



NIH Collaboratory

Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Reengineering Pragmatic Research for Future Pandemics

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Case Scenario

- A new virus, severe acute-respiratory syndrome coronavirus-99, has emerged causing a new disease, COVID-23, threatening to become a global epidemic,
- World-wide, policy, healthcare leaders are poised to address the crisis differently.
- Early data shows SARS- CoV-99 has 5X transmission rate c/w SARS-CoV-2 and COVID-23 case mortality is 3X higher than COVID-19
- Recently, you've been promoted to new position, Pandemic Response Super-Director

The Year is 2023

- And you are the new Pandemic Super-Response Director, with full authority to change the research ecosystem.
- You've organized teams to change the system and each has a magic wand to address the following areas
 - Administrative & Regulatory
 - Study Design & Execution
 - Data
 - Dissemination

The Problem: Will Thousands of Flowers Bloom Work?



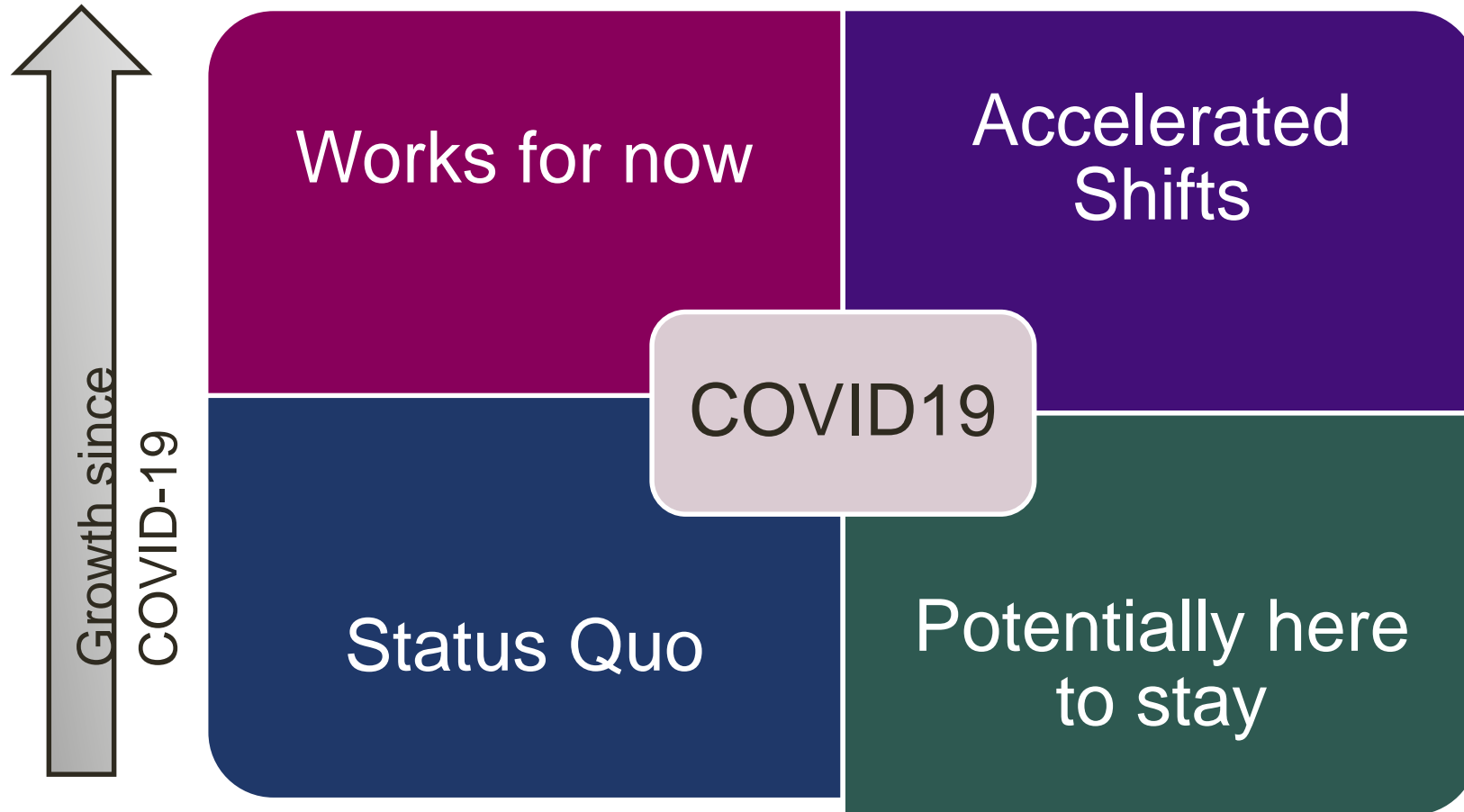
Data source: CTTI's database for Aggregate Analysis of ClinicalTrials.gov (AACT) (<https://aact.ctti-clinicaltrials.org/>).

