. [37,38] Cost effectiveness acceptability curves will be used to present the probability of probiotics being cost effective over a wide range of willingness-to-pay thresholds [21].

Scenario analyses will also be performed with variations of estimates of pairs of potentially influential variables (i.e. costs of probiotics, per day cost of care in ICU and hospital wards) across plausible ranges (variation of costs: 50-150%) to explore potential cost differences in higher- and lower-spending health care jurisdictions to determine if different estimates change the overall results.

All analyses will be undertaken using Excel (Microsoft Corp, Redmond Washington, US), and SAS (Cary, North Carolina, US).

Patient and Public Involvement

Patients or the public were not involved in the development of the research question, design, or conduct, or reporting, or dissemination plans of our research. The burden of the intervention was not assessed the patients themselves.

Ethics and Dissemination

Research ethics approval for E-PROSPECT was granted by the Hamilton Integrated Research Ethics Board (HIREB) of McMaster University (project identifier: REB#:15-322). Informed consent was obtained from each participant in PROSPECT, or their substitute decision-maker, in accordance with local REB approvals. We anticipate that a majority of sites participating in E-PROSPECT will consider central HIREB approval as satisfactory to obtain additional non-specific patient-based costing data from their center. All economic data, as with trial data, will be de-identified, maintained in a password-protected and encrypted laptop or desktop, in locked offices. All de-identified datasets, technical appendices and statistical code will be published alongside the economic evaluation. Knowledge translation of the results will be disseminated to patients, public and healthcare providers through peer-review journals. The CHEERS checklist has been completed (Supplemental Table 5).

Discussion

PROSPECT is the largest trial undertaken of probiotic usage for VAP prophylaxis in critically ill patients. Although probiotics have been shown in prior trials to prevent VAP and CDAD, their relative effects, side-effects and cost-effectiveness remain uncertain. PROSPECT will determine whether probiotics reduce the frequency of VAP and other healthcare-associated complications during critical illness.[18–20]

An economic evaluation jointly considers both costs and effects between alternative treatment options. Thus, physicians, administrators and policy-makers can know whether a new treatment provides good value for the healthcare expenditure. E-PROSPECT will answer these questions and address the cost-effectiveness of probiotics for VAP prevention. The literature currently has a paucity of health economic evaluations, illustrating the importance of E-PROSPECT.[39]

Strengths and Limitations

Some aspects of our methodology have potential limitations. First, the time-horizon is relatively short, with no outpatient follow-up (only reporting in-hospital outcomes). Other studies have utilized relative, non-fixed time horizons in health economic evaluations,[40] including those investigating probiotics.[41,42] We will carefully interpret these cost-effectiveness ratios in context

from the short time horizon. Second, our primary outcome is the incremental cost to avoid a VAP event and other clinically important outcomes, not the incremental cost per quality-adjusted life year gained in a cost-utility analysis [21]. PROSPECT is not designed to measure long-term outcome or downstream life expectancy (hence no lifetime time horizon). However, if PROSPECT shows a difference in hospital survival due to probiotics, this will be addressed as a secondary outcome. As with all efficacy trials, the generalizability and external validity of a health economic evaluation concurrently performed with an RCT may not represent the same treatment effects and costs as in routine clinical practice.

E-PROSPECT has several advantages.[43] First, we reduce the potential for investigator hypothesis-driven biases by pre-specifying our parameters of analysis (subgroup and sensitivity analysis) for the health economic evaluation prior to unblinding of the trial. Second, trial randomization can reduce bias and confounding according to different baseline characteristics between study groups. Third, the concurrent collection of clinical and economic data can reduce the costs of data collection and minimize the possible problem of missing data if attempting to obtain it retrospectively. Fourth, we have chosen to gather costs from healthcare systems from multiple countries participating in the PROSPECT trial. We anticipate a wide variability in institutional reporting patient-specific cost accounting.[28,40] Although this has the potential to introduce variability in cost estimates, this approach will also likely enhance the generalizability of our results. Finally, timely economic data can be useful to healthcare policy-makers to aid in resource allocation decisions. There are several clinician-researchers that are advocating for the embracing the science of value in healthcare,[44] while others state that cost-effectiveness analysis should be mandatory in clinical-effectiveness research to aid in clinical guideline development and public healthcare decision policy.[45] By conducting our economic analysis concurrent with the PROSPECT trial, we take advantage of each of these strengths.[28]

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Abbreviations

AAD = antibiotic-associated diarrhea;
BCA = bias corrected and accelerated;
CEA = Cost-effectiveness analysis;
CDAD = *Clostridioides* Difficile associated diarrhea;
CHEERS = Consolidated Health Economic Evaluation Reporting Standards
CI = confidence interval;
CIHR = Canadian Institute of Health Research;
CFU = colony-forming unit;
CT = computed tomography;
DOT = days of therapy;
DDD = defined daily dose;
ECMO = extracorporeal membrane oxygenation;
GBP = Great Britain Pound;
ICER = incremental cost-efficacy/effectiveness ratio;
ICU = intensive care unit;
OR = odds ratio;
QALY = quality-adjusted life-year
PCR = polymerase chain reaction;
PPP: purchase power parity
PROSPECT =Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial;
RCT = randomized control trial;
SAE = serious adverse events;
SAS = Statistical analysis software;
US = United States;
V-A = veno-arterial;
V-V = veno-venous;
VAC = vacuum-assisted closure;
VAP = ventilator-associated pneumonia;
WHO = World Health Organization;

Footnotes

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The authors declare that they have no competing interests.
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Tables

Table 1: Summary of economic evaluation framework

Question:	Is the use of probiotics as compared to standard care without probiotics cost-effective for the prevention of VAP and other clinically important outcomes in critically ill medical-surgical patients in PROSPECT?
Perspective:	Public payer (in-hospital costs)
Setting:	Ventilated ICU patients (44 centers, 3 countries: 41 Canada, 2 USA, 1 Saudi Arabia)
Comparators:	Probiotics (*Lactobacillus rhamnosus* GG) with standard of care versus standard care without probiotics
Time Horizon:	From ICU participant admission to hospital discharge/death (non-fixed time span)
Discount Rate:	No discounting (no long term follow-up over 1 year)
Clinical Outcomes:	VAP, CDAD, AAD, length of stay and mortality (ICU and hospital)
Costs:	Direct medical costs associated with treatment and complications (ICU and ward costs, personnel, medications, laboratory tests, diagnostic testing and procedures/surgeries)
Evaluation:	Primary outcome: Incremental cost-efficacy ratios (ICERs) per in-hospital VAP event avoided Secondary outcomes: ICERs for other clinically important outcomes: (i.) Incremental cost per CDAD avoided (ii.) Incremental cost per AAD avoided (iv.) Incremental cost per death avoided
Currency (price date):	United States Dollars (2019)
Uncertainty:	Non-parametric bootstrapping to produce confidence intervals (probabilistic sensitivity analysis) Cost sampling from various hospitals (stratified by: location) Sensitivity analyses to deal with structural and methodological uncertainty

AAD = antibiotic associated diarrhea; CDAD = *Clostriodiodes difficile* associated diarrhea; ICER = incremental cost-efficacy/effectiveness ratio; ICU = intensive care unit; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAP = ventilator-associated pneumonia;

Supplemental Table 1: Definitions of clinical outcomes

Supplemental Table 2: Healthcare resource utilization and unit costs (per jurisdiction)

Supplemental Table 3: Health economic evaluation assumptions

Supplemental Table 4: E-PROSPECT Costing Manual

Supplemental Table 5: CHEERS Checklist

Supplemental Table 1: Definitions of clinical outcomes

Clinical Outcome	Definition	Source/Rationale
Ventilator-associated pneumonia (VAP)	The primary outcome is adjudicated VAP. Clinically suspected VAP at participating sites is being centrally adjudicated independently and in duplicate by 2 physicians blinded to allocation and center, informed by the following standardized definition: receiving invasive mechanical ventilation for > 2 days, when there is a new, progressive or persistent radiographic infiltrate on chest radiograph plus any 2 of the following: 1) fever (temperature >38°C) or hypothermia (temperature <36°C); 2) relative leukopenia (<3.0 x 106/L) or leukocytosis (>10 x 106/L); 3) purulent sputum	The American College of Chest Physicians (ACCP) definition did not provide thresholds for leukopenia or leukocytosis. Therefore, the thresholds were obtained from Morrow et al [Morrow] as their VAP definition was also based on the ACCP definition [Grossman]. Any disagreement in adjudication will be resolved through discussion and consensus. Acknowledging that there is no universally accepted gold standard VAP definition [3] , and that in non-immunocompromised patients, routine invasive testing is not associated with improved outcomes [Canadian Critical Care Trials Group], we are also collecting data to allow VAP reporting according to several other definitions [46–49].
Early VAP	Pneumonia arising on day 3, 4 or 5 after the initiation of mechanical ventilation.	We are classifying VAP by early VAP and late VAP, as the etiologic organisms may differ, the antimicrobials prescribed may differ, and the prognosis is often worse for late VAP [50,51]. We will also report a composite outcome of early VAP, late VAP, and post-extubation pneumonia, adjudicated independently and in duplicate by 2 physicians. For the timing of all pneumonia outcomes, we use days rather than hours to inform the classification.
Late VAP	Late VAP is defined as VAP arising on day 6 of mechanical ventilation or later, and including up to 2 days after	

