

Lessons for AKI Research from Pragmatic Trials

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KIDNEY
WEEK 20
22

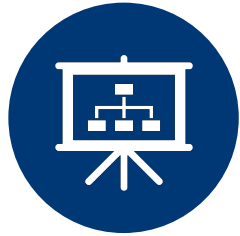
Disclosures

- Miguel A. Vazquez, MD has received grant support from NIH (NIDDK and NIA)
- Participates as non-voting member in the UTSW-DVA JV Oversight Committee

Pragmatic Clinical Trials (PCTs)



Introduction to Pragmatic Clinical Trials



Designs of PCTs and Prior AKI Trials

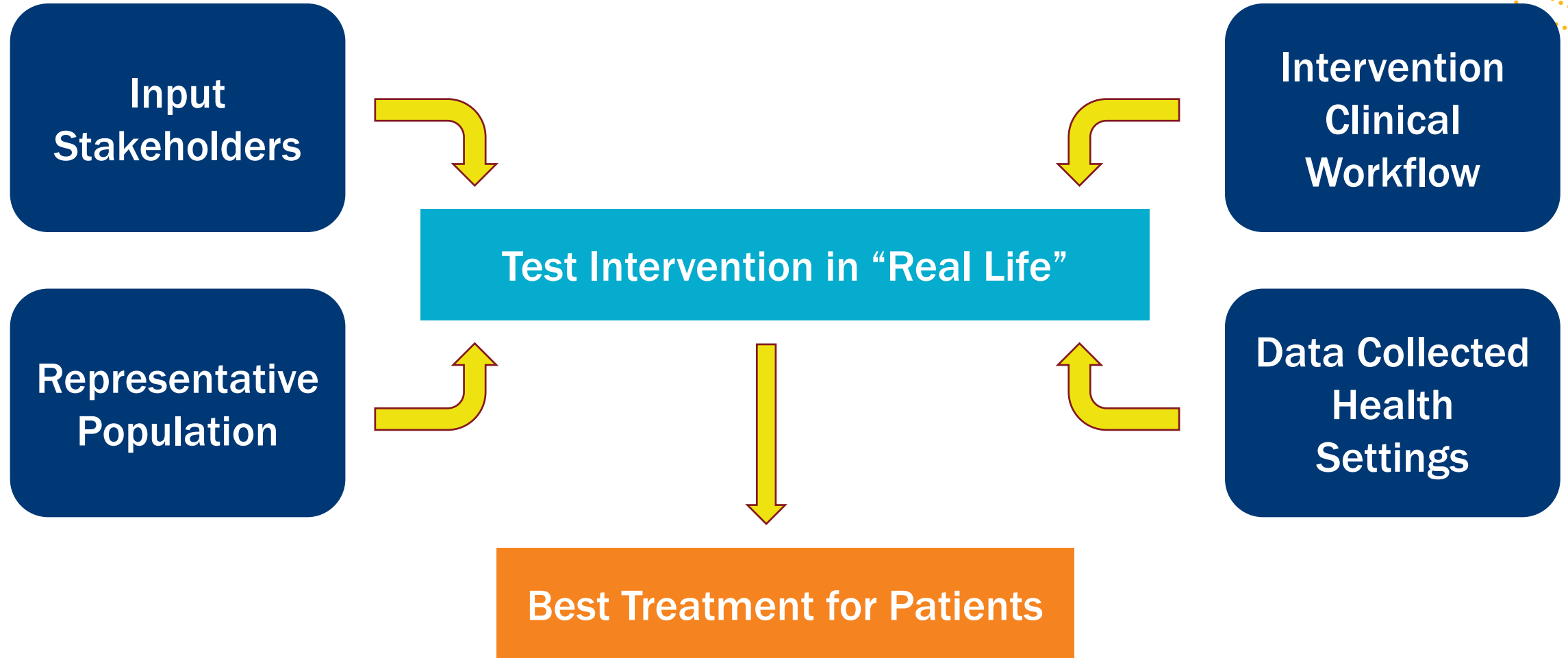


Lessons PCTs in AKI



Future Applications PCTs in AKI

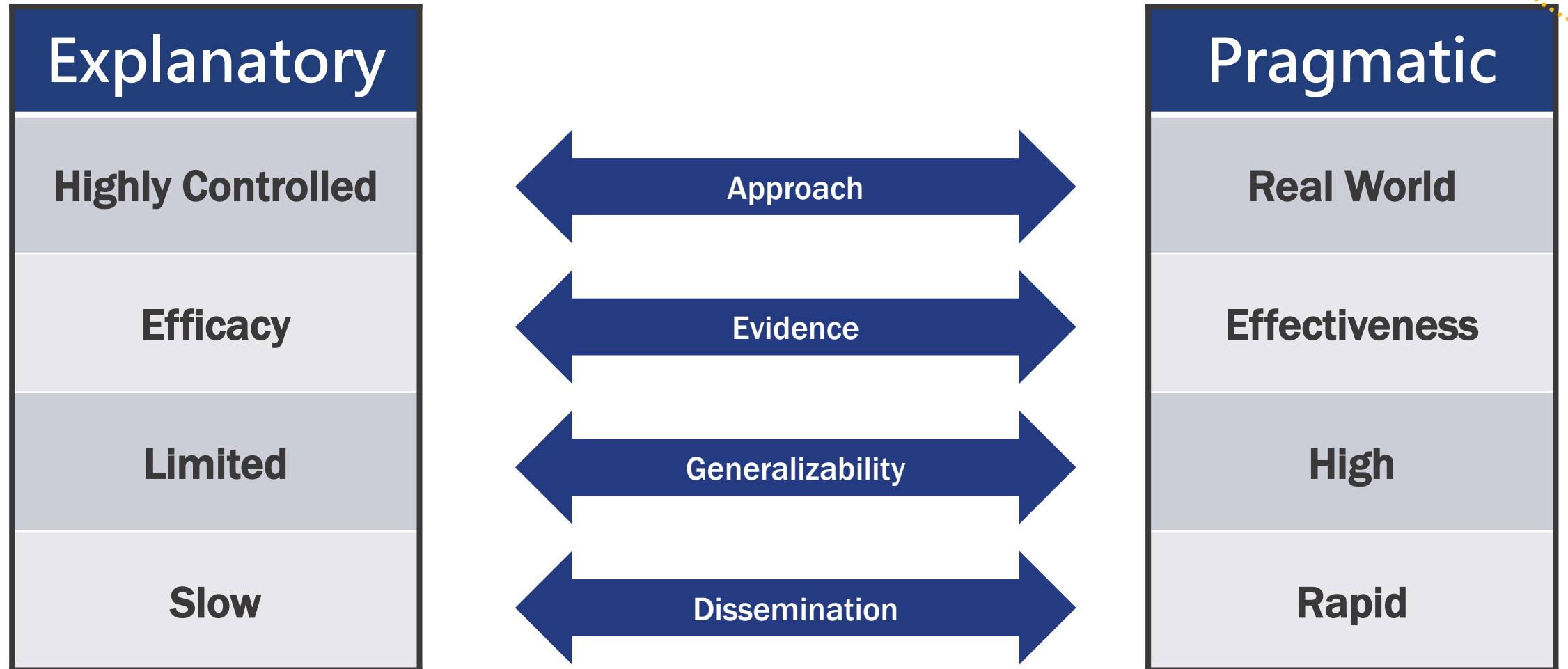
Pragmatic Clinical Trials (ePCTs)



Adapted from Cook et al. *Clinical Trials* 13(5): 504, 2016

