Supplementary Table: advantages and caveats of the different clinical trials designs

	Feature	Advantages	Caveats
Pragmatic trials	**Individualized randomization**	Better control of randomization and balance between groups if a sufficient sample size is attained	- Higher cost - Might not be applicable to some interventions (e.g., bundles, educational procedures, emergent procedures) - Might introduce a selection bias in patients enrolled and decrease generalizability.
	Cluster-level Interventions (randomization)	- Allow the testing of interventions early in the course of disease management - Effective at evaluating community interventions - Allow assessment of more complex interventions - Cheaper to execute - Inclusion of a large number of patients	- Risk of imbalance between groups due to differences in patient characteristics and care - Traditional informed consent is frequently infeasible - Lack of blinding - More complex statistical analysis, - Traditionally limited to interventions considered minimal risk - Confounding may also arise due to a lack of standardization of co-interventions (differences in “usual care”) between clusters - Statistically less powerful than individual patient-level trials
	Cross over cluster randomization	- Reduces the impact of clustering as cluster participates in both the intervention and control arms, considerably improving statistical power - May be powered to detect small but clinically relevant treatment effects and evaluate heterogeneity of treatment effect	- Prospective informed consent is frequently infeasible - Lack of blinding -More complex statistical analysis - Traditionally limited to interventions considered minimal risk - Susceptible to temporal biases, particularly if periods are long or the number of clusters is small
	Stepped wedge cluster randomization	- Well-suited for interventions that cannot be easily removed or undone (e.g., provider education or implement a bundle of care to prevent AKI)	- Risk of temporal bias due to irreversible practice changes over time - Traditional informed consent is frequently infeasible - Lack of blinding - Traditionally limited to interventions considered minimal risk. - Confounding may also arise due to a lack of standardization of “usual care”
Adaptive trials	- Allows the stopping of an intervention as soon as futility, harm, or efficacy have been demonstrated, thereby improving efficiency, patient safety, and reducing costs - Allows optimization of an intervention during trial - Can be used to optimize eligibility criteria (enrichment) - Can be used to minimize the number of patients exposed to harmful/futile therapies (adaptive allocation)		- Budget planning and funding might be challenging to anticipate given the lack of a pre-defined sample size - Requires more statistical support for more frequent and complicated analyses - Requires more pre-trial planning to pre-specify all stopping/continuing rules - If changing allocation ratios, introduces the potential for temporal biases

Platform trials	- Increase efficiency compared to a traditional trial designs - Reduces the cost to evaluate multiple interventions - Improves the speed of trial conduct by avoiding repeated “start-up” and “close-out” periods - Increases efficiency compared to a traditional trial design by using a single master protocol for multiple interventions	- Increases in overall complexity and logistics, particularly for designs that include adaptive features. - May be challenging for institutional review boards and regulatory bodies to review and oversee. - Costs may vary over-time and not align with traditional funding models.