	discontinuation of mechanical ventilation (also relevant for patients with a tracheostomy)	
Post-extubation pneumonia	Pneumonia arising in the ICU following discontinuation of mechanical ventilation (3 or more days after discontinuation), labeled post-extubation pneumonia, to avoid suppressing potentially relevant lung infections that arise in ICU	
Diarrhea	Diarrhea in the ICU: • World Health Organization definition (≥3 loose or watery bowel movements per day • Bristol Stool classification for loose or watery stool (type 6 or 7)	We will record each bowel movement and define diarrhea incorporating 2 metrics [6,52]
Clostridioides difficile–associated diarrhea (CDAD)	Clostridioides difficile in the ICU and prior to discharge from hospital: diarrhea (as previously defined) and laboratory confirmation of C. difficile or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis	Definition from Cohen et al. [53]. Will be adjudicated independently and in duplicate by 2 physicians
Antibiotic-associated diarrhea (AAD)	AAD: diarrhea (as above) defined as following the administration of antibiotics, any day antibiotics are administered or within 1 day after starting any antibiotic	Definition from Thibault et al. [54]
Other healthcare–associated infections	Any infection acquired during the ICU stay, including bloodstream infection, intravascular catheter-related bloodstream infection, intra-abdominal infection, C. difficile infection, urinary tract infection, skin and soft tissue infection, and others.	These individual infections are classified using definitions adapted from the International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit [47], as adapted in prior studies [46]. We will also report a composite outcome of any infections (including pneumonia) acquired during the ICU stay. Secondary infectious outcomes (other than pneumonia and C. difficile) are being centrally adjudicated by 1 physician blinded to allocation and center, based on review of data collected at each participating site.
Serious adverse events (SAE)	Defined as isolation of Lactobacillus spp. in a culture from a sterile site or as the	The rationale for our approach to SAEs [Guidance

	sole or predominant organism cultured from a non-sterile site and results in: 1) persistent or significant disability or incapacity; 2) that is life-threatening, or; 3) that results in death	Document for Industry] accords with our guidelines for academic drug trials in critical care [55]. Any culture obtained by the ICU team and processed by the clinical microbiology laboratory as positive for Lactobacillus spp. is recorded. Any such bacterial sample is sent to a McMaster University research laboratory for strain genotyping to evaluate consistency with the administered L. rhamnosus GG strain

Supplemental Table 2: Healthcare resource utilization and unit costs (per jurisdiction)

Cost Categories	Natural Units	Unit Cost	Total Cost	Source

Study-related drugs • probiotics *(Lactobacillus rhamnosus GG)* □ antibiotics: ○ pipercillin-tazobactam ○ ceftriaxone ○ ceftazidime ○ azithromycin ○ vancomycin ○ metronidazole ○ levofloxacin ○ imipenem ○ meropenem ○ amoxicillin-clavulin ○ cefuroxime ○ linezolid ○ cefazolin ○ cloxacillin ○ ciprofloxacin ○ gentamicin ○ trimethoprimsulfamethoxazole • steroids ○ dexamethasone ○ methylprednisone ○ hydrocortisone ○ prednisone • stress ulcer prophylaxis ○ cimetidine ○ ranitidine ○ famotidine ○ nizatidine ○ lansoprazole ○ dexlansoprazole ○ pantoprazole ○ esomeprazole ○ omeprazole ○ rabeprazole • laxatives/motility agents ○ domperidone ○ metoclopramide ○ erythromycin ○ senna ○ dulcolax ○ golytely ○ glycerin ○ lactulose				

○ colace ○ citro-mag ○ PegLyte ○ pancreatic enzymes ○ enema □ opiates ○ morphine ○ hydromorphone ○ demerol ○ fentanyl ○ oxycodone ○ percocets				
Laboratory testing • complete blood count • creatinine • arterial blood gas • lactate • albumin • blood cultures • urine cultures • sputum/tracheal aspirate/bronchoalveolar lavage cultures • *C. difficile* polymerase chain reaction (PCR), toxin assays, ELISA, cell culture, LAMP • other aerobic/anaerobic cultures ○ thoracentesis ○ paracentesis				
Personnel (*per diem or hourly wage)* • most responsible physician ○ ICU ○ Hospital • consultation physicians • nursing • pharmacist • respiratory therapist • physical therapist • social work • ICU administrative and/or clerical staffing				

Radiology • portable chest or abdominal radiographs • computerized tomography (CT) scan: chest, abdomen, pelvis, sinusitis, head • MRI: head, chest, joint				

□ abdominal ultrasound				

Procedural costs: • central venous catheter, peripherally inserted central catheter, arterial lines • chest tube • naso- or oro-gastric tube • percutaneous endoscopic gastrostomy (PEG) tube • tube feed • fiber • protein supplement • ventilator circuit changes • endotracheal tubes (with or without subglottic suction) • invasive ventilation (ventilator days) ○ heat moisture exchange ○ heated humidifier • non-invasive positive pressure ventilation • high-flow nasal cannula • vasopressor/inotropic agents • VAP prevention bundles ○ chlorhexidine usage ○ bacterial filters ○ oral decontamination ○ gut decontamination ○ oral antibiotic paste • colonoscopy (cautery, epinephrine injection) • echocardiograms (transthoracic/transesophageal) • bronchoscopy • thoracostomy • tracheostomy • interventional radiology drain • intermittent hemodialysis • continuous renal replacement therapy • fecal management device				

Operative costs • laparotomy (toxic megacolon, bowel perforation) • colectomy • thoracotomy • open abdominal wound (vacuum-assisted closure (VAC) devices)				
surgeon surgical assistant anesthesiology nursing				
Overhead costs ICU days ward days				

CT = computerized tomography; ELISA = enzyme-linked immunosorbent assay; ICU = intensive care unit; LAMP = loop-mediated isothermal amplification; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilatorassociated pneumonia;

Supplemental Table 2: Health economic evaluation assumptions

Assumption	Rationale
Prophylactic and therapeutic probiotic administration outside the ICU • If no prophylactic/therapeutic probiotics was used prior to trial enrollment, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will be used for duration of stay in the ICU with no other probiotic co-administration; • If open label probiotics were used in the ICU, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will still be used for duration of stay in the ICU (coadministered); • After the duration of ICU stay (transfer to the ward), we assume that there will be no further probiotic administration	Ward-based/pre-admission ICU prophylactic and therapeutic probiotic administration was not directly measured
Variability in investigations and treatment practice of disease/illness • Based on variability in incidence of disease/illness, we will investigate the incidence of each illness severity, and average resource utilization for a particular illness. • We will utilize the mean costs for a particular illness (we will attempt to directly derive this variability from the case report forms)For patients who undergo multiple investigations, treatment (medications/procedures/surgeries) for a particular disease/illness, we will assume the lowest number of potential interventions to treat the disease/illness, as well as mean resource utilization for such events from PROSPECT	Various clinical diagnoses will have variability in severity, and therefore, variability in the way they are investigated and treated (i.e. *C. difficile* could be investigated/treated with only culture assay, abdominal x-ray and antibiotics to colectomy). Based on prior scoping reviews for VAP/CDAD, there will be variability in the resource utilization of each treatment/test based on illness severity, which may drive differences in resource utilization

Investigations of other infectious outcomes • For those illnesses that are only investigated if positive or indeterminate cultures are detected (i.e. endocarditis), we will assume there is a potential minimum and maximal resource utilization that would be used to investigate/treat a specific diagnosis • Certain assumptions will need to be made for healthcare resource utilization for certain services, investigations, procedures/surgeries, as they may not be explicitly captured in PROSPECT, but can be gleaned indirectly from the case report forms • For example: ○ central-line blood stream infections would be assumed to warrant a replacement or previous venous or arterial catheters; ○ broncho-alveolar lavage (BAL) cultures were assumed to have a bronchoscopy procedure to perform them ○ CDAD was assumed to have an abdominal x-ray (at a minimum) for radiological investigation ▪ At a maximum, a proportion of patients would receive at CT abdo, colonoscopy/flexible sigmoidoscopy, laparotomy, colectomy, fecal transplant, vacuum-assisted closure device ○ empyema/lung abscess would be assumed to be diagnosed by CT chest, and treated with a chest tube (with a proportion of patients with tissue plasminogen activator into the pleural cavity, or VATS thoracotomy with decortication and irrigation and debridement) ○ abdominal x-rays can be used to count the number of abdominal drains inserted ▪ a proportion of patients were assumed to receive an abdominal ultrasound, CT abdo, MRI abdo ○ we will assume that a positive blood culture with specific organisms (known to cause endocarditis) would warrant a transthoracic echocardiogram ± transesophageal echocardiogram; ○ confirmed endocarditis would be investigated with a transthoracic echocardiogram ± transesophageal echocardiogram ○ mediastinitis would be assumed to be	There are certain investigations or interventions that would be expected to be associated with various disease state suspicions (and given correct circumstances, we would assume these would be tested/treated in these ways)

diagnosed by CT or MRI chest ▪ at a maximum, they would receive an thoracotomy/sternotomy for an I&D and potential VAC dressing ○ initiation (on the first day) of intermittent hemodialysis or continuous renal replacement therapy would incur a cost of central venous hemodialysis line placement ○ suspected meningitis/encephalitis case would warrant a lumbar puncture ± CT or MRI head; ○ osteomyelitis would warrant a NM scan or MRI; ○ biliary tract infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, ERCP, percutaneous transhepatic cholecystostomy (PTC) tube, cholecystectomy ○ pancreatic infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, MRI abdo, abdominal drain or aspiration ○ typhilitis would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo ○ toxic megacolon would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo ○ urinary tract infection would be assumed to have at a urinalysis and urine culture ○ sinusitis would be assumed to have investigations at baseline ▪ At a maximum, a proportion of patients would receive at CT head ○ septic arthritis would be assumed to have an aspiration culture at a minimum ▪ At a maximum, a proportion of patients would receive an orthopedic surgery for I&D	

○ PEG tube insertion would be assumed to be placed when 1st record on the daily data form of PEG tube utilization (Daily Form 4.2 of 3) ○ Tracheostomy insertion would be assumed to be placed when 1st record on the daily data form (Daily Form 4.1 of 3 – Mechanical airway in place today)	
Imputation of missing data ▯ For those patients with missing data from a clinical outcomes perspective, multiple imputation methods will be utilized – including generalized estimating equations (GEEs) ▯ For missing unit costs (which are not attainable from public jurisdiction databases or trial site -specific inquiries), we will utilize costing -ratio methodology	We will utilize standard multiple imputation methods to handle missing clinical outcome data, or costing-ratio methodology for missing unit costs