Califf and Sugarman *Clinical Trials* 12: 436, 2015

Randomized Clinical Trials



Cook et al. Clin Trials 13: 504, 2016

Living Textbook NIH PCT Collaboratory 2022

Dimensions: Pragmatism in a Trial

Who and Where

- Eligibility
- Recruitment
- Setting
- Organization

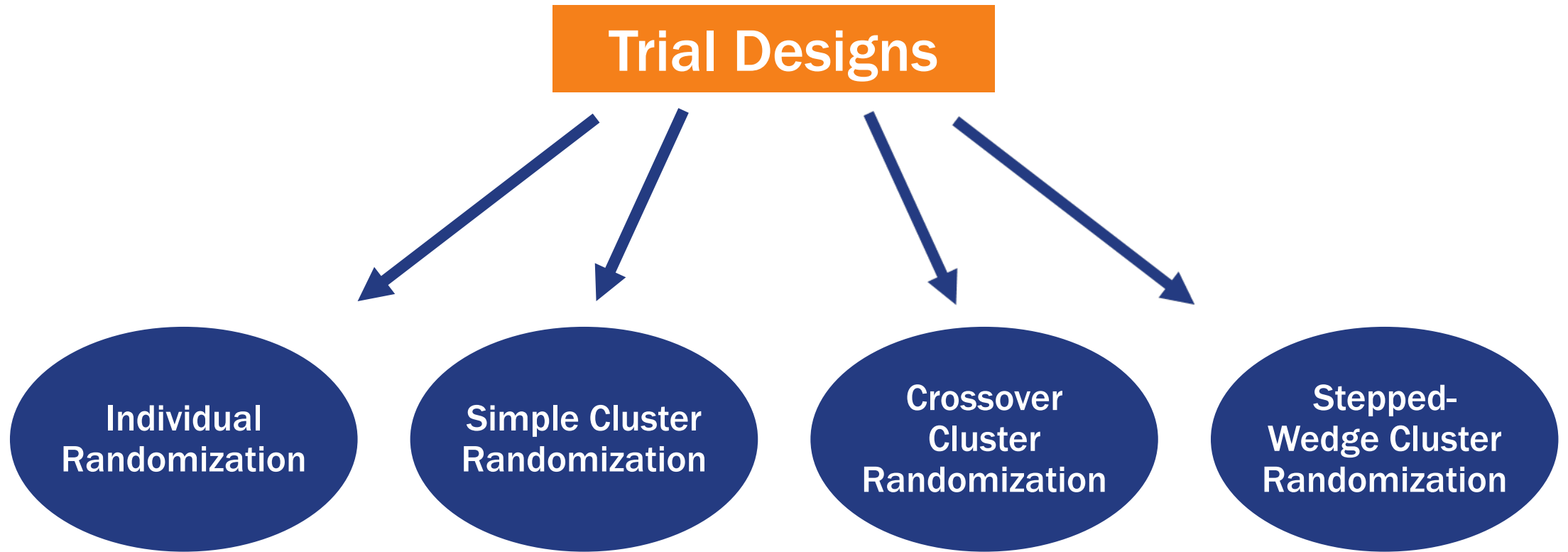
How

- Flexibility: Delivery
- Flexibility: Adherence
- Follow-Up

What

- Primary Outcome
- Primary Analysis

Pragmatic Clinical Trials



Adapted from Cook et al. Clin Trials 13: 504, 2016

Living Textbook NIH PCT Collaboratory 2022

Simple Cluster Randomization (A vs B or A vs A+)

Cluster	Time Period				
	Baseline	1	2	3	4
1	—	Usual	Usual	Usual	Usual
2	—	INT	INT	INT	INT
3	—	INT	INT	INT	INT
4	—	Usual	Usual	Usual	Usual

