# Pragmatic, Adaptive Trials for Efficient Answers

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# Outline

1. Background
2. Crisis and innovation
3. The learning health system
4. Trial design considerations

# Background

- Learning Health Systems Researcher
  - NICHD K23: “A Learning Health Systems Approach to Precision Sedation and Analgesia for Critically Ill Children”
  - NINDS R01: “A Biodigital Rapid Alert for Identifying Neuromorbidity in Critically Ill Children”
- Operations Informatics
  - UPMC Department of Critical Care Medicine
    - >40 Adult and Pediatric ICUs
    - Cerner x2, Epic x2, Allscripts, Medtech
- Embedded Clinical Trials
  - EHR to support traditional EDC
  - Workflow integration

# Crisis and innovation

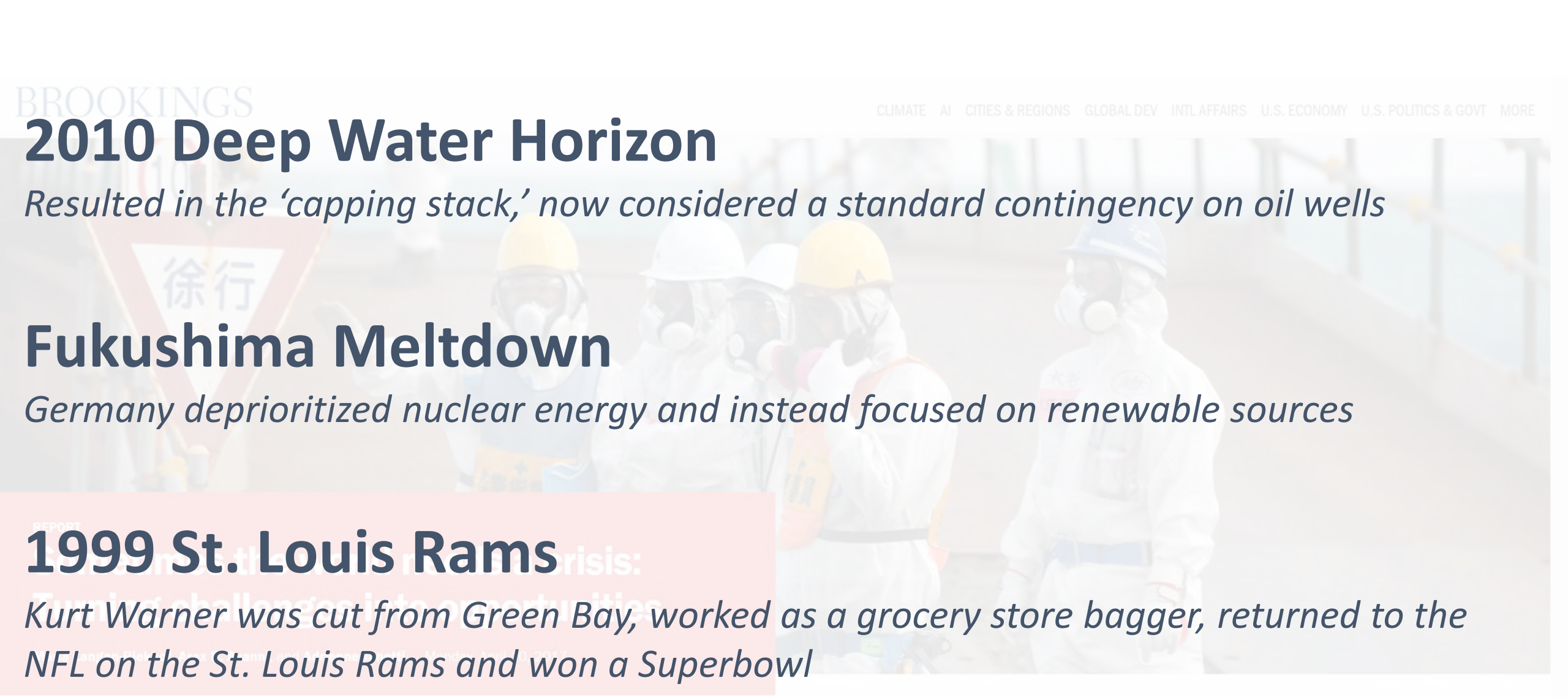
BROOKINGS

CLIMATE AI CITIES & REGIONS GLOBAL DEV INTL AFFAIRS U.S. ECONOMY U.S. POLITICS & GOVT MORE


REPORT

# Sometimes the world needs a crisis: Turning challenges into opportunities

**Maria Langan-Riekhof**, **Arex B. Avanni**, and **Adrienne Janetti** · Monday, April 10, 2017



## 2010 Deep Water Horizon

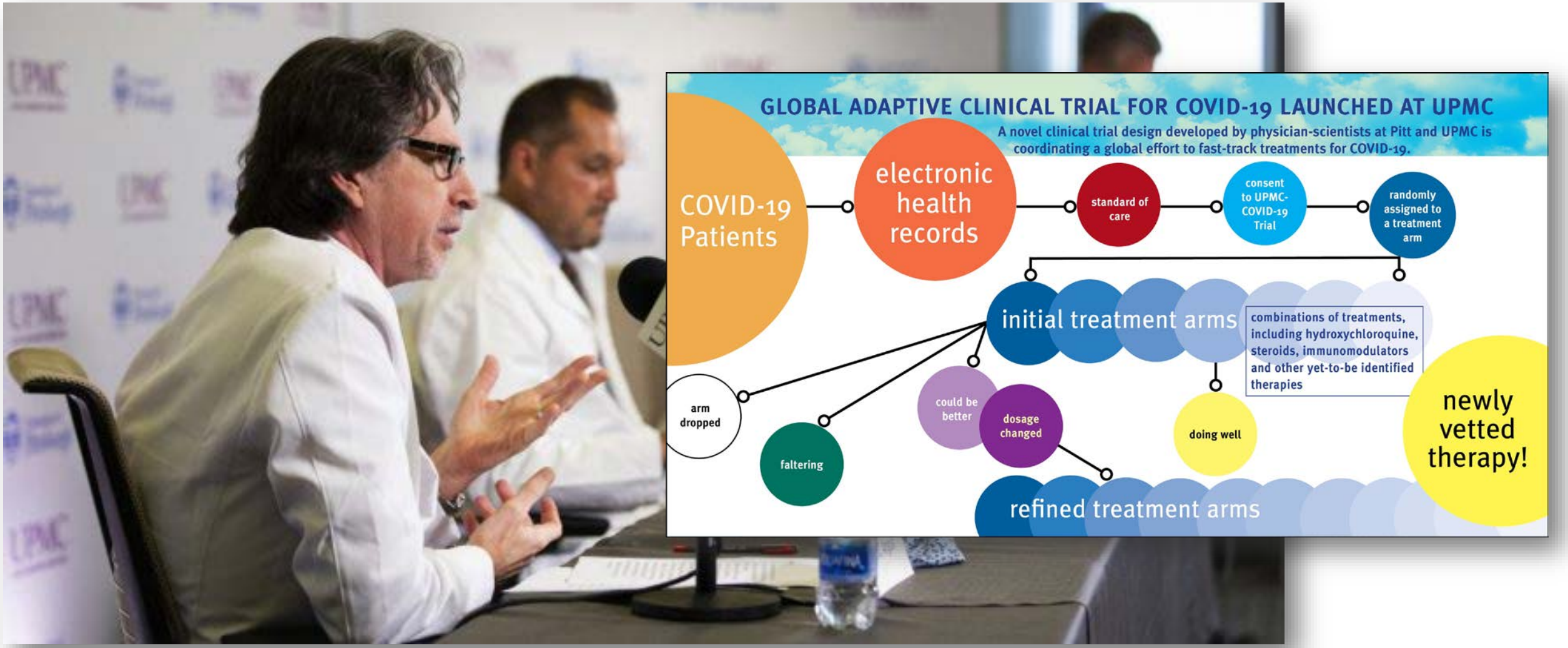
*Resulted in the 'capping stack,' now considered a standard contingency on oil wells*