BAL = broncho-alveolar lavage; CDAD = C. Difficile-associated diarrhea; CT = computerized tomography; CXR = chest x-ray; ERCP = endoscopic retrograde cholangio-pancreatography; ICU = intensive care unit; I&D: irrigation & debridement; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal

Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilatorassociated pneumonia; VATS = video-assisted thorascopic surgery

Supplemental Table 3: Health economic evaluation assumptions

Assumption	Rationale
Prophylactic and therapeutic probiotic administration outside the ICU • If no prophylactic/therapeutic probiotics was used prior to trial enrollment, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will be used for duration of stay in the ICU with no other probiotic co-administration; • If open label probiotics were used in the ICU, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will still be used for duration of stay in the ICU (co-administered); • After the duration of ICU stay (transfer to the ward), we assume that there will be no further probiotic administration	Ward-based/pre-admission ICU prophylactic and therapeutic probiotic administration was not directly measured
Variability in investigations and treatment practice of disease/illness • Based on variability in incidence of disease/illness, we will investigate the incidence of each illness severity, and average resource utilization for a particular illness. • We will utilize the mean costs for a particular illness (we will attempt to directly derive this variability from the case report forms)For patients who undergo multiple investigations, treatment (medications/procedures/surgeries) for a particular disease/illness, we will assume the lowest number of potential interventions to treat the disease/illness, as well as mean resource utilization for such events from PROSPECT	Various clinical diagnoses will have variability in severity, and therefore, variability in the way they are investigated and treated (i.e. *C. difficile* could be investigated/treated with only culture assay, abdominal x-ray and antibiotics to colectomy). Based on prior scoping reviews for VAP/CDAD, there will be variability in the resource utilization of each treatment/test based on illness severity, which may drive differences in resource utilization

Investigations of other infectious outcomes • For those illnesses that are only investigated if positive or indeterminate cultures are detected (i.e. endocarditis), we will assume there is a potential minimum and maximal resource utilization that would be used to investigate/treat a specific diagnosis • Certain assumptions will need to be made for healthcare resource utilization for certain services, investigations, procedures/surgeries, as they may not be explicitly captured in PROSPECT, but can be gleaned indirectly from the case report forms • For example: o central-line blood stream infections would be assumed to warrant a replacement or previous venous or arterial catheters; o broncho-alveolar lavage (BAL) cultures were assumed to have a bronchoscopy procedure to perform them o CDAD was assumed to have an abdominal x-ray (at a minimum) for radiological investigation ▪ At a maximum, a proportion of patients would receive at CT abdo, colonoscopy/flexible sigmoidoscopy, laparotomy, colectomy, fecal transplant, vacuum-assisted closure device o empyema/lung abscess would be assumed to be diagnosed by CT chest, and treated with a chest tube (with a proportion of patients with tissue plasminogen activator into the pleural cavity, or VATS thoracotomy with decortication and irrigation and debridement) o abdominal x-rays can be used to count the number of abdominal drains inserted ▪ a proportion of patients were assumed to receive an abdominal ultrasound, CT abdo, MRI abdo o we will assume that a positive blood culture with specific organisms (known to cause endocarditis) would warrant a transthoracic echocardiogram ± transesophageal echocardiogram; o confirmed endocarditis would be investigated with a transthoracic echocardiogram ± transesophageal echocardiogram o mediastinitis would be assumed to be	There are certain investigations or interventions that would be expected to be associated with various disease state suspicions (and given correct circumstances, we would assume these would be tested/treated in these ways)

diagnosed by CT or MRI chest ▪ at a maximum, they would receive an thoracotomy/sternotomy for an I&D and potential VAC dressing ○ initiation (on the first day) of intermittent hemodialysis or continuous renal replacement therapy would incur a cost of central venous hemodialysis line placement ○ suspected meningitis/encephalitis case would warrant a lumbar puncture ± CT or MRI head; ○ osteomyelitis would warrant a NM scan or MRI; ○ biliary tract infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, ERCP, percutaneous transhepatic cholecystostomy (PTC) tube, cholecysectomy ○ pancreatic infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, MRI abdo, abdominal drain or aspiration ○ typhilitis would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo ○ toxic megacolon would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo ○ urinary tract infection would be assumed to have at a urinalysis and urine culture ○ sinusitis would be assumed to have investigations at baseline ▪ At a maximum, a proportion of patients would receive at CT head ○ septic arthritis would be assumed to have an aspiration culture at a minimum ▪ At a maximum, a proportion of patients would receive an orthopedic surgery for I&D ○ PEG tube insertion would be assumed to be placed when 1st record on the daily data form of PEG tube utilization (Daily Form 4.2 of 3) ○ Tracheostomy insertion would be assumed to be placed when 1st record on the daily	

data form (Daily Form 4.1 of 3 – Mechanical airway in place today)	
Imputation of missing data • For those patients with missing data from a clinical outcomes perspective, multiple imputation methods will be utilized – including generalized estimating equations (GEEs) • For missing unit costs (which are not attainable from public jurisdiction databases or trial site-specific inquiries), we will utilize costing-ratio methodology	We will utilize standard multiple imputation methods to handle missing clinical outcome data, or costing-ratio methodology for missing unit costs

BAL = broncho-alveolar lavage; CDAD = C. Difficile-associated diarrhea; CT = computerized tomography; CXR = chest x-ray; ERCP = endoscopic retrograde cholangio-pancreatography; ICU = intensive care unit; I&D: irrigation & debridement; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia; VATS = video-assisted thorascopic surgery

Supplemental Table 4: E-PROSPECT Costing Manual

E-PROSPECT: The economic evaluation of PROSPECT (Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial)

Operations Manual

Costing Methodology and Definitions

Data Collection

Clinical Outcomes: Clinical data on every patient will be collected as part of PROSPECT. Site coordinators have already participated in the main clinical randomized controlled trial (RCT), and undergone intensive training session to review the methods and case report forms (CRFs) of the main trial. The Methods Centre at McMaster University will manage PROSPECT data, providing patient characteristics, tests, treatments, and outcomes (e.g., infections, adverse events, duration of stay in ICU and hospital, and mortality in ICU and hospital). We will obtain variable names from the Methods Centre at McMaster to associate them with costs.

Resource utilization: To determine the incremental cost of patients receiving probiotics compared to placebo (with usual care), the resources consumed by patients in PROSPECT will be collected. Enrolled patients are in the intensive care unit (ICU), and are randomized to receive probiotics or placebo, with daily follow-up to identify relevant outcomes. In determining incremental costs, only resources which differ between the two treatment groups need to be identified. However, because the resources that will differ are uncertain, the economic evaluation will be conducted alongside to the RCT as a sub-study, with all important resources being ascertained and analyzed. Once resources are identified, resource utilization and the unit costs of each item for each given patient needs to be calculated.

For purposes of a health economic evaluation, resources will be translated into monetary values. Resource utilization variables associated with the direct medical costs of critically ill patients include: (1) medications; (2) laboratory testing; (3) personnel; (4) radiology testing; (5) procedures/surgeries, and (6) complications/adverse clinical outcomes. Overhead costs include: (1) ICU costs and (2) ward costs. A comprehensive list of direct medical resource utilization elements associated with critically ill patients will be identified. Previous studies (Fowler et al. - Pilot) discovered that public and private-funded institutions have considerable variability in patient costing, and that line-by-line item costs are not available routinely. Many summary cost measures tend to “roll-up” individual items costs rather than listing them as unit costs, which would not allow for a linkage of costs and clinical events (the later measured as part of the PROSPECT CRFs).

This previously established cost-gathering methodology (Fowler et al. – Pilot) captures hospitalspecific line item costs, according to important variables that we anticipate will drive costs and possible cost-effectiveness. These “big ticket items” are determined by: (1) a systematic review (SR) of probiotics economic evaluations for preventing healthcare-associated infections (ventilator-associated pneumonia, *Clostridiodes difficile*-associated diarrhea, antibiotic-associated diarrhea) in hospitalized

patients (Lau 2019), (2) the PROSPECT CRFs, and (3) experts in healthcare-associated infections in the ICU. If additional costing and utilization information cannot be gleaned from these sources, then certain methodological assumptions (Table 4) will be made regarding resource utilization for potential routine utilization for specific diagnoses/complications.

Further to this, we will be conducting a pilot phase of unit cost acquisition at a sampling of sites to determine which unit costs can be feasibly obtained. It is possible that the pilot phase of this work may inform changes to this protocol, as well as the analysis of the economic evaluation. For example, if a unit cost for a particular line-item is deemed to be small and not a major driver of costs, then that line-item may be removed from the final analysis. The same would apply if a specific line-item has a low clinical incidence rate or no difference in clinical outcome/resource utilization between intervention and control groups, as little to no incremental difference in costs would exist between the two arms. Once the list of line-items has been pared down to those which are deemed to be major cost drivers, clinically relevant, but also feasible to obtain, this new line-item list will be surveyed across all sites.

Unit costs will be obtained from various sources including: (1) departments within participating hospitals, (2) provincial/state/country source databases. Costs conversion will involve collecting costs in their natural currency units from the participating center, and then converting to American dollars in the year of publication (2020). Discounting will not be applied for short-term (<1 year) time-horizon events.

Unit Costs

A unit cost differs from a charge:

- Costs are the expenses incurred by the hospital for the service/procedure rendered.
- Charge is the amount that hospital requires drug companies/researchers to pay for a service/procedure to be conducted at their hospital. A charge usually consists of the cost of performing the service/procedure plus a mark-up fee.
- Hospitals may have a charge-to-cost conversion for unit costs – which we will try to obtain.