Pros: Simple, lower risk cross-contamination

Cons: Less interest HS, differences between clusters---ICC

Adapted from Cook et al. Clinical Trials 13:504, 2016

Cluster with Multiple Crossover

Cluster	Time Period				
	Baseline	1	2	3	4
1	—	Usual	INT	Usual	INT
2	—	INT	Usual	INT	Usual
3	—	INT	Usual	INT	Usual
4	—	Usual	INT	Usual	INT

Pros: All groups receive the intervention

Cons: Carryover effect from one period to the next

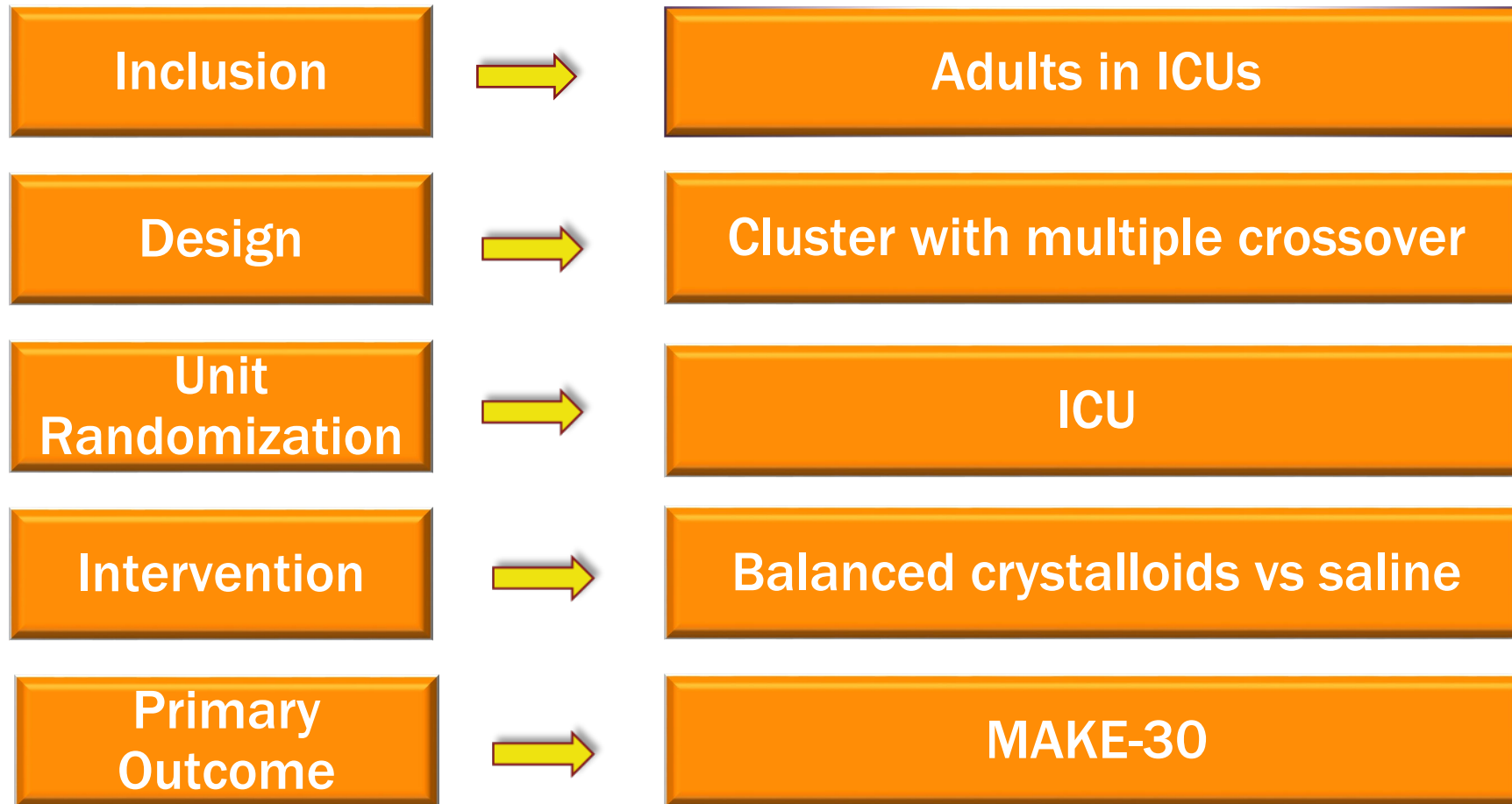
Adapted from Cook et al. Clinical Trials 13:504, 2016

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

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and Todd W. Rice, M.D., for the SMART Investigators
and the Pragmatic Critical Care Research Group*

Balanced Crystalloids versus Saline in Critically Ill Adults



NEJM 378: 829, 2018

Balanced Crystalloids versus Saline

Outcome	Balanced Crystalloids	Saline	Adjusted Odds Ratio (95% CI)	P Value
MAKE-30	1139 (14.3%)	1211 (15.4%)	0.90 (0.82 to 0.99)	0.04
In-hospital death	818 (10.3%)	875 (11.1%)	0.90 (0.80 to 1.01)	0.06
New RRT	189/7558 (2.5%)	220/7458 (2.9%)	0.84 (0.68 to 1.02)	0.08
Final creatinine >200% baseline	487/7558 (6.4%)	494/7458 (6.6%)	0.96 (0.84 to 1.11)	0.60

Large PCT addressing AKI, Importance composite endpoint

NEJM 378: 829, 2018

Stepped Wedge



Cluster	Time Period				
	Baseline	1	2	3	4
1	Usual	INT	INT	INT	INT
2	Usual	Usual	INT	INT	INT
3	Usual	Usual	Usual	INT	INT
4	Usual	Usual	Usual	Usual	INT