## Fukushima Meltdown

*Germany deprioritized nuclear energy and instead focused on renewable sources*

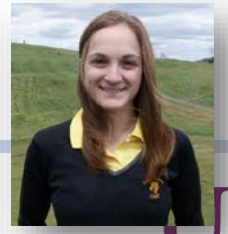
## 1999 St. Louis Rams

*Kurt Warner was cut from Green Bay, worked as a grocery store bagger, returned to the NFL on the St. Louis Rams and won a Superbowl*









University of Pittsburgh

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# Learning Health System

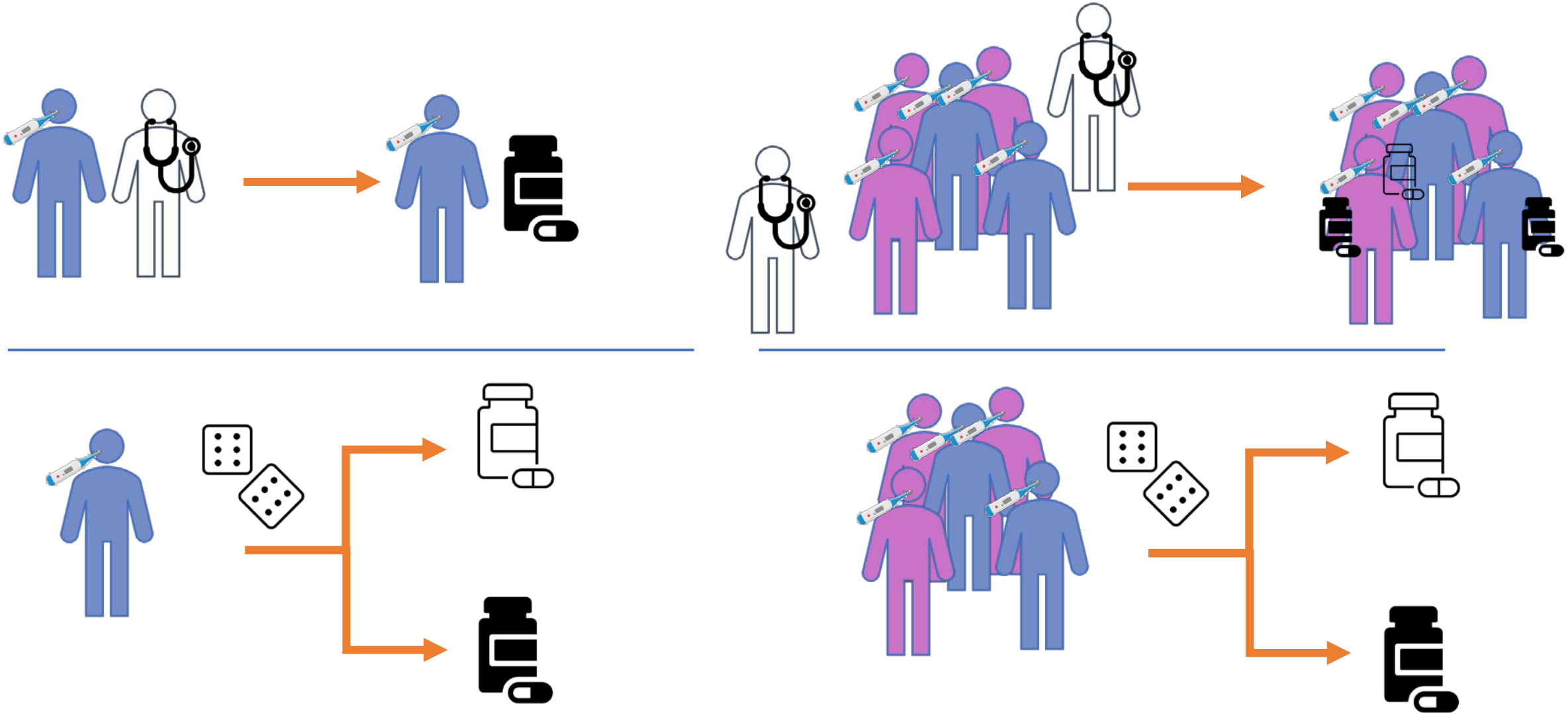
# The Learning Health System

*A system in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the care process, patients and families as active participants in all elements, and new knowledge is captured as an integral by-product of the care experience.*