Unit costs will be obtained by several methods:

1) Hospital budgets

Ideally, all costs would reflect expenses in the hospital budget. This information will be obtained from hospital financial departments if available. However, in most cases, unit costs are not available for reasons such as: item costs are presented in bulk quantity costs, or item costs are several years outdated, or prices cannot be disclosed due to agreement with suppliers.

2) Government reimbursement

If hospital budget costs are not available, costs will be obtained from government sources/databases. In public healthcare systems, the country's government is mostly accountable for reimbursements of services rendered. We will obtain unit costs from a government schedule of benefits, which delineate the reimbursement for each procedure or test by laboratories, hospitals and healthcare professionals. If the schedule of fees is unavailable or have restricted access, the information will be collected through contact with medical professionals (i.e. pharmacist, ICU manager, etc.) from PROSPECT-associated hospitals. In jurisdictions in which there is a mix of both private and public healthcare (i.e. US), the total private health

care fee (i.e. Medicare Benefits Schedule Book) or equivalent government medical benefits schedule may be used.

3) Charge to Cost Ratios

If costs cannot be acquired, the amount that a hospital charges for a procedure, either to patients or to investigators for clinical trials will be used where cost-to-charge ratios are available. We will use cost:charge ratios that relate to individual costs, as opposed to "rolled-up" ratios, as much as possible.

General Costing Procedures

The PROSPECT site investigators list (maintained by the McMaster Methods Centre) will be used to identify who to initially contact for costing information. An introductory e-mail will be sent to select site investigators (and to the research coordinator, if known) to inform them of E-PROSPECT and to request their assistance to obtain costing information from their site during the pilot phase of unit cost acquisition. If there is no response by the PROSPECT site investigators, individuals will be contacted 2 more times via telephone, email. If there is still no response, or if the site investigators decline to participate, the site's unit costs will be excluded from analysis. Once pilot phase testing is completed, the new line-item unit cost list will be sent to all sites for the remaining unit costs which could not be acquired from public databases.

The general procedure for initiating the costing exercise at each hospital will be as follows:

1. We will contact the PROSPECT site investigator and research coordinator to identify the most appropriate person to identify the requested costs.

2. We will contact these individuals, inform them of E-PROSPECT, and request the hospital-related costs. In some cases, PROSPECT site investigators may prefer to contact these individuals themselves. The e-mail (below) will be sent to contacts.

3. For each cost item, we will ask about the relevant person at the hospital who is most responsible for knowing/determining the hospital-specific cost (e.g. radiology, pharmacy, ICU personnel) will be contacted.

4. We will ask if a hospital specific cost exists for each variable.

5. We will determine if the cost is an actual cost, or "charge". If the item is a charge, a hospital line-item specific cost-to-charge ratio will be required.

6. If the cost is generalizable to a broader geography (health region laboratory cost, provincial physician reimbursement rate, etc.), then we will obtain these costs from the investigators and compare these to the hospital specific costs. Significant discrepancies will be further interrogated to determine whether the difference is real, and which best approximates actual cost (vs. charge). Notations will be made on the dataset and used for future decisions about which numbers to apply to the eventual economic analyses. The list of study variables, definitions, and documentation examples for sources of variable values is below.

Sample Communication to Identified Individuals at E-PROSPECT Sites

Dear colleague,

I am helping with the economic evaluation of the PROSPECT study (E-PROSPECT). We are in the process of gathering costing data on key variables and suspected drivers of cost from all sites involved in PROSPECT (in Canada, the US, and Saudi Arabia). The site principal investigator(s)/research coordinator(s) has passed on your contact information as an individual who could hopefully assist us with ***unit cost*** *collection for E-PROSPECT.*

Our goal primarily is:

To collect unit costs for specific items in PROSPECT, NOT for any patient-specific data.

We are looking for the unit costs to be listed in your **local currency** for this **year (2019)**.

A unit cost is defined as:

A **unit cost** is the **expenditure/cost** spent on **one unit** of a particular medication, diagnostic test, investigation, procedure, surgery or personnel in health care.

For example:

- For a specific antibiotic (i.e. ceftriaxone), we are looking for the unit cost for this medication
  - The specific cost (unit cost) at the particular dose (1 unit) that your institution pays for the medication *(*i.e. Ceftriaxone: $50.00 CDN per 1 gram of medication)
- For a specific diagnostic test (i.e. echocardiogram), we are looking for the unit cost per 1 test *(i*.e. transthoracic echocardiogram: $119.00 CDN per 1 echocardiogram)
- For a specific personnel (i.e. nurse), we are looking for the per diem (day) cost for that staff member *(*i.e. Nurse: $200.00 CDN per day)
- For overhead cost, we are looking for the per diem (day) cost for 1 day stay in the ICU and 1 day stay on the ward ○ *We request the per diem day cost broken down into its component parts (i.e. personnel, devices, etc.), as we will need to ensure that we do not double-count the cost of items*

- *Attached to this costing manual (and also in the data extraction spreadsheet) are key variables we are hoping to obtain from your site*
- *If either yourself, or someone else at your center is able to put us in touch with someone to contact at your site, that would be greatly appreciated.*
- *Sometimes there is a costing person attached to ICU or a costing/charging department. Sometimes we have found it necessary to track down someone in radiology, pharmacy, ICU, lab services, etc. Could you please put us on the right track with names/emails or by forwarding this request? - We would like to include your names in the publications arising from this work.*

Thanks very much for your help and continued support of PROSPECT.

Sincerely,

Dr. Vincent Lau, MD, FRCPC, McMaster HRM MSc(c)

Supervised by: Drs. Deborah J. Cook, Bram Rochwerg, Feng Xie, Jennie Johnstone and Rob Fowler E-PROSPECT COST LIST

Pharmacy Costs - Just Tell us Who to Contact: □

probiotics *(Lactobacillus rhamnosus GG)*

- antibiotics: ○ pipercillin-tazobactam ○ ceftriaxone ○ ceftazidime ○ azithromycin ○ vancomycin ○ metronidazole
  - ○ levofloxacin ○ imipenem ○ meropenem
  - ○ amoxicillin-clavulin ○ cefuroxime ○ linezolid ○ cefazolin ○ cloxacillin ○ ciprofloxacin ○ gentamicin ○ trimethoprim-sulfamethoxazole
- steroids ○ dexamethasone ○ methylprednisone ○ hydrocortisone ○ prednisone
- stress ulcer prophylaxis ○ cimetidine ○ ranitidine ○ famotidine ○ nizatidine ○ lansoprazole ○ dexlansoprazole ○ pantoprazole ○ esomeprazole ○ omeprazole ○ rabeprazole
- laxatives/motility agents ○ domperidone ○ metoclopramide ○ erythromycin ○ senna ○ dulcolax ○ golytely ○ glycerin
  - ○ lactulose ○ colace ○ citro-mag ○ PegLyte ○ pancreatic enzymes
  - ○ enema
- opiates ○ morphine ○ hydromorphone ○ demerol ○ fentanyl ○ oxycodone ○ percocets

<u>Clinical Laboratory Costs</u> - Just Tell us Who to Contact:

- complete blood count
- creatinine
- arterial blood gas
- lactate
- albumin
- blood cultures
- urine cultures
- sputum/tracheal aspirate/bronchoalveolar lavage cultures
- *C. difficile* polymerase chain reaction (PCR), toxin assays, ELISA, cell culture, LAMP
- other aerobic/anaerobic cultures ○ thoracentesis ○ paracentesis

<u>General ICU and Ward Costs/Personnel</u> - Just Tell us Who to Contact:

- most responsible physician ○ ICU ○ Hospital
- consultation physicians (general surgery, thoracic surgery, gastroenterology, infectious disease specialists, respirology)
- nurse

- pharmacist
- respiratory therapist
- physical therapist
- social worker
- ICU clerk
- ICU days (generic cost)
- ward days (generic cost)

Radiology Costs - Just Tell us Who to Contact:

- portable chest radiograph
- portable abdominal radiograph
- computerized tomography (CT) scan: chest, abdomen, pelvis, sinusitis, head
- MRI: head, chest, joint
- abdominal ultrasound

Procedural Costs - Just Tell us Who to Contact:

- central venous catheter, peripherally inserted central catheter, arterial lines
- chest tube
- naso- or oro-gastric tube
- percutaneous endoscopic gastrostomy (PEG) tube
- tube feed
- fiber
- protein supplement
- ventilator circuit changes
- endotracheal tubes (with or without subglottic suction)
- invasive ventilation (ventilator days) ○ heat moisture exchange ○ heated humidifier
- non-invasive positive pressure ventilation
- high-flow nasal cannula
- vasopressor/inotropic agents
- VAP prevention bundles ○ chlorhexidine usage ○ bacterial filters ○ oral decontamination ○ gut decontamination ○ oral antibiotic paste
- colonoscopy (cautery, epinephrine injection)
- echocardiograms (transthoracic/transesophageal)
- bronchoscopy
- thoracostomy
- tracheostomy
- interventional radiology drain
- intermittent hemodialysis
- peritoneal dialysis
- continuous renal replacement therapy
- fecal management device

Cost reimbursed by the governing authority to the primary physician for procedure that is rendered at a hospital. Costs often include a Professional component, and a Technical component.

The *professional component* consists of:

A. Providing clinical supervision, including approving, modifying and/or intervening in the performance of the procedure where appropriate, and quality control of all elements of the technical component of the procedure.
B. Performance of any clinical procedure associated with the diagnostic procedure which is not separately billable (e.g. injections which are an integral part of the study) and of any fluoroscopy.
C. Where appropriate, post-procedure monitoring, including intervening except where this constitutes a separately billable service.
D. Interpreting the results of the diagnostic procedure.
E. Providing premises for any aspect(s) of A and D that is(are) performed at a place other than the place in which the procedure is performed.