Pros: All clusters receive and stay on the intervention

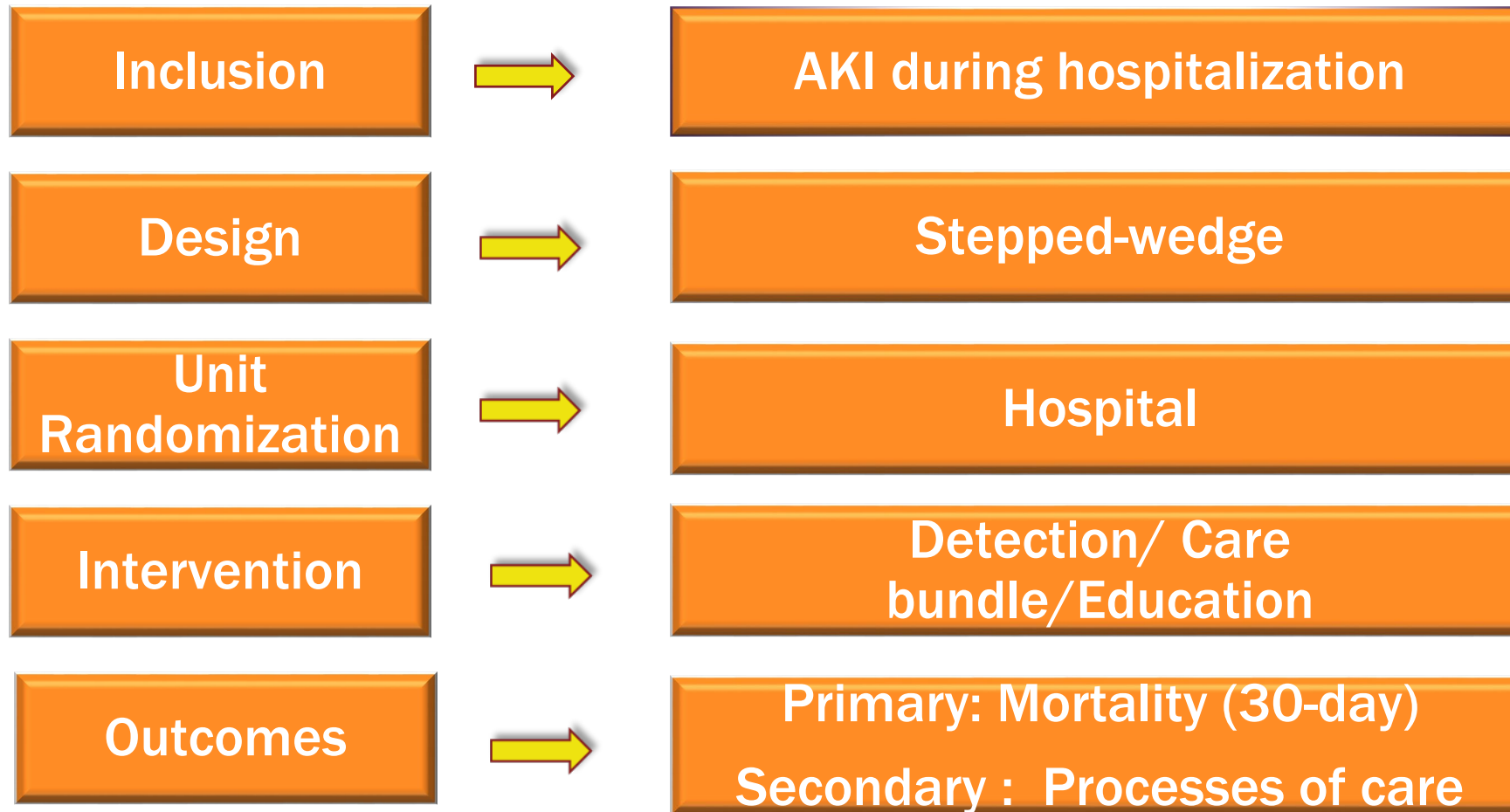
Cons: Most vulnerable to changes in practice

Adapted from Cook et al. Clinical Trials 13:504, 2016

An Organizational-Level Program of Intervention for AKI: A Pragmatic Stepped Wedge Cluster Randomized Trial

Nicholas M. Selby ,^{1,2} Anna Casula,³ Laura Lamming,⁴ John Stoves,⁵ Yohan Samarasinghe,⁶ Andrew J. Lewington,⁷ Russell Roberts,⁴ Nikunj Shah ,⁸ Melanie Johnson,⁹ Natalie Jackson,⁹ Carol Jones,⁸ Erik Lenguerrand,³ Eileen McDonach,⁴ Richard J. Fluck,² Mohammed A. Mohammed,⁴ and Fergus J. Caskey,³

An Organizational-Level Program Intervention for AKI



An Organizational-Level Program of Intervention for AKI: Mortality

Intervention (reference = control)