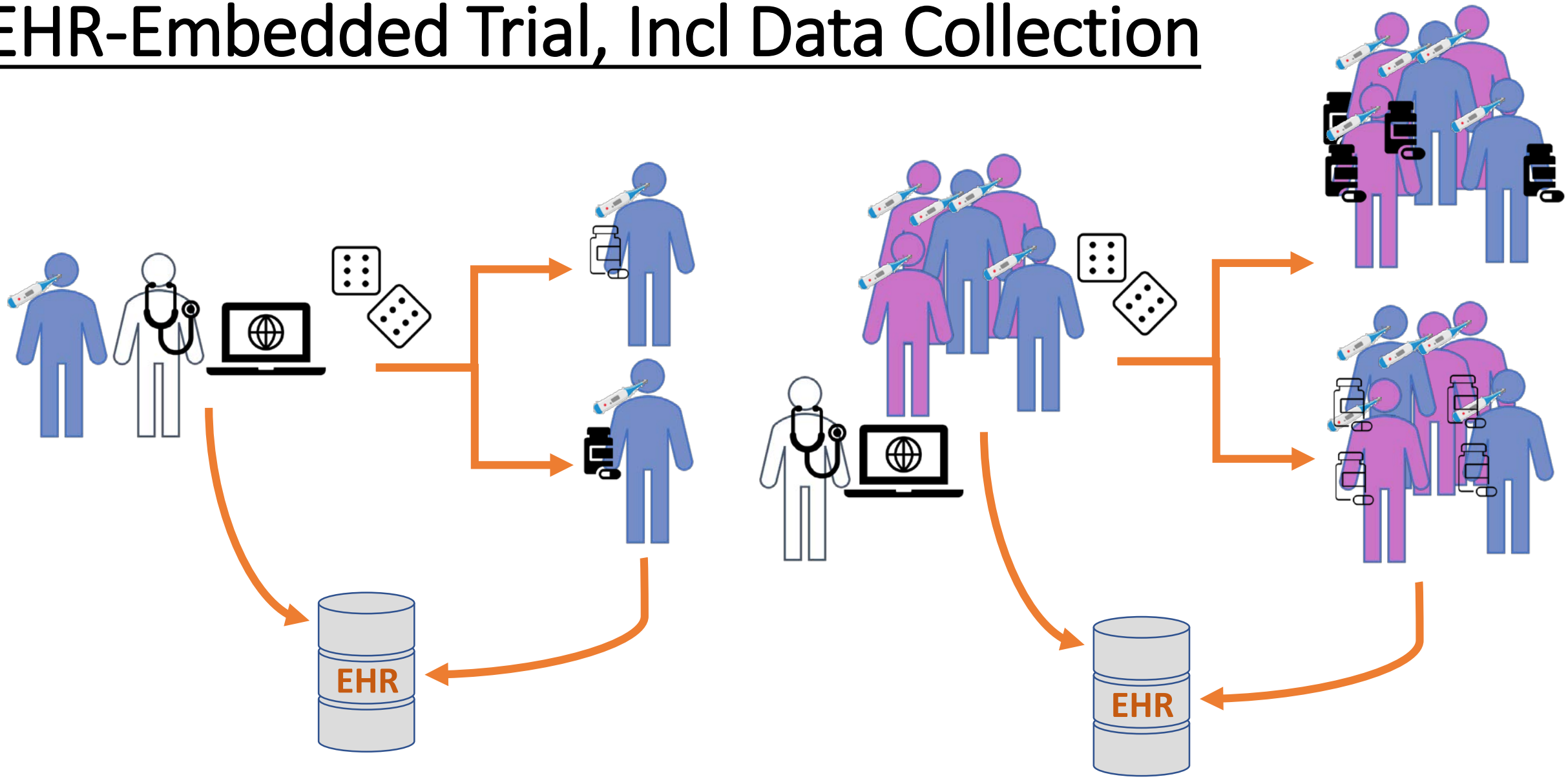
(IOM, Best Care at Lower Cost, 2012)

