NIH Collaboratory *Rethinking Clinical Trials®*

Health Care Systems Research Collaboratory

Changes in Study Design & Analysis

April 14, 2021
Steering Committee Meeting
Moderator: Liz Turner, PhD
Co-Lead, Biostatistics and Design Working Group
In partnership with Co-Lead Patrick Heagerty, PhD

Panel

- ACP PEACE
  - James Tulsky, MD
  - Angelo Volandes, MD
- PRIM-ER
  - Corita Grudzen, MD
- HiLo
  - Myles Wolf, MD

Goal of the Discussion

- Discuss adaptations to study design necessary due to COVID-19
- Discuss adaptations to measurement necessary due to COVID-19
- Review how analysis plans changed due to COVID-19
- Share ongoing issues faced because of COVID-19
- Share opportunities from COVID-19

ACP PEACE

Advance Care Planning: Promoting Effective & Aligned Communication in the Elderly

- Step-wedge cluster randomized trial
- 4500 pts. >64 in 36 onc. clinics

MAYO CLINIC

DukeHealth

Northwell Health℠

		UH3					
STEPS (clinic clusters)	Baseline	1	2	3	4	5	6
1, 2		✓					
3, 4							
5, 6							
7, 8							
9, 10							
11, 12							

VITAL talk

ADVANCE CARE PLANNING DECISIONS

ACP PEACE

Advance Care Planning: Promoting Effective & Aligned Communication in the Elderly

		UH3				
STEPS (clinic clusters)		Baseline	1	2	3	4
1, 2		✓				
3, 4			✓	✓	✓	✓
5, 6				✓	✓	✓
7, 8, 9					✓	✓
10, 11, 12						✓

- Step 1&2 ACP rates prior to, and after, the intervention
- Examine intervention effect post-COVID-19 using data from the remaining ten clusters

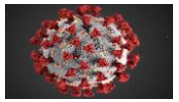
- **COVID-19 effect:** We will estimate the pre-COVID ACP rate from the original baseline plus Step 1, and the post-COVID ACP rate using Step 2 data. We will also examine trends over time.

OPPORTUNITY: COVID-19 SUPPLEMENT

Sep 2019

Pre-Covid

09/15/2019 – 03/14/2020

March 2020 

Covid

03/15/2020– 09/14/2020

Dec 2020 

Intervention

12/15/2020– 06/14/2021

- Goal: To determine whether the ACP PEACE intervention can rapidly effect COVID related advance care planning in a primary care population
  - 15,000 primary care patients >64
  - We've trained, remotely, 178 Northwell Health primary care clinicians
  - Rolling out videos in all clinics - in person, remotely using codes, and texting links
  - Intervention period began Dec 15, 2020 and ends June 15, 2021

PRIM-ER *Primary Palliative Care for Emergency Medicine*

- Stepped-wedge cluster-randomized trial testing the effects of implementing primary palliative care in emergency medicine on healthcare utilization and survival
- 35 emergency departments across 18 health systems

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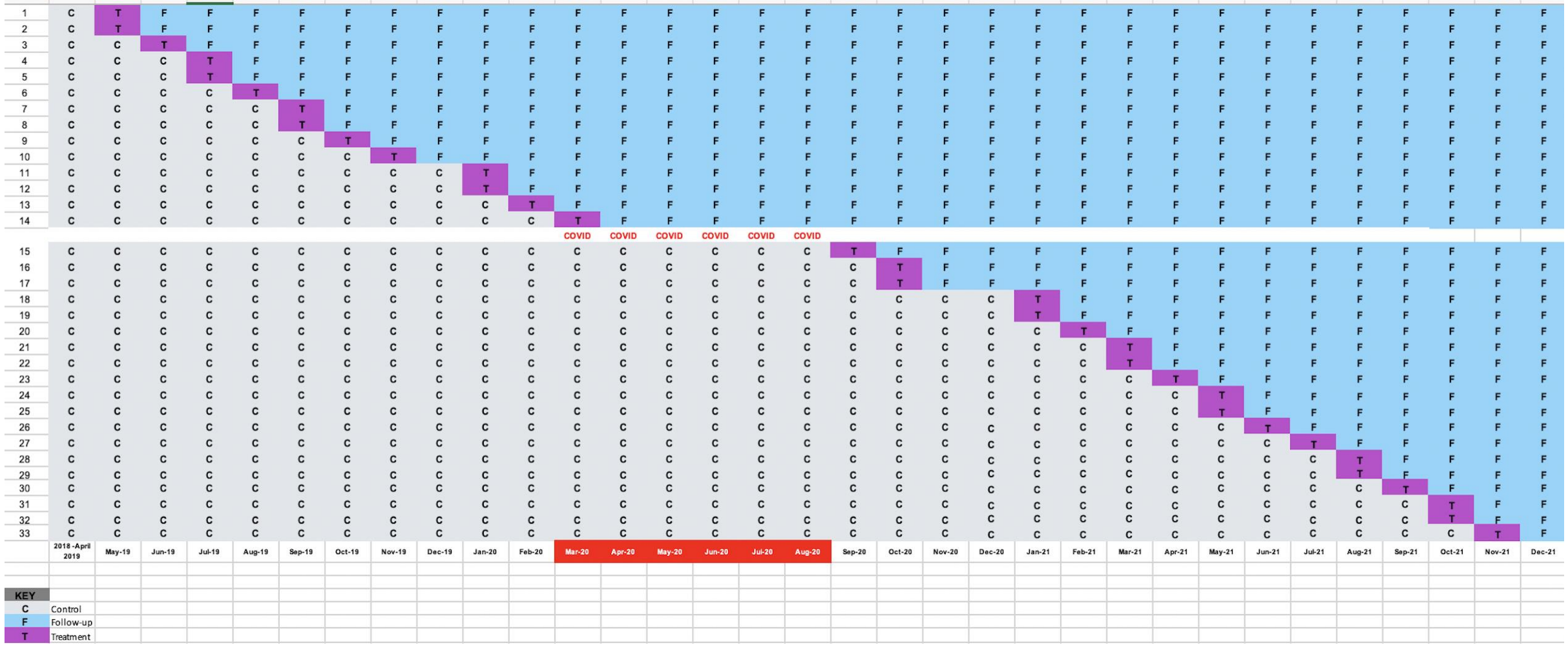
PRIM-ER Data Collection