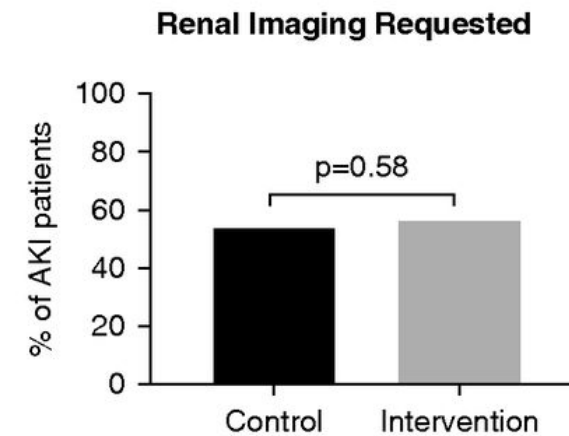
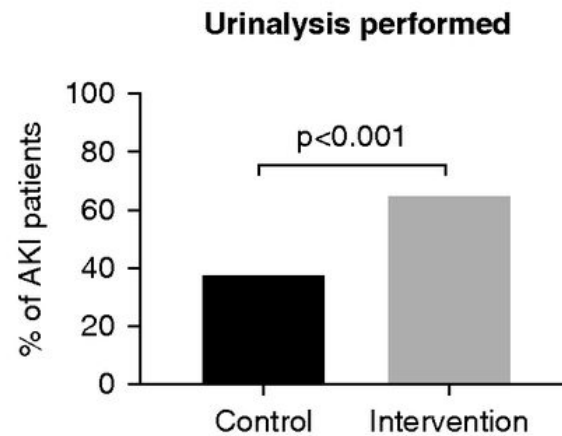
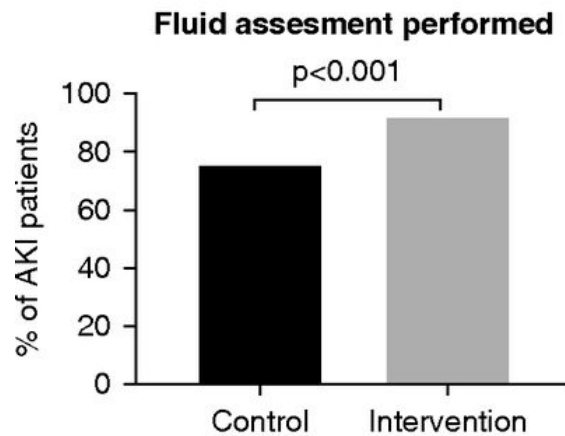
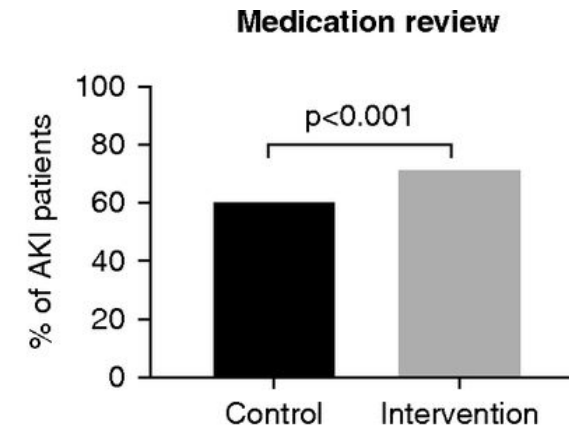
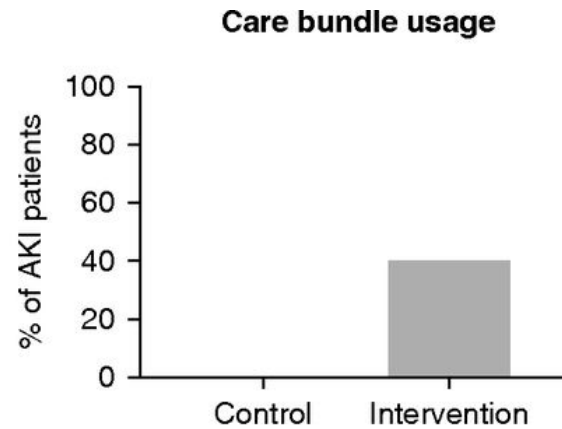
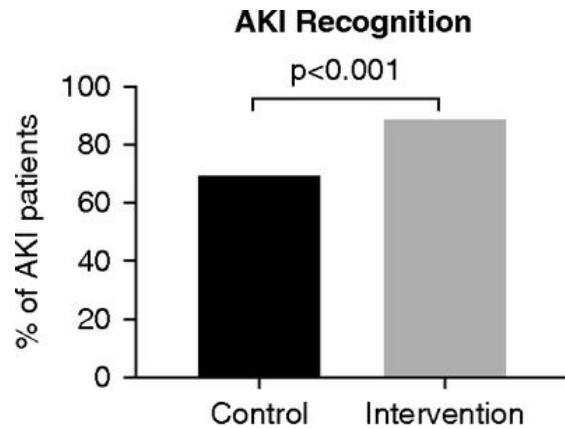
Odds ratio

1.04 95% CI (0.91 to 1.21)



P- Value

0.55

Improvement in Processes of Care with Intervention



An Organizational-Level Program of Intervention for AKI: A Pragmatic Stepped Wedge Cluster Randomized Trial

Nicholas M. Selby ,^{1,2} Anna Casula,³ Laura Lamming,⁴ John Stoves,⁵ Yohan Samarasinghe,⁶ Andrew J. Lewington,⁷ Russell Roberts,⁴ Nikunj Shah ,⁸ Melanie Johnson,⁹ Natalie Jackson,⁹ Carol Jones,⁸ Erik Lenguerrand,³ Eileen McDonach,⁴ Richard J. Fluck,² Mohammed A. Mohammed,⁴ and Fergus J. Caskey,³

- Intervention had no effect on primary outcome (mortality)
- Improved LOS, duration AKI and processes of care in AKI (importance of secondary outcomes)

