Appendix 1: Objectives, Outcomes, Hypothesis and Methods of Analysis

Objectives	Outcomes	Hypothesis	Methods of Analysis
1) **Primary:** To compare the effects of *Lactobacillus rhamnosus* GG versus placebo on:	Ventilator-associated pneumonia (VAP)	*Lactobacillus rhamnosus* GG will reduce the risk of the primary outcome	Cox proportional hazards
2) **Secondary:** To compare the effects of *Lactobacillus rhamnosus* GG versus placebo on:	a) Early VAP, late VAP, post-ventilation ICU-acquired pneumonia, and a composite of all three.	*Lactobacillus rhamnosus* GG will reduce the risk	Cox proportional hazards
	b) Clostridium difficile	*Lactobacillus rhamnosus* GG will reduce the risk	Cox proportional hazards
	c) Any infection acquired during the ICU stay	*Lactobacillus rhamnosus* GG will reduce the risk	Cox proportional hazards
	d) Diarrhea in the ICU	*Lactobacillus rhamnosus* GG will reduce the risk	Cox proportional hazards
	e) Antibiotic-associated diarrhea	*Lactobacillus rhamnosus* GG will reduce the risk	Cox proportional hazards
	f) Antimicrobial use	*Lactobacillus rhamnosus* GG will reduce the risk	Independent samples paired t-test or Wilcoxon rank sum test
	g) Duration of mechanical ventilation, ICU stay and hospital stay	*Lactobacillus rhamnosus* GG will have no effect	Independent samples paired t-test or Wilcoxon rank sum test
	h) ICU mortality and hospital mortality	*Lactobacillus rhamnosus* GG will have no effect	Cox proportional hazards
	i) Serious adverse events	*Lactobacillus rhamnosus* GG will have no effect	Cox proportional hazards
3) **Sensitivity Analyses:** i. Compare proportion of patients with VAP in the two groups.	VAP	Results remain robust	i. Mantel-Haenszel Chi square test ii. Competing risk

ii. Check for competing risk of death iii. Efficacy analysis iv. Include all VAP events that occur after the day of randomization				analysis iii. Cox proportional hazards iv. Cox proportional hazards
4) **Subgroup Analyses:** i. Medical vs surgical vs trauma patients ii. >75 years vs 65 – 75 years vs <65 years old iii. Frail patients versus not frail patients iv. Antibiotics prior to randomization vs no antibiotics prior to randomization v. Pneumonia at baseline vs no pneumonia	VAP	Treatment effects may be attenuated in one group compared to another group (see text for details)	Cox proportional hazards with interaction test between each subgroup variable and treatment group evaluating the credibility of subgroup findings using our 11 previously published criteria [60]

Legend for Appendix 1: In all analyses, results will be expressed as estimate of effect, corresponding 95% and associated p-values. All tests will be two-sided using alpha = 0.05 level of significance in accordance with a superiority hypotheses.