The *technical component* consists of:

A. Preparing the patient for the procedure.
B. Performing the diagnostic procedure or assisting in the performance of fluoroscopy.
C. Making arrangements for any appropriate follow-up care.
D. Providing records of the results of the procedure to the interpreting physician.
E. Discussion with, and providing information and advice to, the patient or patient's representative(s), whether by telephone or otherwise, on matters related to the service.
F. Preparing and transmitting a written, signed and dated interpretive report of the procedure to the referring physician.
G. Providing premises, equipment, supplies and personnel for all specific elements of the technical and professional components except for the premises for any aspect(s) of A and D of the professional component that is(are) not performed at the place in which the procedure is performed.

<u>Operative Costs</u> - Just Tell us Who to Contact:

- laparotomy (toxic megacolon, bowel perforation)
- colectomy
- thoracotomy
- open abdominal wound (vacuum-assisted closure (VAC) devices)
- surgeon
- surgical assistant
- anesthesiology
- nursing

<u>Definition of Variables, Source Documentation for Values</u>

NOTE THAT DEFINITIONS MAY DIFFER ACROSS JURISDICTIONS. PLEASE USE THE DEFINITIONS AS A GUIDELINE.

Drug costs

Unit cost to be paid by the hospital to the drug company as negotiated between the hospital and the drug company. The cost is usually found in the hospital drug formulary, or is known to the hospital pharmacy contact.

Resource Utilization and Unit Costs

Variable	Definition	Unit for costing determination (dose and route)	Unit cost	Source	Captured in PROSPECT CRF
Study-related drugs					
probiotics *(Lactobacillus rhamnosus GG)*	Live microorganisms which when administered in adequate amounts confer a health benefit on the host	1×10^{10} colony forming units (cfu)		iHealth/pharmacy contact (name, date)	Form 4.1 and 5
Antibiotics:					
pipercillintazobactam	Amino-penicillin antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
ceftriaxone	Third-generation cephalosporin antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
ceftazidime	Third-generation cephalosporin antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
azithromycin	Macrolide antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
vancomycin	Glycopeptide antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
metronidazole	Nitroimadazole antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
levofloxacin	Fluoroquinolone antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
imipenem	Carbapenem antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
meropenem	Carbapenem antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
amoxicillinclavulin	Amino-penicillin antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
cefuroxime	Second-generation cephalosporin antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
linezolid	Oxazolidinones			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
cefazolin	First-generation cephalosporin antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
cloxacillin	Amino-penicillin antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
ciprofloxacin	Fluoroquinolone antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1

□ gentamicin	Aminoglycoside antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
□ trimethoprimsulfamethoxazole	Dihydrofolate reductase inhibitor/sulfonamide antibiotic			E.g. hospital formulary pharmacy contact (name, date)	Form 7.1
Steroids:					
□ dexamethasone	Glucocorticoid steroid			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ methylprednisone	Glucocorticoid/mineralocorticoid steroid			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ hydrocortisone	Glucocorticoid/mineralocorticoid steroid			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ prednisone	Glucocorticoid/mineralocorticoid steroid			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
Stress ulcer prophylaxis:					
□ cimetidine	Histamine H2 receptor blocker gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ ranitidine	Histamine H2 receptor blocker gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ famotidine	Histamine H2 receptor blocker gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ nizatidine	Histamine H2 receptor blocker gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ lansoprazole	Proton pump inhibitor antacid gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ dexlansoprazole	Proton pump inhibitor gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ pantoprazole	Proton pump inhibitor gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ esomeprazole	Proton pump inhibitor gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ omeprazole	Proton pump inhibitor gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ rabeprazole	Proton pump inhibitor gastric acid suppressor			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
Laxatives/motility agents					
□ domperidone	Anti-dopamine (D2) receptor blocker anti-emetic			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ metoclopramide	Anti-dopamine (D2) receptor blocker anti-emetic			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2

□ erythromycin	Macrolide antibiotic/Motilin receptor agonist (increased gut motility)			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ senna	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ dulcolax	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ golytely	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ glycerin	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ lactulose	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ colace	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ citro-mag	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ PegLyte	Laxative			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ pancreatic	Laxative			E.g. hospital formulary	Form 4.2

enzymes				pharmacy contact (name, date)	
□ enema	Colonic irrigation			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
Opiates					
□ morphine	Mu-receptor opiate			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ hydromorphone	Mu-receptor opiate			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ demerol	Synthetic opiate (phenylpiperidine)			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ fentanyl	Synthetic opiate			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ oxycodone	Synthetic opiate			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
□ percocets	Synthetic opiate			E.g. hospital formulary pharmacy contact (name, date)	Form 4.2
Laboratory testing					
□ complete blood count	A complete blood count gives important information about the kinds and numbers of cells in the blood, especially red blood cells, white blood cells and platelets.	1 test		E.g. BC Health Guide Complete Blood Count (CBC): http://www.bchealthguide.org/kbase/topic/medtest/hw4260/descrip.htm	Form 4.1 & 14

□ creatinine	Creatinine tests measure the level of the waste product creatinine in your blood and urine.	1 test		E.g. BC Health Guide Creatinine and Creatinine Clearance http://www.bchealthguide.org/kbase/topic/medtest/hw4322/descrip.htm	Form 14
□ arterial blood gas	"An arterial blood gas (ABG) test measures the acidity (pH) and the levels of oxygen (PO2) and carbon dioxide (PCO2), bicarbonate (HCO3), and oxygen saturation in the blood."	1 test		E.g. BC Health Guide Arterial Blood Gases: http://www.bchealthguide.org/kbase/topic/medtest/hw2343/descrip.htm Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 9.2
□ lactate	"A lactic acid test is a blood test that measures the level of lactic acid made in the body. Most of it is made by muscle tissue and red blood cells. When the oxygen level in the body is normal, carbohydrate breaks down into water and carbon dioxide. When the oxygen level is low, carbohydrate breaks down for energy and makes lactic acid"	1 test		E.g. BC Health Guide Lactate: https://www.healthlinkbc.ca/medicaltests/hw7871 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 11.1 & 14
□ albumin	"Albumin is a protein that is produced in the liver and released into the blood. It helps prevent blood from leaking out of blood vessels, carries medicines and other substances through the blood, and is important for tissue growth and healing."	1 test		E.g. BC Health Guide Albumin: https://www.healthlinkbc.ca/health-topics/tv7859 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 14
□ blood cultures	"A blood culture is a test on a sample of blood to check for bacteria, a fungus, or sometimes viruses in the bloodstream. The test may be done if a doctor suspects a blood infection. A blood culture may help determine the specific organism causing an infection and select the appropriate	1 culture		E.g. BC Health Guide Blood Cultures: https://www.healthlinkbc.ca/healthtopics/stb117065 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B, 8.1 & 9.2 & 10
	antibiotic to treat it."				
□ urine cultures	"A urine culture is a test to find germs (such as bacteria) in the urine that can cause an infection. Urine in the bladder is normally sterile. This means it does not contain any bacteria or other organisms (such as fungi). But bacteria can enter the urethra and cause a urinary tract infection (UTI)."	1 culture		E.g. BC Health Guide Urine Cultures: https://www.healthlinkbc.ca/medicaltests/hw5973 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 12

□	sputum cultures	"Sputum is a thick fluid made in the lungs and in the airways leading to the lungs. A sputum culture is a test to find germs (such as bacteria or a fungus) that can cause an infection. A sample of sputum is added to a substance that promotes the growth of germs. If no germs grow, the culture is negative. If germs that can cause infection grow, the culture is positive. The type of germ may be identified using a microscope or chemical tests. Sometimes other tests are done to find the right medicine for treating the infection. This is called sensitivity testing."	1 culture		E.g. BC Health Guide Sputum Cultures: https://www.healthlinkbc.ca/medicaltests/hw5693 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 9
□	tracheal aspirate	See sputum cultures	1 culture		E.g. BC Health Guide Sputum Cultures: https://www.healthlinkbc.ca/medicaltests/hw5693 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 9
□	bronchoalveolar lavage cultures	Bronchoscopy is a procedure that allows your doctor to look at your airway through a thin viewing instrument called a bronchoscope. During a bronchoscopy, your doctor will examine your throat, larynx, trachea, and lower airways. (See sputum cultures)	1 culture		E.g. BC Health Guide Bronchoscopy/Sputum Cultures: https://www.healthlinkbc.ca/medicaltests/hw200474 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 9
□	*C. difficile* polymerase chain reaction (PCR)	*C. difficile*, also known as *C.diff,* are bacteria that live in the bowel of up to 7% of people without causing illness. Your intestines also normally contain many good bacteria that help you digest food and stay healthy. When antibiotics are taken to treat an illness, these good bacteria may be killed. *C.diff bacteria* are not killed by common antibiotics and continue to grow, which may cause you to become sick.	1 test		E.g. BC Health Guide C. Difficile: https://www.healthlinkbc.ca/healthlinkbcfiles/clostridium-difficile Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 14
□	*C. difficile* toxin assays	*C. diff* produces toxins that can cause damage to the cells in the intestines. The most common symptom of *C.diff infection* is diarrhea. In fact, it is the most frequent cause of infectious diarrhea in hospitals and health care facilities. *C. diff* infections may lead to serious illness.	1 test		E.g. BC Health Guide C. Difficile toxin assay: https://www.healthlinkbc.ca/healthlinkbcfiles/clostridium-difficile Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1,14
□	*C. difficile* ELISA (enzyme-linked immunosorbent	Antisera against Clostridium difficile toxin B were prepared in sheep and rabbit and were used in indirect	1 test		E.g. C. Difficile ELISA: https://www.ncbi.nlm.nih.gov/pubmed/2325114	Form 4.3, 4B , 8.1, 14