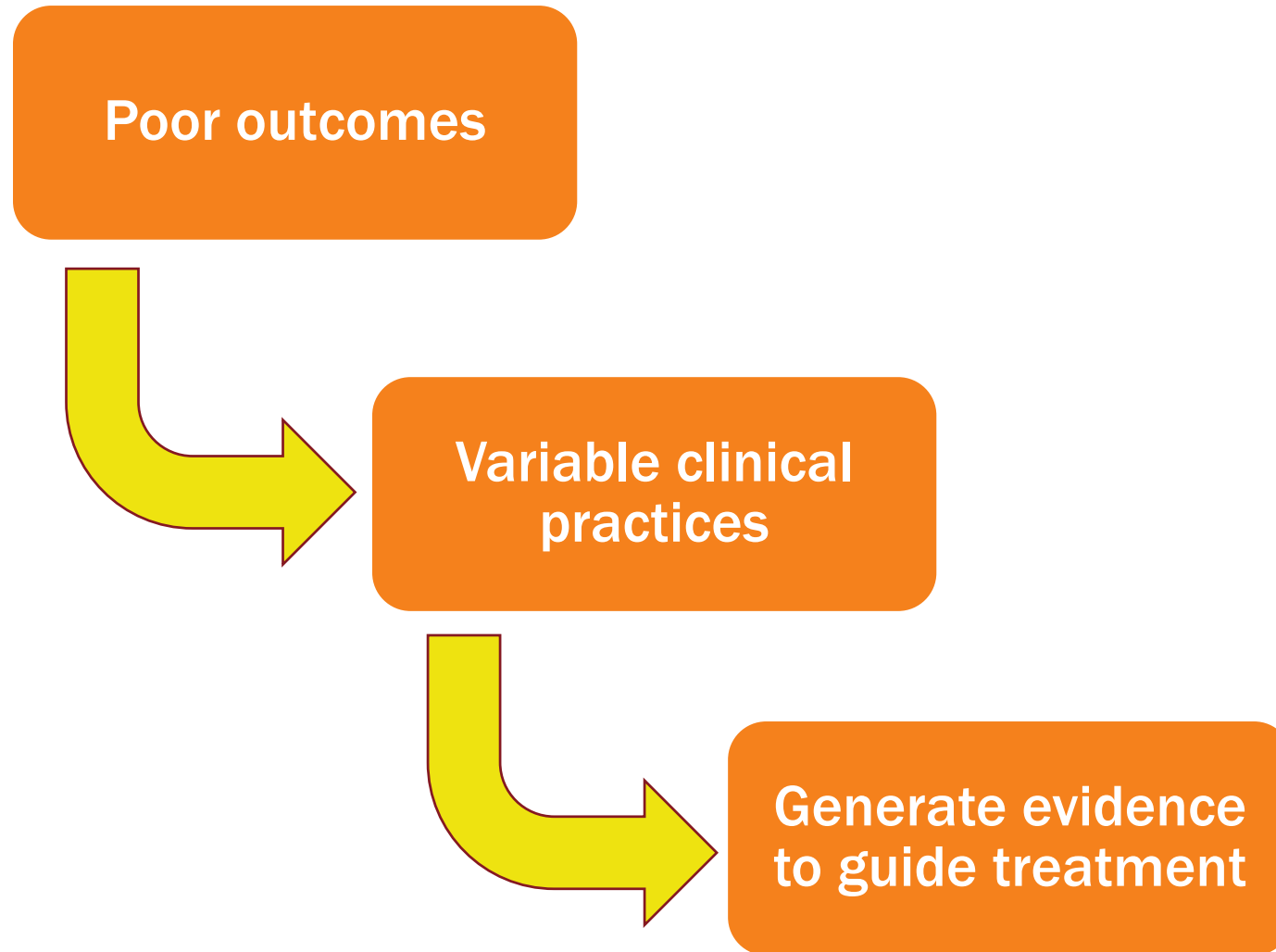
Momentum for Large ePCTs in Nephrology

Trial	Population	Intervention	Design and Outcomes	Status
TIME	HD patients	Duration of Dialysis	Cluster-simple parallel group <u>Mortality</u>	Completed N=7,053
ICD-Pieces	CKD patients (coexistent DM and HTN)	Guidelines-based care	Cluster-simple parallel group <u>Hospitalizations</u>	Completed N=11,000
HiLo	HD patients	Less stringent phosphorus targets	Patient-level randomization <u>Mortality + Hospital.</u>	In progress N=4,400

NIH Pragmatic Clinical Trials Collaboratory

JASN 30: 890, 2019; NCT02019225; NCT02587936; NCT04095039

Potential Value of Pragmatic Trials in AKI



Planning Pragmatic Trials in AKI

Potential Areas

- Prevention
- Treatment
- Post AKI Care

Interventions

- Early detection
- Testing
- Fluid management
- Pharmacologic TX
- Modality RRT
- Timing RRT
- Dosing RRT
- Care bundles

Outcomes

- MAKE
- Duration RRT
- Time to recovery
- ESKD
- Patient-centered

Adapted from *J Crit Care* 44: 337, 2018, *Nephrol Dialysis and Transp*: 1, 2022 and *JASN* 33: 1459, 2022