*Courtesy of https://learninghealthcareproject.org/background/learning-healthcare-system/*

# Traditional Division Between Research and Practice



# EHR-Embedded Trial, Incl Data Collection



# The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study

## Rationale and Design

Derek C. Angus[1], Scott Berry[2], Roger J. Lewis[2,3,4], Farah Al-Beidh[5], Yaseen Arabi[6], Wilma van Bentum-Puijk[7], Zahra Bhimani[8], Marc Bonten[7,9], Kristine Broglio[2], Frank Brunkhorst[10], Allen C. Cheng[11,12], Jean-Daniel Chiche[13], Menno De Jong[14], Michelle Detry[2], Herman Goossens[15], Anthony Gordon[5], Cameron Green[12], Alisa M. Higgins[12], Sebastiaan J. Hullegie[7], Peter Kruger[16], Francois Lamontagne[17], Edward Litton[18], John Marshall[8,19], Anna McGlothlin[2], Shay McGuinness[12,20,21], Paul Mouncey[22], Srinivas Murthy[23], Alistair Nichol[12,24,25], Genevieve K. O'Neill[12], Rachael Parke[20,21,26], Jane Parker[12], Gernot Rohde[27,28], Kathryn Rowan[22], Anne Turner[21], Paul Young[21,29], Lennie Derde[7,30], Colin McArthur[21,31], and Steven A. Webb[12,18,32]