	assay)	and sandwich enzyme-linked immunosorbent assays (ELISA) for the detection of toxin B. Polyvinyl chloride and polystyrene microtitration plates were tested as solid phases for the assay. Both assays had a lower limit of detection for toxin B of 1 ng/ml. They were used to detect the presence of toxin B in 210 human faecal specimens and also in the culture supernatant fluids of C. difficile strains isolated from the faecal samples. There was a close correlation between the results of sandwich ELISA and those of cytotoxicity tests and isolation of C. difficile. Our sandwich ELISA method seems to be useful as a presumptive test for detection of C. difficile toxin B				
□	*C. difficile* cell culture	Cell culture cytotoxicity is performed by using a fibroblast cell line in a microtiter format read at 4 h, 24 h, and 48 h from a stool sample for C. Difficile.	1 test		E.g. C. Difficile cell culture https://www.ncbi.nlm.nih.gov/pubmed/10764962?dopt=Abstract	Form 4.3, 4B , 8.1, 14
□	*C. difficile* LAMP (loop mediated isothermal amplification)	*Clostridium difficile* infection (CDI) remains a diagnostic challenge for clinicians. More recently, loopmediated isothermal amplification (LAMP) has become readily available for the diagnosis of CDI, and many studies have investigated the usefulness of LAMP for rapid and accurate diagnosis of CDI.	1 test		E.g. Clostridium difficile LAMP: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624739/	Form 4.3, 4B , 8.1, 14
□	anaerobic cultures	A culture is a test to find germs (such as bacteria or a fungus) that can cause an infection. A sensitivity test checks to see what kind of medicine, such as an antibiotic, will work best to treat the illness or infection. For a culture, a sample of body fluid or tissue is added to a substance that promotes the growth of germs. If no germs grow, the culture is negative. If germs that can cause infection grow, the culture is positive. The type of germ may be identified using a microscope or chemical tests. Bacteria usually grow quickly in a culture (2 days), while other types of organisms, such as a fungus, can take longer. A culture and sensitivity test may be done on many different body fluids, such as urine, mucus, blood, pus, saliva, breast milk, spinal fluid, or discharge from the vagina or penis.	1 test		E.g. BC Health Guide Culture and Sensitivity: https://www.healthlinkbc.ca/healthtopics/stc123799 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 11

□ aerobic cultures	A culture is a test to find germs (such as bacteria or a fungus) that can cause an infection. A sensitivity test checks to see what kind of medicine, such as an antibiotic, will work best to treat the illness or infection. For a culture, a sample of body fluid or tissue is added to a	1 culture		E.g. BC Health Guide Culture and Sensitivity: https://www.healthlinkbc.ca/healthtopics/stc123799 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 11
	substance that promotes the growth of germs. If no germs grow, the culture is negative. If germs that can cause infection grow, the culture is positive. The type of germ may be identified using a microscope or chemical tests. Bacteria usually grow quickly in a culture (2 days), while other types of organisms, such as a fungus, can take longer.				
□ thoracentesis	Thoracentesis is a procedure to remove fluid from the space between the lungs and the chest wall called the pleural space. It is done with a needle (and sometimes a plastic catheter) inserted through the chest wall. Ultrasound pictures are often used to guide the placement of the needle. This pleural fluid may be sent to a lab to determine what may be causing the fluid to build up in the pleural space. Normally only a small amount of pleural fluid is present in the pleural space. A buildup of excess pleural fluid (pleural effusion) may be caused by many conditions, such as infection, inflammation, heart failure, or cancer. If a large amount of fluid is present, it may be hard to breathe. Fluid inside the pleural space may be found during a physical examination and is usually confirmed by a chest X-ray.	1 culture		E.g. BC Health Guide Thoracentesis: https://www.healthlinkbc.ca/medicaltests/hw233202 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 9
□ paracentesis	Paracentesis is a procedure to take out fluid that has collected in the belly (peritoneal fluid). This fluid buildup is called ascites. Ascites may be caused by infection, inflammation, an injury, or other conditions, such as cirrhosis or cancer. The fluid is taken out using a long, thin needle put through the belly. The fluid is sent to a lab and studied to find the cause of the fluid buildup. Paracentesis also may be done to take the fluid out to relieve belly pressure or pain in people with cancer or cirrhosis.	1 culture		E.g. BC Health Guide Paracentesis: https://www.healthlinkbc.ca/medicaltests/hw198220 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3, 4B , 8.1, 11
Personnel (*per diem or hourly wage)*					

□ ICU	First day of Comprehensive Care rendered by "an Intensive Care physician who provides both Critical Care and Ventilation Support to patients in the Intensive Care Area. The service includes initial consultation and assessment and subsequent examinations, often including comprehensive critical care procedures such as endotracheal intubation, tracheal toilet, artificial ventilation and all necessary measures for respiratory support, emergency resuscitation, insertion of intravenous lines, cutdowns, intraosseous infusion, arterial and/or venous catheters pressure infusion set and pharmacological agents, insertion	First episode/first day Daily rate (Day 2-30)		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 3

	of C.V.P lines, defibrillation, cardioversion and usual resuscitative measures, insertion of urinary catheters and nasogastric intubation with or without anaesthesia, securing and interpretation of blood gases and laboratory tests, oximetry, transcutaneous blood gases, intracranial pressure monitoring interpretation and assessment when indicated (excluding insertion of I.C.P. measuring device)." Fee that is reimbursed to an Intensive Care physician for Comprehensive Care as defined above for a patient's hospitalization from day 2 to 30 inclusive.				
□ Ward physician	"Admission assessment is a general assessment rendered to a patient on admission" to a longterm care institution: nonemergency in-patient services, including chronic care hospitals Fee that is reimbursed to a physician for services to a patient in chronic care or convalescent hospital during the "First 4 subsequent visits… per month". "A subsequent visit is any routine assessment following the patient's admission to a long-term care institution." Fee that is reimbursed to the Most Responsible Physician at the day of discharge for rendering a subsequent visit. Completion of discharge summary by the physician within 48 hours of discharge, arrangement for followup of patient and prescription of	First episode/first day. Daily rate. Last day.		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 3

□	consultation physicians (i.e. general surgery, thoracic surgery, gastroenterology, infectious disease specialists, respirology)	"Admission assessment is a general assessment rendered to a patient on admission" to a longterm care institution: nonemergency in-patient services, including chronic care hospitals	First episode/first day.		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 3
□	nursing	Provide direct nursing care to patients, deliver health education programs and provide consultative services regarding issues relevant to the practice of nursing.	Hourly wage		E.g. Service Canada- Labour Market Information- Job Descriptions. Similar definitions exist for other jurisdictions. http://www.labourmarketinformation.ca/standard.asp?ppid=82&lcode=E&prov=1&gaid=1&occ=3214&job=&search_key=1&search_type=&employer_potential=&new_search= Similar definitions exist for other jurisdictions.	Form 3
□	pharmacist	Compound and dispense prescribed pharmaceuticals and provide consultative services to both clients and health care providers.	Hourly wage		E.g. Service Canada- Labour Market Information- Job Descriptions. Similar definitions exist for other jurisdictions.	Form 3

					http://www.labourmarketinformation.ca/standard.asp?ppid=82&lcode=E&prov=1&gaid=1&occ=3214&job=&search_key=1&search_type=&employer_potential=&new_search= Similar definitions exist for other jurisdictions.	
□	respiratory therapist	Respiratory therapists assist physicians in the diagnosis, treatment and care of patients with respiratory and cardiopulmonary disorders.	Hourly wage		E.g. Service Canada- Labour Market Information- Job Descriptions. Similar definitions exist for other jurisdictions. http://www.labourmarketinformation.ca/standard.asp?ppid=82&lcode=E&prov=1&gaid=1&occ=3214&job=&search_key=1&search_type=&employer_potential=&new_search= Similar definitions exist for other jurisdictions.	Form 3

□ physical therapist	Assess patients and plan and carry out individually designed treatment programs to maintain,	Hourly wage		E.g. Service Canada- Labour Market Information- Job Descriptions. Similar definitions exist for other jurisdictions. http://www.labourmarketinformation.ca/standard.asp?ppid=82&lcode=E&prov=1&gaid=1&occ=3214&job=&search_key=1&search_type=&employer_potential=&new_search= Similar definitions exist for other jurisdictions.	Form 3
□ social work	Help individuals, couples, families, groups, communities and organizations develop the skills and resources they need to enhance social functioning and provide counseling, therapy and referral to other supportive social services	Hourly wage		E.g. Service Canada- Labour Market Information- Job Descriptions. Similar definitions exist for other jurisdictions. http://www.labourmarketinformation.ca/standard.asp?ppid=82&lcode=E&prov=1&gaid=1&occ=3214&job=&search_key=1&search_type=&employer_potential=&new_search= Similar definitions exist for other jurisdictions.	Form 3
□ unit clerk/clerical worker	Medical secretaries perform a variety of secretarial and administrative duties in doctor's offices, hospitals, medical clinics and other medical settings.	Hourly wage		E.g. Service Canada- Labour Market Information- Job Descriptions. Similar definitions exist for other jurisdictions. http://www.labourmarketinformation.ca/standard.asp?ppid=82&lcode=E&prov=1&gaid=1&occ=3214&job=&search_key=1&search_type=&employer_potential=&new_search= Similar definitions exist for other jurisdictions.	
Radiology					
□ portable chest or abdominal radiographs	The chest/abdominal x-ray, performed portably at the patient's bedside, in the ICU or ward, usually performed as one film, in the anterior-posterior position.	1 test		E.g. Chest X-ray (Radiography): http://www.radiologyinfo.org/en/info.cfm?pg=chestrad&bhcp=1	Form 9, 11, 14
□ computerized tomography (CT) scan: chest, abdomen, pelvis, sinusitis, head	Computed tomography of the chest, abdomen, pelvis or sinuses/head, to diagnose infections	1 test		E.g. Radiology Info (Web site developed and funded by: American College of Radiology (ACR) and Radiological Society of North America (RSNA)) CT Angiography (CTA): http://www.radiologyinfo.org/en/info.cfm?pg=angioct	Form 9, 11, 14, 20