Pragmatic Trials and Clustering in AKI Trials

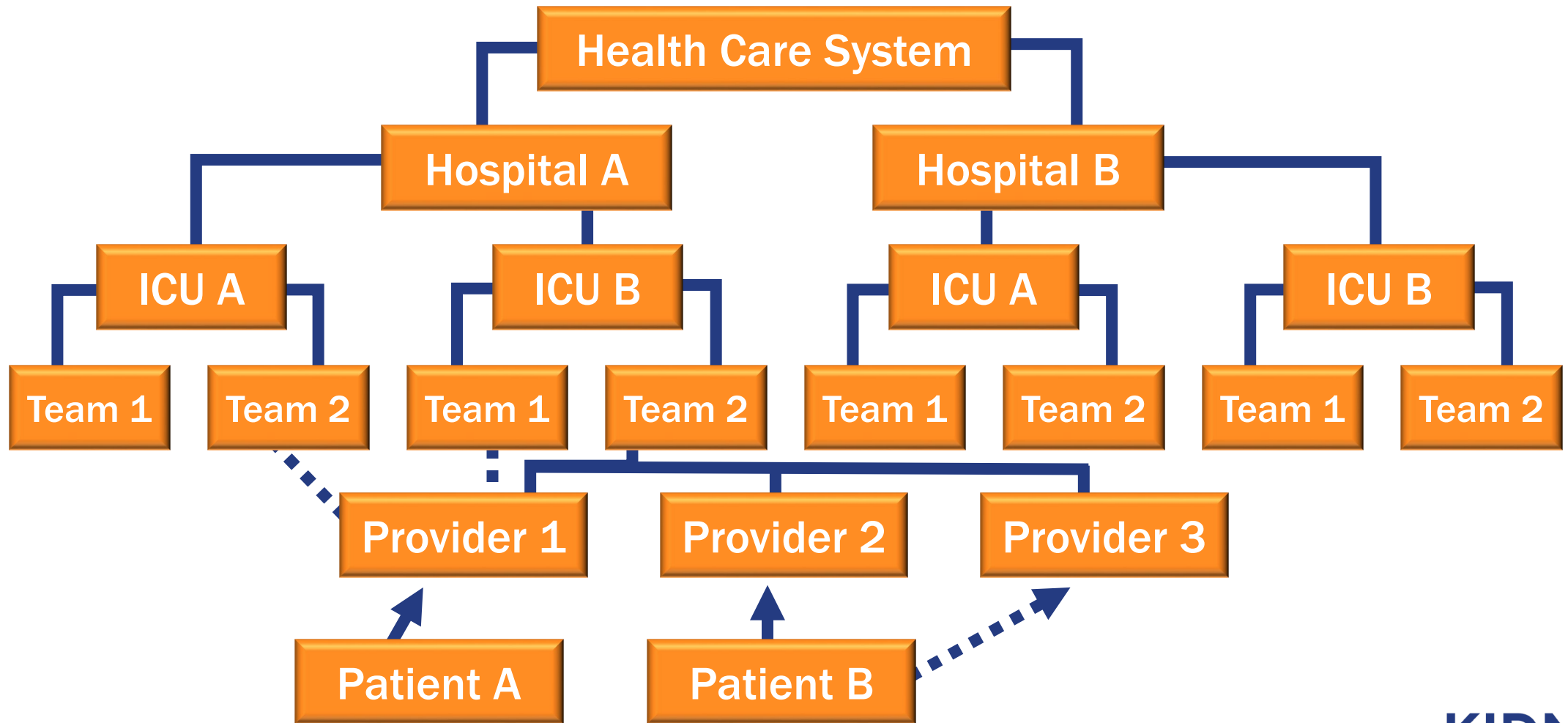


Diagram Adapted from Cook et al. *Clinical Trials* 13: 504, 2016

PCTs and Disparities in Kidney Research

Recruitment

- Broaden inclusion
- Automate screening
- Select diverse sites

Implementation

- Standardize intervention
- Facilitate uptake
- Promote sustainability

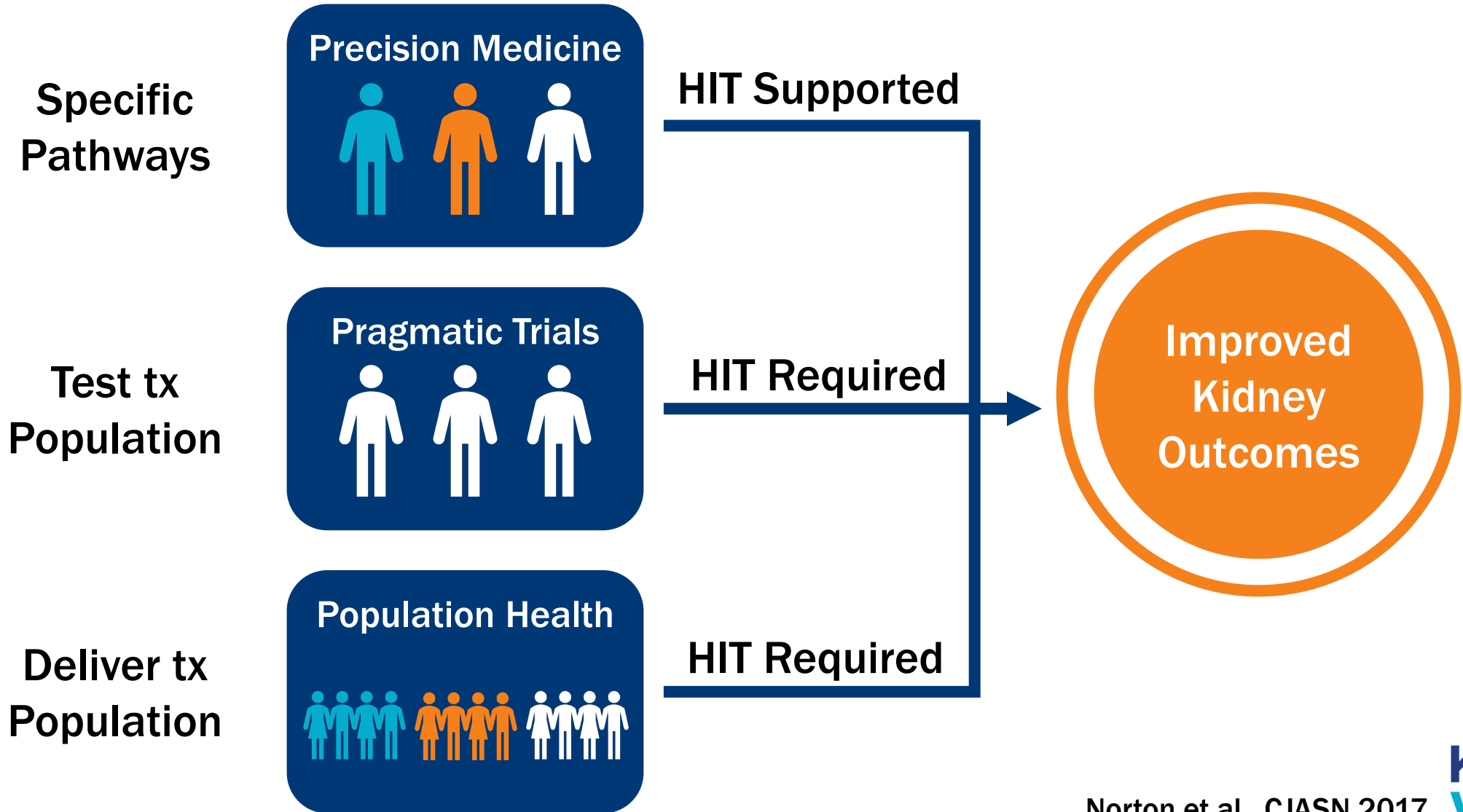
Dissemination

- Inform decision makers
- Embed intervention
