Study Synopsis

Protocol Title	BALANCE+: A Platform Trial for Gram Negative Bloodstream Infections
Protocol Number	
Study Design and Phase	Perpetual multiple domain randomized controlled platform trial
Setting	International, multi-centre
Sample Size – BALANCE+ vanguard	The initial vanguard phase will target 72 patients for most domains
Sample size – BALANCE+ main platform	Successful domains will transition into the BALANCE + perpetual platform trial, which will have no fixed sample size
Platform Entry Criteria	*Inclusion criteria:* • admitted to a participating hospital • positive blood culture with Gram negative (GN) bacterium *Exclusion criteria:* • patient's goals of care are for palliation with no active treatment • moribund patient, not expected to survive > 72 hours There are additional domain-specific inclusion/exclusion criteria
Domains • **intervention arms**	De-escalation versus no de-escalation domain • No de-escalation ○ continue on the same empiric GN antibiotic(s) being used prior to blood culture finalization ○ companion antibiotics in a combination regimen (eg, vancomycin, azithromycin, aminoglycoside or metronidazole) can be discontinued at discretion of clinical team ○ if patient has a syndrome requiring prolonged duration (> 14 days) de-escalation is allowable after day 14 • De-escalation ○ empiric GN antibiotic(s) switched to narrower spectrum agent to which the blood culture isolate is susceptible (within 24 hours) ○ companion antibiotics in a combination regimen can be discontinued at discretion of clinical team (and will be encouraged to do so in this arm if not needed for another indication) Oral beta-lactam versus non beta-lactam domain • Non-beta-lactam arm: an oral fluoroquinolone (ciprofloxacin, moxifloxacin or levofloxacin) or trimethoprim-sulfamethoxazole

	• Beta-lactam arm: an oral beta-lactam agent including, but not limited to, amoxicillin, amoxicillin-clavulanate, cephalexin, cefadroxil, or cefixime Central vascular catheter retention versus replacement domain • Central vascular catheter retention arm: original line retained until non-functional, or no longer needed • Central vascular catheter replacement arm: replace the vascular catheter as soon as possible and within a maximum of 72 hours from blood culture finalization Low-risk AmpC domain • Cephalosporin arm: participants will be treated with ceftriaxone (at standard doses) during intravenous treatment, with oral step-down allowed to any susceptible agent • Carbapenem arm: participants will be treated with a carbapenem (at standard doses) during intravenous treatment, with oral step-down allowed to any susceptible agent Follow-up blood culture domain • Follow-up blood culture arm: participants will undergo routine repeat blood culture collection (at least one blood culture set) 4±1d from the calendar date of the index positive blood culture collection • No follow-up blood culture arm: participants will undergo no *routine* repeat blood culture collection between 4±1d from the calendar date of the index positive blood culture collection
Primary Feasibility Outcomes of BALANCE+ vanguard	• Domain-specific recruitment rate • Domain-specific protocol adherence
Primary Outcome of BALANCE+ domains	De-escalation versus no de-escalation domain • Patient-centered, ordinal Desirability of Outcome Ranking (DOOR) outcome: (dead at 90 days) < (alive at 90 days with reinfection and readmission) < (alive at 90 days with reinfection or readmission) < (alive at 90 days with neither reinfection nor readmission) • tie-breaker within ordinal levels: new antimicrobial resistance (AMR) colonization or infection from routine cultures Oral beta-lactam versus non beta-lactam domain • ordinal DOOR outcome: (dead at 90 days) < (alive at 90 days with reinfection and readmission) < (alive at 90 days with reinfection or readmission) < (alive at 90 days with neither reinfection nor readmission)

	• tie-breaker within ordinal levels: new AMR colonization or infection from routine cultures Central vascular catheter retention versus replacement domain • ordinal DOOR outcome: (dead at 90 days) < (alive at 90 days with reinfection and readmission) < (alive at 90 days with reinfection or readmission) < (alive at 90 days with neither reinfection nor readmission) • no tie-breaker Low-risk AmpC domain • ordinal DOOR outcome: (dead at 90 days) < (alive at 90 days with reinfection and readmission) < (alive at 90 days with reinfection or readmission) < (alive at 90 days with neither reinfection nor readmission) • tie-breaker within ordinal levels: new AMR colonization or infection from routine cultures Follow-up blood culture domain • ordinal DOOR outcome: (dead at 90 days) < (alive at 90 days with reinfection and readmission) < (alive at 90 days with reinfection or readmission) < (alive at 90 days with neither reinfection nor readmission) • no tie-breaker
Secondary Outcomes of BALANCE+	• 90-day mortality • 90-day reinfection • 90-day all cause readmission • 90-day AMR colonization/infection • 90-day Clostridioides difficile infection (CDI) • 30-day mortality • 60-day mortality • additional domain-specific secondary outcomes
Statistical Analysis BALANCE+ vanguard	• descriptive point estimates and 95% confidence intervals for domain-specific recruitment rates and protocol adherence • analyzed overall and by participating site
Statistical Analysis BALANCE+ Main Platform	• regular Bayesian interim analyses with uninformative priors • conducted at every 500th BALANCE+ platform enrolment • domains closed only if they meet pre-specified, stringent decision criteria for stopping based on superiority, non-inferiority or futility