- Qualitative data: RE-AIM framework to evaluate institutional leadership support and QI processes
- Quantitative data: Baseline Attitudes and Knowledge Survey
- Sites achieving intervention milestones
- Medicare Claims analyses

PRIM-ER COVID-19 Impact

- Change in sequencing for stepped-wedge design; implementation interruption/pause for six months
- Heterogeneity of treatment effect due to change in population characteristics and practice patterns
- Competing priorities for Emergency Departments
- Intervention format changes-virtual education
- Greater provider/nurse receptivity to interventions post- COVID-19

Updated Stepped Wedge Timeline



	2018 -April 2019	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21
												COVID	COVID	COVID	COVID	COVID	COVID																

KEY	
C	Control
F	Follow-up
T	Treatment

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HiLo *Pragmatic Trial of Higher vs Lower Serum Phosphate Targets in Patients Undergoing Hemodialysis*

Goal: HiLo will test which of two phosphate management strategies will confer superior clinical outcomes in patients with ESRD undergoing hemodialysis:

- Lo: Usual target phosphate of <5.5 mg/dl; or
- Hi: Less strict target phosphate of ≥6.5 mg/dl

Design: Pragmatic, multicenter RCT, clinical outcomes trial; n=4400

Primary outcome: Hierarchical composite of all-cause mortality & all-cause hospitalization (adaptation of Finkelstein-Schoenfeld method for cluster-RCT)

Pragmatic features: Cluster randomization; broad entry criteria; no traditional on-site study staff; eConsent; remote site monitoring; reliance on EHR with no CRFs; no AE reporting; outcomes based on EHR with no adjudication

COVID-19 and HiLo: Design

- ESRD is an extremely high risk population for COVID19-related outbreaks and death
- Three design issues:
  1. “All hands on deck” in dialysis units – less time for study
  2. “Cohorting” of COVID+ patients into specific units risks that patients would move from/to units that are/aren’t on study or are in different arms
  3. Increased risk for within cluster outbreaks that would increase ICC of primary outcome and thereby reduce power
- Mitigation:
  1. Delay site activation, accept slow enrollment in already activated sites
  2. Put cohort units on hold; delay activation of units expected to be cohort sites
  3. Increase the number of clusters while reducing the n per cluster

COVID-19 and HiLo: Measurement

- Obtain data on COVID-19 associated hospitalizations and deaths to support future sensitivity analyses
  - Based on timing of COVD positivity
  - Timing of subsequent hospitalizations and deaths
  - Will need to define windows of associated versus not associated with COVID-19…(1 month?)

COVID-19 and HiLo: Analysis

- Ultimately, few outbreaks within units
- Fortunately small number of patients affected
- We opted to maintain primary analysis unchanged
- We will plan a pre-specified secondary analysis in which we censor for COVID-associated deaths and exclude COVID-19 associated hospitalizations
- To be included in final SAP

Impacts of COVID-19

- Goal: facilitate information sharing / planning for "GSP"
- Outreach to Collaboratory projects
- General Themes:
  - Design / Redesign
  - Conduct
  - Analysis
- PICOT and CONSORT to support proposed guidance

PICOTs

- Framing the scientific **question** is crucial for clarity
- The scientific question is then linked to a statement of **research aims** or **research objectives**
- Aims or objectives then lead to hypotheses (and this helps to guide design and analysis decisions!)
- **Q**: Is there a way to help structure the specification of questions or aims?

PICOTs

P	Patient population
I	Intervention of interest
C	Comparison intervention
O	Outcome(s)
T	Time*

*Note that the time (T) component of the PICOT question isn't always required.

PICOTs

PICOT(t) – temporal impacts on each

P	Patient population	P(t) - Change in enrolled patients
I	Intervention of interest	I(t) - Change in intervention delivered
C	Comparison intervention	C(t) - Change in comparison group / usual care
O	Outcome(s)	O(t) - Change in outcome collection / missingness / mean level
T	Time*	T(t) - Change in the timing of effect / interaction with covid(t)

*Note that the time (T) component of the PICOT question isn't always required.

PICOT(t) – temporal impact on each element

- **Q:** How should we approach measurement for each of these aspects?
- **Q:** How should we approach adaptation of SAPs to shed light on these aspects?
- **Q:** How should we approach trial reporting to shed light on each of these aspects?

Impacts of COVID-19

- Development of guidance
- Consideration of PICOT & of CONSORT
  - "Consolidated Standards of Reporting Trials"
  - Key elements:
    - Flow diagram detailing enrollment/follow-up
    - Checklist of reporting guidelines inc. elements of PICOT
- Continued learning from Collaboratory projects & monthly working group meetings


Q&A

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.