□ MRI: head, chest, joint	Magnetic resonance imaging (MRI) is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures that are inside the body. During the MRI test (also called an MRI scan), you usually lie on your back on a table that is part of the MRI scanner. Your head, chest, and arms may be held with straps to help you stay still. The table will then slide into the round opening of the magnet.	1 test		E.g. BC Health Guide MRI: https://www.healthlinkbc.ca/healthtopics/zm6243 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 20
□ abdominal ultrasound	An abdominal ultrasound takes pictures of the organs and other structures in your upper belly. It uses sound waves to show images on a screen.	1 test		E.g. BC Health Guide Abdominal Ultrasound: https://www.healthlinkbc.ca/medicaltests/hw1430 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 11, 20
Procedural costs:					
□ central venous catheter	Insertion of an intravenous catheter for administration of fluid or measurement of pressures, to a central vein (internal jugular, femoral, subclavian sites).	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 10
□ peripherally inserted central catheter	Insertion of an intravenous catheter for administration of fluid or measurement of pressures, to a peripheral vein	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 10
□ dialysis catheter	See central venous catheter	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 10
□ arterial lines	Insertion of an intravenous catheter for administration of fluid or measurement of pressures, to a artery	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 10
□ chest tube	Thoracostomy tube for drainage of pleural cavity	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 9.1
□ naso- or oro-gastric tube	Feeding tube (inserted through nose or mouth)	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care	Form 4.2

				Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	

□ percutaneous endoscopic gastrostomy (PEG) tube	Feeding tube inserted into through the abdominal wall into the stomach	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 4.2
□ tube feed	Liquid enteral nutrition administered through a feeding tube	1 item and/or 1 procedure		E.g. hospital formulary pharmacy contact (name, date) Similar definitions exist for other jurisdictions.	Form 4.2
□ fiber	Fibre includes all parts of plant foods that your body can't digest or absorb. Fibre is also known as roughage or bulk. Insoluble fibre helps promote regularity and a healthy digestive system. You get this type of fibre from wheat bran, whole grains, and some vegetables. Soluble fibre helps lower blood cholesterol levels and control blood sugar levels. You get this type of fibre from oats, barley, psyllium, oranges, dried beans and lentils. A high fibre diet may also help prevent colon cancer. Eating high fibre foods may help you feel full for a longer time, which helps with appetite and weight control.	1 item and/or 1 procedure		E.g. hospital formulary pharmacy contact (name, date) Similar definitions exist for other jurisdictions.	Form 4.2
□ protein supplement	Protein is composed of various types of amino acids, provides the raw material for muscle construction and repair, as well as playing an important role in the immune system, the endocrine (hormone production) system, and the transmission of nerve impulses throughout the nervous system. A supplement is any addition to an patient's regular diet to achieve a particular nutritional goal; a supplement may be a natural or a synthetic product. Supplements are available in fluid, powder, and solid food formulations.	1 item and/or 1 procedure		E.g. hospital formulary pharmacy contact (name, date) Similar definitions exist for other jurisdictions.	Form 4.2
□ ventilator circuit changes	Ventilator circuit refers to the tubing that connects the ventilator to the patient, as well as any devices that might be connected to the circuit. Routine changes of this circuit vary from jurisdiction to jurisdiction	1 item and/or 1 procedure		https://www.ncbi.nlm.nih.gov/pubmed/20406515 E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	PROSPECT Site Information
□ endotracheal tubes (with subglottic suction)	An endotracheal tube is a flexible plastic tube that is placed through the mouth into the trachea (windpipe) to help a patient breathe. The endotracheal tube is then connected to a ventilator, which delivers oxygen to the lungs Subglottic suctioning capabilities help remove secretions below the glottis, and help reduce ventilatorassociated pneumonia	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 3, 4.1

endotracheal tubes (without subglottic suction)	An endotracheal tube is a flexible plastic tube that is placed through the mouth into the trachea (windpipe) to help a patient breathe. The endotracheal tube is	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist	Form 3, 4.1
	then connected to a ventilator, which delivers oxygen to the lungs. Some tubes do not have subglottic suctioning capabilities			for other jurisdictions.	
invasive ventilation (ventilator days)	Invasive mechanical ventilation can become a lifesaving intervention for your patients with respiratory and breathing difficulties. The term “invasive” is used if it involves any instrument penetrating via the mouth (such as an endotracheal tube), nose, or the skin (such as a tracheostomy tube through a stoma, a surgically-created hole in the windpipe) to serve as an artificial airway. The objectives of mechanical ventilation are primarily to provide oxygen, remove carbon dioxide, decrease the work of breathing and reverse lifethreatening conditions such as hypoxemia, or insufficient oxygenation of arterial blood, and acute progressive respiratory acidosis, or build-up of carbon dioxide in the blood	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 3, 4.1
heat moisture exchange	Heat and Moisture Exchangers (HME) are devices used in mechanically ventilated patients intended to help prevent complications due to "drying of the respiratory mucosa, such as mucus plugging and endotracheal tube (ETT) occlusion." HMEs are one type of commercial humidification system, which also include non-heated-wire humidifiers and heated-wire humidifiers.	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	PROSPECT Site Information
heated humidifier	Heated humidifiers or heated breathing circuits are typically a sealed heated wire within one limb of the breathing circuit. Sterile water is introduced into the circuit and the servomechanism controlled heater maintains temperature. These devices are prone to hazards, such as overheating, condensation, changes in the compressible volume of the circuit, leaks in the tubing, and obstruction, if they are not connected correctly.	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	PROSPECT Site Information

□ non-invasive positive pressure ventilation	Noninvasive ventilation (NIV) refers to the administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube). Noninvasive positive pressure ventilation (NIPPV) assists a person in taking a full breath and helps to maintain an adequate oxygen supply to the body. NIPPV provides ventilatory support to a person through the upper airways	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.	Form 4.1
□ high-flow nasal cannula	High-flow nasal cannula (HFNC) therapy is an oxygen supply system capable of delivering up to 100% humidified and heated oxygen at a flow rate of up to 60 liters per minute	1 item and/or 1 procedure		E.g. Ministry of Health and Long Term Care Schedule of Benefits: Physician Services Similar definitions exist for other jurisdictions.0	Form 4.1
Vasopressor agents					
□ norepinephrine	norepinephrine (vasopressor agent: primarily alpha receptor agonist with some beta activity) that is given continuously as a diluted liquid	Per microgram or milligram		E.g. hospital formulary pharmacy contact (name, date)	Form 4.1
□ vasopressin	vasopressin (vasopressin receptor agonist) that is given continuously as a diluted liquid	Per microgram or milligram		E.g. hospital formulary pharmacy contact (name, date)	Form 4.1
□ phenylephrine	phenylephrine (primarily alpha receptor agonist) that is given continuously as a diluted liquid	Per microgram or milligram		E.g. hospital formulary pharmacy contact (name, date)	Form 4.1
Inotropic agents					
□ epinephrine	epinephrine (both alpha and beta agonist) that is given continuously as a diluted liquid	Per microgram or milligram		E.g. hospital formulary pharmacy contact (name, date)	Form 4.1
□ dobutamine	dobutamine (primarily beta agonist) that is given continuously as a diluted liquid	Per microgram or milligram		E.g. hospital formulary pharmacy contact (name, date)	Form 4.1
□ milrinone	milrinone (phosphodiesterase inhibitor) that is given continuously as a diluted liquid	Per microgram or milligram		E.g. hospital formulary pharmacy contact (name, date)	Form 4.1
□ dopamine	dopamine (primarily beta agonist, with some alpha activity) that is given continuously as a diluted liquid	Per microgram or milligram		E.g. hospital formulary pharmacy contact (name, date)	Form 4.1
VAP prevention bundles					
○ chlorhexidine usage	chlorhexidine oral washes (site specific)	1 item/1 procedure		E.g. hospital formulary pharmacy contact (name, date)	PROSPECT Site Information
○ bacterial filters	bacterial filters (site specific)	1 item/1 procedure		E.g. hospital formulary pharmacy contact (name, date)	PROSPECT Site Information
○ oral decontamination	oral decontamination (site specific	1 item/1 procedure		E.g. hospital formulary pharmacy contact (name, date)	PROSPECT Site Information
○ gut decontamination	Gut decontamination (site specific)	1 item/1 procedure		E.g. hospital formulary pharmacy contact (name, date)	PROSPECT Site Information

○	oral antibiotic paste	oral antibiotic paste (site specific)	1 item/1 procedure		E.g. hospital formulary pharmacy contact (name, date)	PROSPECT Site Information
□	colonoscopy (cautery, epinephrine injection)	A colonoscopy is an examination of a patient's large intestine (colon and rectum), often to find areas of inflammation or bleeding. using a colonoscope with fiber optic visualization, performed usually in the ICU, occasionally in the endoscopy suite of a hospital."	1 item/1 procedure		E.g. BC Health Guide Colonoscopy: http://www.bchealthguide.org/kbase/topic/medtest/hw209694/descrip.ht m Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 14
□	transesophageal echocardiograms	In a transesophageal echocardiogram, a transducer is inserted through the mouth and down the throat into the esophagus. High-pitched sound waves (ultrasound) are sent through the transducer to produce an image of the heart and sometimes the aorta. This method allows a clear view of the valves and their ability to function. It provides a better view of heart valves than a standard transthoracic echocardiogram, but the procedure is more complicated	1 item/1 procedure		E.g. BC Health Guide Transesophageal echocardiogram: https://www.healthlinkbc.ca/healthtopics/stt11675 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 8, 20
□	transthoracic echocardiograms	An echocardiogram (also called an echo) is a type of ultrasound test that uses high-pitched sound waves that are sent through a device called a transducer. The device picks up echoes of the sound waves as they bounce off	1 item/1 procedure		E.g. BC Health Guide Echocardiograms: https://www.healthlinkbc.ca/medicaltests/hw212692 Ministry of Health and Long Term Care	Form 8, 20

		the different parts of your heart. These echoes are turned into moving pictures of your heart that can be seen on a video screen.			Schedule of Benefits: Laboratory Services	
□	bronchoscopy	A bronchoscopy examines the patient's airway with a flexible fiberoptic bronchoscope, to determine if there may be an infection, obstruction due to secretions, a mass	1 item/1 procedure		E.g. BC Health Guide Bronchoscopy: http://www.bchealthguide.org/kbase/topic/medtest/hw200474/descrip.htm Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 8, 9
□	thoracostomy	After lung surgery, one or more chest tubes are used to drain fluid and blood out of the chest cavity. The chest tubes also help the lungs refill with air.	1 procedure		E.g. BC Health Guide Chest Tube: https://www.healthlinkbc.ca/healthtopics/zm2679 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 8, 9

