Pragmatic Trial Design

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Time	Section
0:18	**Traditional Model** • Infographic (understand biology/identify treatment targets→ identify treatments surrogate outcomes→ safety in humans→ efficacy in patients→ implementation into practice • Tend to be too narrow and at the same time too broad • Too expensive, too difficult, too long, diffuse slowly into care (17 years in average) • Over-estimates benefit and under-estimate harm; focus on new drugs and neglect existing therapies
05:33	**Pragmatic (table)** • Question→"Does the intervention work in practice?" • Setting→ Real-world clinical setting • Population→ Heterogeneous, limited exclusions • Providers→ Representative of usual practice • Intervention→ Flexibly applied
06:21	**Comparative Effectiveness** • Common ICU therapies for which the effect on patients is unknown

07:36	**Arbitrary Variation in Clinical Care**
	• Very common situation: Patient with a common condition with at least two available therapies
	  o Would be great!: Evidence one therapy superior for the patient
	  o Most of the time: neither therapy known to be superior for the patient
	  ▪ Arbitrary decision between therapy A and therapy B
	  ▪ Patient experiences all the benefits and risks from the therapy (but knowledge is not gained and care for future patients is not improved)

10:07	**Clinical Care vs. Research** • Healthcare→ they've been largely separated from each other
11:39	**Learning Healthcare System** • One world that's integrated together • Patients, clinicians, community members, hospital leaders, community engagement experts, researchers, quality and safety, ethicists, biostatisticians, bioinformaticians, students, implementation scientists all on one team • Common treatments for common conditions→ results become generalizable, representative, personalized→ deliver interventions as part of clinical care

13:23	**Example: Balanced crystalloids vs. saline**
	• 15,000-patient trial conducted without study personnel for $25,000
	• Arbitrary decisions were being made
	• No data that tells us about patient outcomes
	• Pragmatic Trial Design
	  o Isotonic Solutions and Major Adverse Renal Events Trial (SMART)
	  o Cluster-randomized, multiple-crossover trial
	  o Adults admitted to 5 ICUs at Vanderbilt

18:36	**Design Efficiencies** • Cluster-level designs • Leveraging the electronic health record
18:54	**Cluster-randomized trial** • Intra-cluster correlation: patients are more similar to other patents in their cluster • Patient-level RCT→ 1,000 patients • Clusters of 4 patients→ 1,150 patients • Clusters of 200 patients→ 9,950 patients

19:34	**Cluster-crossover Trial**
	• Intervention delivered at cluster level, but cluster can change
	• Challenges:
	  ○ Intra-cluster correlation
	  ○ Intra-period correlation
	  ○ Temporal changes
	  ○ Carry-over (washout)
	  ▪ Patient-level
	  ▪ Provider-level

20:12	**Stepped-wedge trial** • You want a lot of steps
20:33	**Leveraging the HER for RCTs** • Screening, consent, randomization, delivery, monitoring, data collection
22:25	**How do we integrate pragmatic comparative effectiveness trials into critical care to create Learning Healthcare System?** • Challenge the idea that arbitrary variation in clinical care is safe than structured variation in a clinical trial • Develop new approaches for involving patients and community members in research when prospective informed consent is impracticable due to urgency or scale • Innovate approaches to embedding each step of a clinical trial within clinical care (e.g. HER for eligibility, enrollment, randomization, delivery of the intervention, data collection) • Develop and apply novel clinical trial designs better suited for pragmatic comparative effectiveness research • Aim to understand the effects of common interventions for all patients who would be exposed to an intervention in practice & develop tools to estimate effects of interventions for individual patients rather than average effects
25:15	**Bonus Slide at the end about their own study**