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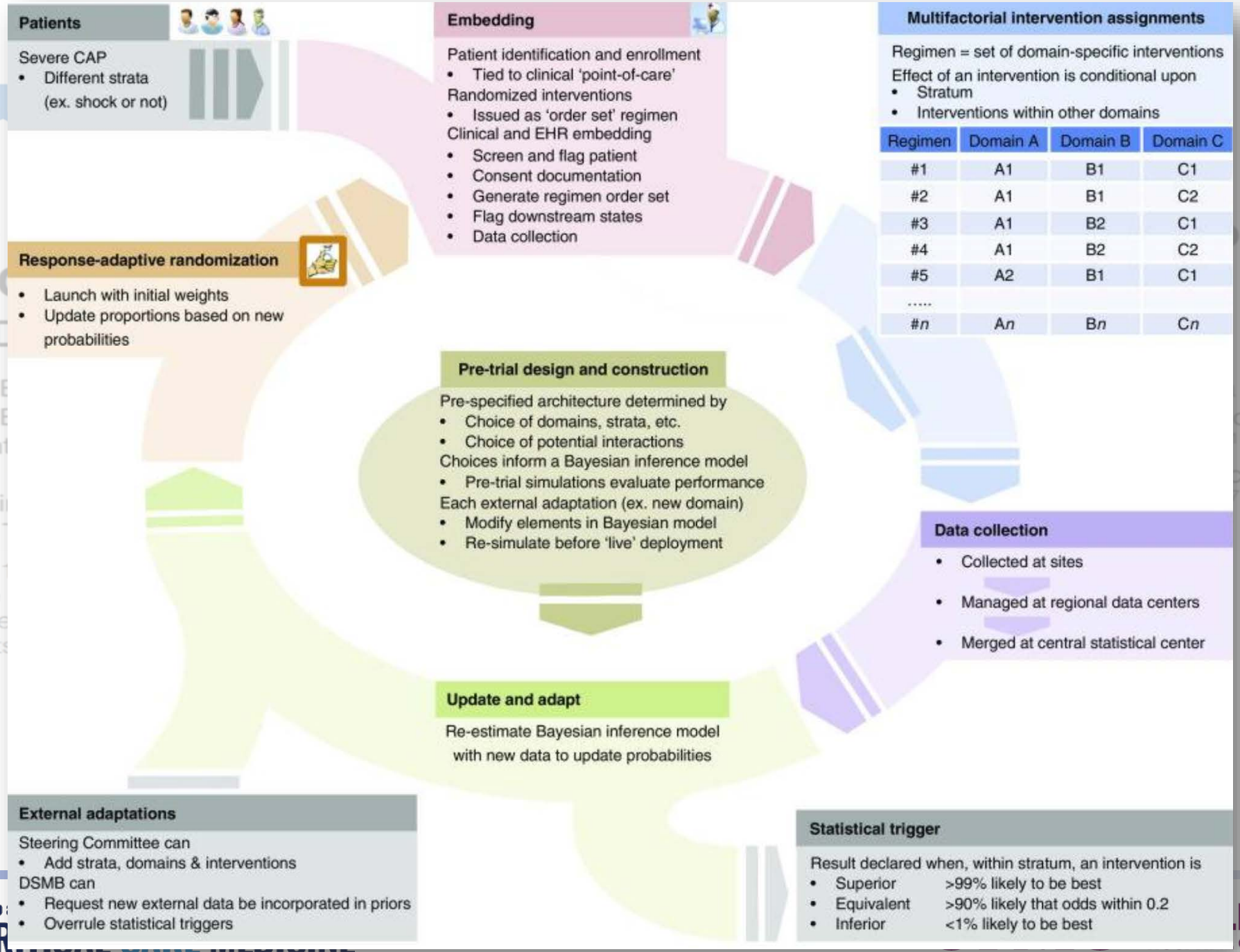
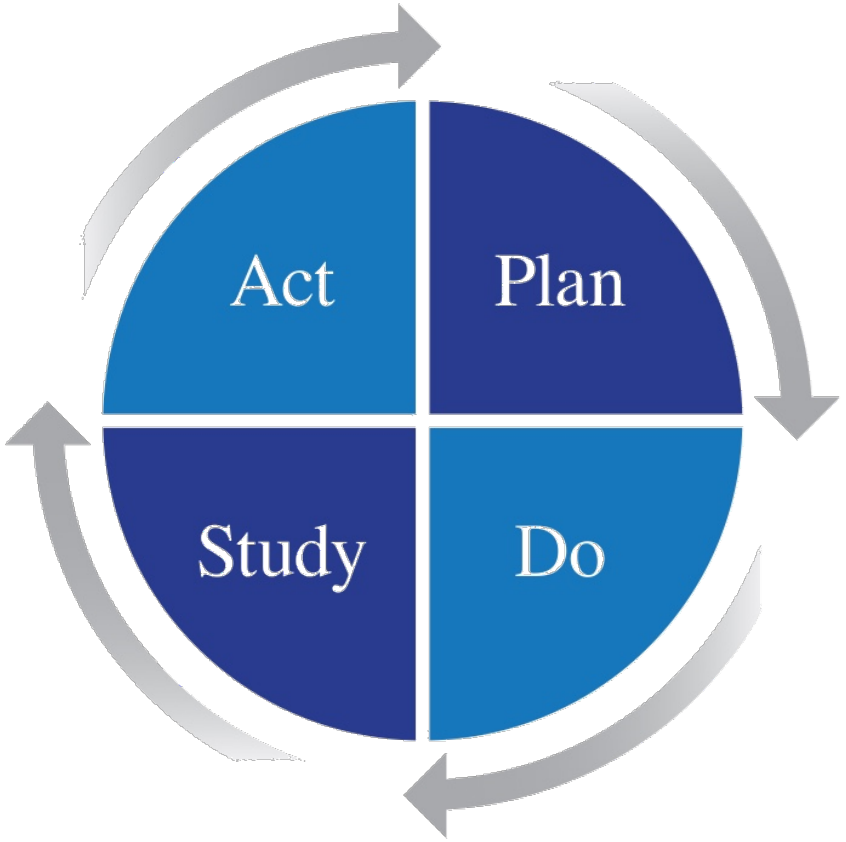
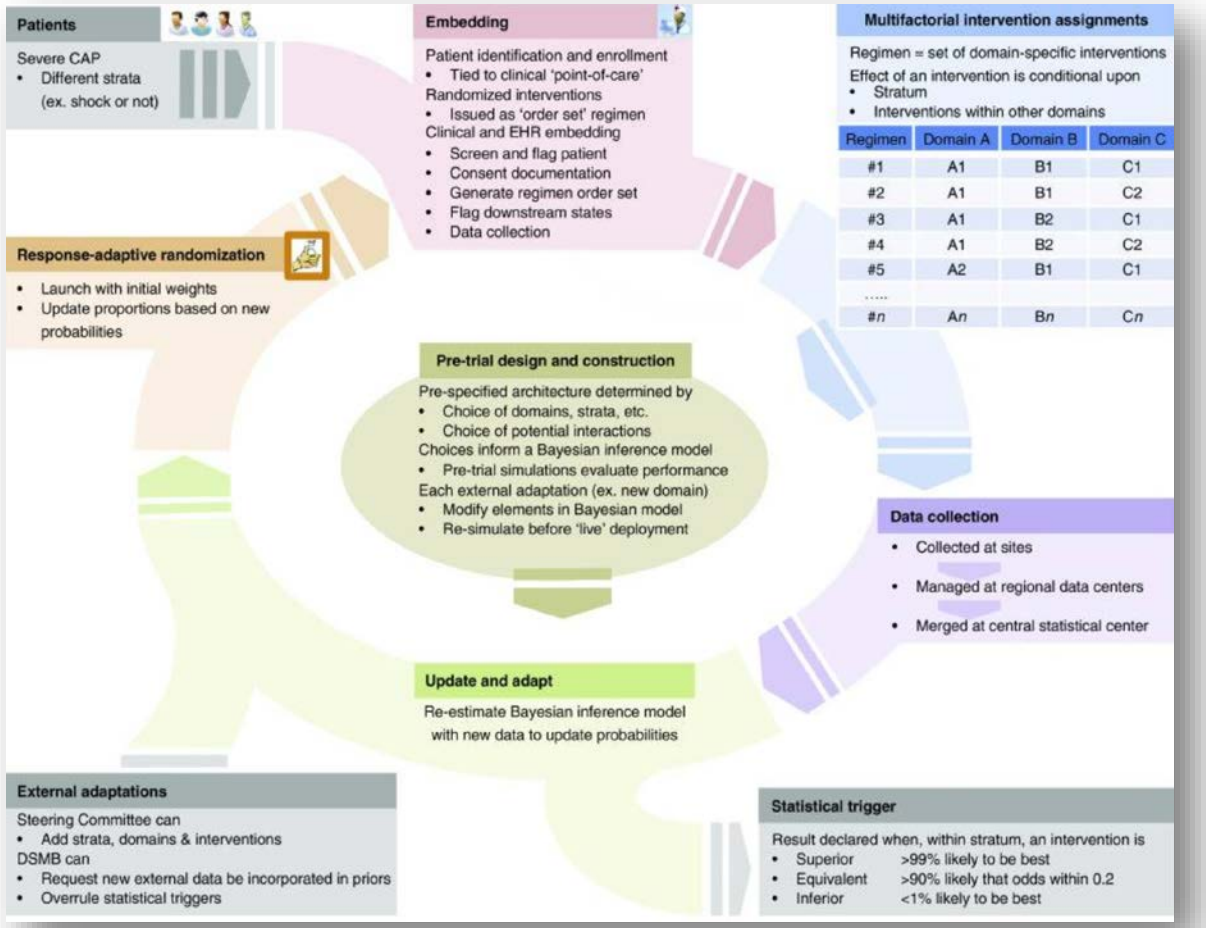
| | |
|---|---|
| R | **Randomization.** Once the design is specified, sites are recruited and trained, appropriate oversight and approval is obtained, and all study execution procedures are deployed, the study launches. The trial begins by randomizing patients with fixed allocations to each treatment arm, proportional to the number of arms. Later, randomization weights are adjusted based on updated probabilities from the Bayesian inference model. |
| E | **Embedding.** A key element of the design is tight integration with clinical operations, including using a clinical 'moment', or 'point-of-care' to flag and enroll patients and to deliver the treatment regimen as an 'order set'. Ideally, embedding will take advantage of electronic health record data, not only to help flag and enroll patients, but to deliver patient order sets and to facilitate on-going monitoring and data collection. |
| M | **Multifactorial intervention assignments.**The treatment regimens themselves are assigned as a regimen, containing each randomized intervention within each domain. In settings with standard ICU order sets, the regimen would ideally be generated automatically, with inclusion of standard non-randomized ICU care elements as well as those randomized items that are part of REMAP-CAP. |
| A | **Adaptation.**The heart of the trial is the monthly update of the Bayesian inference model. Each month, the SAC runs the Bayesian inferencemodel using the updated trial data to generate an updated posterior probability for all trial outcomes. If the model generates a probability that has crossed a predetermined threshold, it triggers a platform conclusion. Otherwise, the probabilities are used to update the randomizationweights. |
| P | **Platform.** The entire trial is envisioned, like all adaptive platform trials, as a learning engine that can test multiple interventions both in parallel and sequentially. Thus, the focus is on the condition, CAP, itself, and not on any particular intervention. This approach allows a standard approach for enrollment and data collection to be built once and then run perpetually, providing numerous efficiencies. |
| | **Data collection.** Data, ideally via the EHR, is uploaded to regional coordinating centers (RCCs), responsible for local data management and auditand feedback of sites. The RCCs forward data to the statistical analysis committee (SAC). |