□ tracheostomy	Tracheostomy is surgery that is sometimes used to treat obstructive sleep apnea (OSA), failure to wean from ventilator or pulmonary toilet. In this surgery, the surgeon creates a permanent opening in the neck to the windpipe (trachea). He or she then puts a tube into the opening to let air in.	1 procedure		E.g. BC Health Guide Tracheotomy: https://www.healthlinkbc.ca/healthtopics/hw49093 Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.1
□ interventional radiology drain	Centesis is a procedure to take out fluid that has collected in a cavity The fluid is taken out using a long, thin needle put through the belly. The fluid is sent to a lab and studied to find the cause of the fluid buildup. Paracentesis can also leave a drain	1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 9
□ intermittent hemodialysis	Dialysis is a mechanical process that performs the work of healthy kidneys. Hemodialysis uses a manmade membrane (dialyzer) to remove wastes and extra fluid from the blood. It also restores the proper balance of certain minerals in the blood (electrolytes). The fluid used to filter or clean the blood is called dialysate. Hemodialysis is usually done in a hospital or dialysis centre. Before dialysis can begin, the doctor has to create a dialysis access. In hemodialysis, the access is the place where the dialysis needles are inserted, to carry the blood to and from the dialysis machine. For the best access, the doctor builds a connection, called a fistula, between an artery and a vein in the forearm. Or the doctor uses a tube called a graft to connect the artery and a vein. Sometimes a plastic tube (central venous catheter) is placed in the neck.	1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 4.1
□ continuous renal replacement therapy	Continuous veno-venous haemodiafiltration	1 item/1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 4.1
□ peritoneal dialysis	Peritoneal dialysis through abdominal cannulae	1 item/1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 4.1
□ fecal management device	Flexiseal device for fecal management	1 item/1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 4.3

□ fecal transplant	*Clostridium difficile* colitis (or *C. difficile* colitis) is inflammation of the large intestine (colon) caused by a certain type of bacteria (*Clostridium difficile*). It sometimes occurs after a hospital stay or antibiotic treatment. Symptoms (which can be mild or severe) include stomach cramps, diarrhea, nausea, vomiting, and fever. The first step in treatment for *C. difficile* colitis is to stop taking the antibiotics that caused the infection, if possible. Treatment also may include taking an antibiotic that specifically kills *C. difficile*. You may get a medicine called a bile salt binder (such as cholestyramine) that can help control the diarrhea. And probiotics, which are bacteria that help keep the natural balance of organisms (microflora) in the intestines, may be helpful for people who have repeated *C. difficile* infections. In some cases, a fecal transplant can be done that restores good bacteria to the colon and helps get rid of the *C. difficile* infection.	1 procedure		E.g. BC Health Guide Fecal Transplant: http://www.bchealthguide.org/kbase/topic/medtest/hw200474/descrip.htm Ministry of Health and Long Term Care Schedule of Benefits: Laboratory Services	Form 4.3
Operative costs					
□ laparotomy (toxic megacolon, bowel perforation)	"Laparotomy is a surgical procedure that allows the surgeon to see and inspect the abdominal cavity for structural problems. This encompasses the surgeon fee; separate costs include the time for other operating room personnel, including nurses (often 2), an assistant physician, and overhead costs for the operating room (cleaning, power, etc.), captured variably at each hospital.	1 procedure		E.g. BC Health Guide Surgery for laparotomy: http://www.bchealthguide.org/kbase/topic/detail/surgical/tv2567/detail.htm	Form 14
□ colectomy	Toxic megacolon is a rare but dangerous condition that occurs when the colon swells to many times its normal size. It is usually a complication of an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease. Severe inflammation and ulceration can weaken muscles in the colon, causing the colon to swell. Symptoms may include a swollen belly, abdominal pain or tenderness, rapid heartbeat, or fever. Over time, holes	1 procedure		E.g. BC Health Guide Toxic megacolon: https://www.healthlinkbc.ca/health-topics/tb1915 Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 14

	(perforations) may form in the colon, and stool may spill into the abdominal cavity, causing a serious infection. This can be lifethreatening. Toxic megacolon is an emergency that requires immediate medical treatment to prevent dehydration and shock. Surgery may be needed to remove all or part of the colon (colectomy).				
□ thoracotomy	"one or more chest tubes are used to drain fluid and blood out of the chest cavity. The chest tubes also help the lungs refill with air."	1 procedure		E.g. BC Health Guide Chest tube: https://www.healthlinkbc.ca/healthtopics/zm2679 Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 9.1
□ open abdominal wound (vacuumassisted closure (VAC) devices)	Negative-pressure wound therapy (sometimes called "vacuum-assisted closure"). A sterile sponge or a special gauze that fights germs is placed in the sore. It's covered with a sticky bandage that does not allow any air in. The small vacuum is then turned on and kept on at all times until the next treatment. The vacuum pulls drainage from the wound and gently pulls the blood supply close to the surface of the sore. This brings nutrients to the sore and helps new tissue grow.	1 procedure		E.g. BC Health Guide Negative-pressure wound therapy: https://www.healthlinkbc.ca/healthtopics/abp5591 Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 14
□ surgeon	"Laparotomy is a surgical procedure that allows the surgeon to see and inspect the abdominal cavity for structural problems. This encompasses the surgeon fee; separate costs include the time for other operating room personnel, including nurses (often 2), an assistant physician, and overhead costs for the operating room (cleaning, power, etc.), captured variably at each hospital.	1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 4.1, 14

□ surgical assistant	See above in Laparotomy-surgical fee; Assistance at surgery include: a) Preparing or supervising preparation of the patient for the procedure b) Performing the procedure by any method, or assisting another physician in the performance of the procedure(s), assisting with carrying out of all recovery room procedures and transfer of the patient to the recovery room, and any ongoing monitoring and detention rendered during the immediate post-operative and recovery period, when indicated. c) Making arrangements for any related assessments, procedures, or therapy	1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 4.1, 14

	(including obtaining any specimens from the patient) and/or interpreting results. d) When medically indicated, monitoring the condition of the patient for post-procedure follow-up until the first post-operative visit. e) Discussion with and providing any advice and information, including prescribing therapy to the patient or the patient's representative(s), whether by telephone or otherwise, on matters related to the service Providing premises, equipment, supplies and personnel for services for any aspect(s) of a, c, d and e that is (are) performed in a place other than the place in which the surgical procedure is performed.				
□ anesthesiology	See above in Laparotomy- surgical fee; the anesthesia component including pre-operative assessment of the patient, anesthesia during the procedure and post-operative care until the patient is discharged back to the care of the next responsible physician (e.g. the intensive care physician or surgeon)	1 procedure		E.g. Ontario Ministry of Health and Long Term Care Schedule of Benefits: Physician Services. Similar definitions exist for other jurisdictions.	Form 4.1, 14
□ nursing	See above in Laparotomy-surgical fee; nurses assist surgery.	Per hour For 1 procedure		E.g. as defined at hospital level and associated costs of nursing per hour or procedure in the operating room	Form 4.1, 14
Overhead costs					

□ ICU days	The definition for the ICU where the most intensive life-supporting care can be provided. In the Ontario context, ICU's are designated Level III (all levels of cardiac and respiratory and other organ life support can be provided; nursing:patient ratio is usually 1:1 or 1:2); Level II (often patients can receive intravenous vasoactive medications, and occasionally have endotracheal intubation, but not mechanical ventilation; nursing ration is often 1:2–4); Level I ICU (can provide respiratory or cardiographic monitoring, possibly an arterial blood pressure or central venous catheter, but not generally intravenous vasoactive medications; nursing ratio often 1:3–4) - We will require the cost breakdown of component parts of the ICU stay (as to prevent double-counting of items)	1 day		E.g. critical care directorate web site of jurisdiction	Form 3, 4, 17, 18
□ ward days	General in-patient ward bed in acute care hospital - We will require the cost breakdown of component parts of the ICU stay (as to prevent double-counting of items)	1 day		E.g. Ontario ministry of health and long-term care	Form 3, 4, 4B 17, 18

CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; ELISA = enzyme-linked immunosorbent assay; IABP = intra-aortic balloon pump; ICU = intensive care unit; LAMP = loop-mediated isothermal amplification; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; V-A = venous-arterial; V-V = veno-venous; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia;

Supplemental Table 5: CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4-5
		Present the study question and its relevance for or practice decisions.	Page 4-5 health policy
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, Table1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 5, 8
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not applicable
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable

Section/item	Item No	Recommendation	Reported on page No
Estimating resources and costs	13°	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 5-6
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 5-7
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 5-7
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Page 5-7
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Not applicable
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 7
Discussion			

Study findings, describe how they reached. Discuss generalizability of the knowledge.		limitations, 22 Summarise key study findings and generalizability, and support the conclusions limitations current knowledge and the findings and how the findings fit with current	Page 7
Other			
Source of funding	23	Describe how the study was funded and the role of	Page 9
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 5-7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Not applicable
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 6-7

Section/item	Item No	Recommendation	Reported on page No
		the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist