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