# PDSA Cycle




# REMAP Design



# REMAP COVID Findings at Present

- **Corticosteroids associated with improved organ support-free days**

  *JAMA. 2020 Oct 6;324(13):1317-1329.*

- **Treatment with Interleukin 6 antagonists improve survival**

  *N Engl J Med. 2021 Apr 22;384(16):1491-1502.*

- **Lopinavir-ritonavir, hydroxychloroquine or both worsen outcomes including survival**

  *Intensive Care Med. 2021 Aug;47(8):867-886.*

- **Therapeutic anticoagulation improves survival in noncritically ill patients and does not improve survival in critically ill patients (MPRCT: REMAP, ATTACC & ACTIV-4a)**

  *N Engl J Med. 2021 Aug 26;385(9):790-802.*

  *N Engl J Med. 2021 Aug 26;385(9):777-789.*

- **Convalescent plasma has a low likelihood of improving outcomes**

  *JAMA. 2021 Nov 2;326(17):1690-1702.*

- **Aspirin and P2Y12 platelet inhibitors have a low likelihood of improving outcomes**

  *JAMA. 2022 Apr 5;327(13):1247-1259.*

# Trial design considerations

# LHS Trials

- Span the full range of study designs, e.g.
  - N of 1
  - Stepped wedge
  - Cluster randomized
  - Patient-level randomization
  - Response adaptive, patient-level randomization within a platform trial
- Spectrum of simple -> complex
- Spectrum of ‘embeddedness’

# Different questions and solutions

- **Comparative effectiveness**
  - Examine currently accepted standards of care
  - Role of consent/assent  - is it always needed?
  - Tracking data by leveraging existing infrastructure
  - QI infrastructure for trial conduct
- **Processes of care**
  - Good fit for cluster randomization
  - Sweeping QI/PI approaches don’t seek consent
  - QI infrastructure for trial conduct
- **Investigational drugs**
  - Greater required overhead
  - Consent/assent required
  - Regulatory compliance requires substantial resources

# Summary

- Existing resources can be leveraged for investigation
  - Potentially easier during times of crisis
- Crisis yields innovation
- The learning health system
- Trial design considerations


# Thank You

## Questions/Discussion

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