- Target policies to promote equity

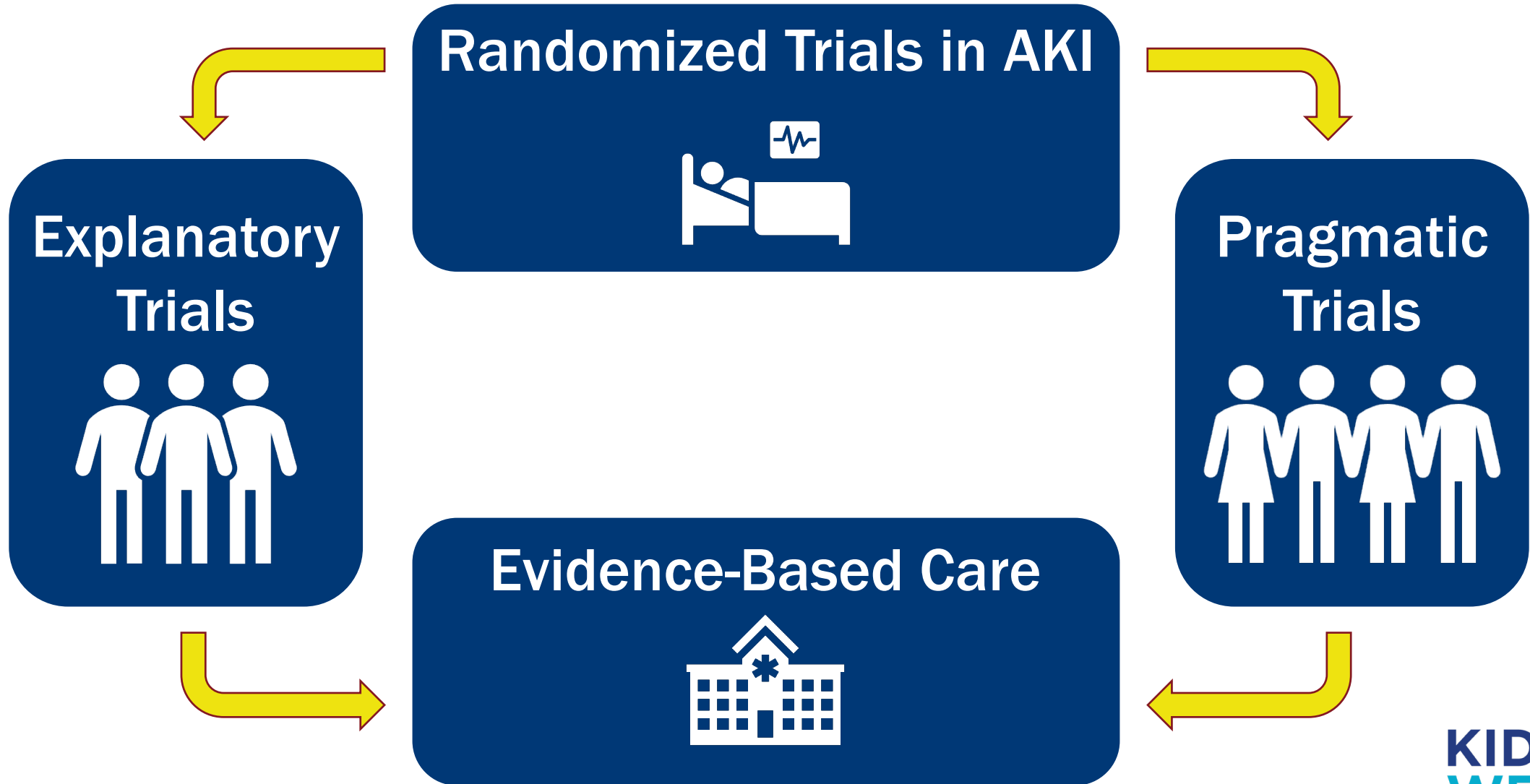
PCTs in Nephrology

- Generate evidence in the “real world”
- Active input various stakeholders
- More generalizable
- More collaborative
- Rigorous conduct
- Lower costs
- Less control...

Initiatives to Improve Kidney Health



Future of AKI Trials



Acknowledgements

- ICD- Pieces Team: (Co-PI R. Toto) and support NIDDK
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