The Opportunity Costs: Duplication + Inefficiency

	All studies N=558	Industry N=242	NIH N=35	No external N=241	Other N=40
Recruitment status at time of data download, n/N (%)					
Not yet recruiting	75/558 (13.4%)	28/242 (11.6%)	3/35 (8.6%)	37/241 (15.4%)	7/40 (17.5%)
Recruiting	361/558 (64.7%)	166/242 (68.6%)	23/35 (65.7%)	147/241 (61.0%)	25/40 (62.5%)
Enrolling by invitation	18/558 (3.2%)	6/242 (2.5%)	1/35 (2.9%)	8/241 (3.3%)	3/40 (7.5%)
Active, not recruiting	61/558 (10.9%)	29/242 (12.0%)	4/35 (11.4%)	26/241 (10.8%)	2/40 (5.0%)
Completed	26/558 (4.7%)	10/242 (4.1%)	3/35 (8.6%)	13/241 (5.4%)	0/40 (0.0%)

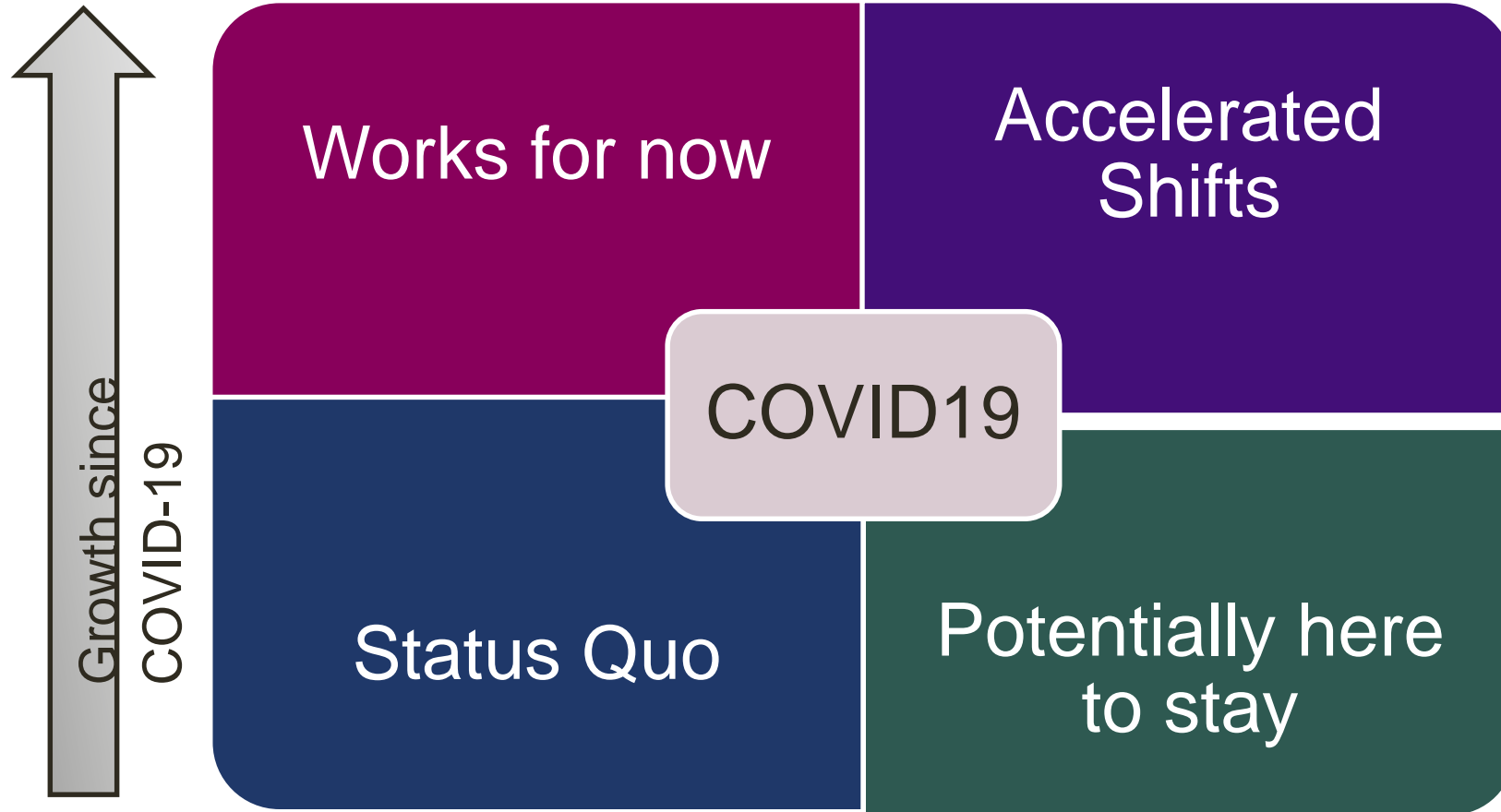
[Very few completed, most in recruiting/not yet recruiting status, and only ~5% estimated will ever matter]

What will stick post-COVID-19?



Intent to use post-COVID-19

What will stick post-COVID-19?



PANDEMIC
RESPONSE
MEMORY



ADMINISTRATIVE SUCCESS?

Administrative Opportunities

Problems



Delays due to contracting



Delays due to IRB



Delays in local approvals

Solutions

- Emergency contracting rules
- Use “commercial”-grade central IRB
- Offload research-specific tasks
- Public rewards

Update the 1950 Defense Production Act?

- **Title I: Priorities and Allocations**, which allows the President to require persons (including businesses and corporations) to prioritize and accept contracts for materials and services as necessary to promote the national defense.
- **Title III: Expansion of Productive Capacity and Supply**, which allows the President to incentivize the domestic industrial base to expand the production and supply of critical materials and goods. Authorized incentives include loans, loan guarantees, direct purchases and purchase commitments, and the authority to procure and install equipment in private industrial facilities.

81st CONGRESS } HOUSE OF REPRESENTATIVES { REPORT
2d Session } { No. 2759

DEFENSE PRODUCTION ACT OF 1950

JULY 28.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. SPENCE, from the Committee on Banking and Currency, submitted the following

REPORT

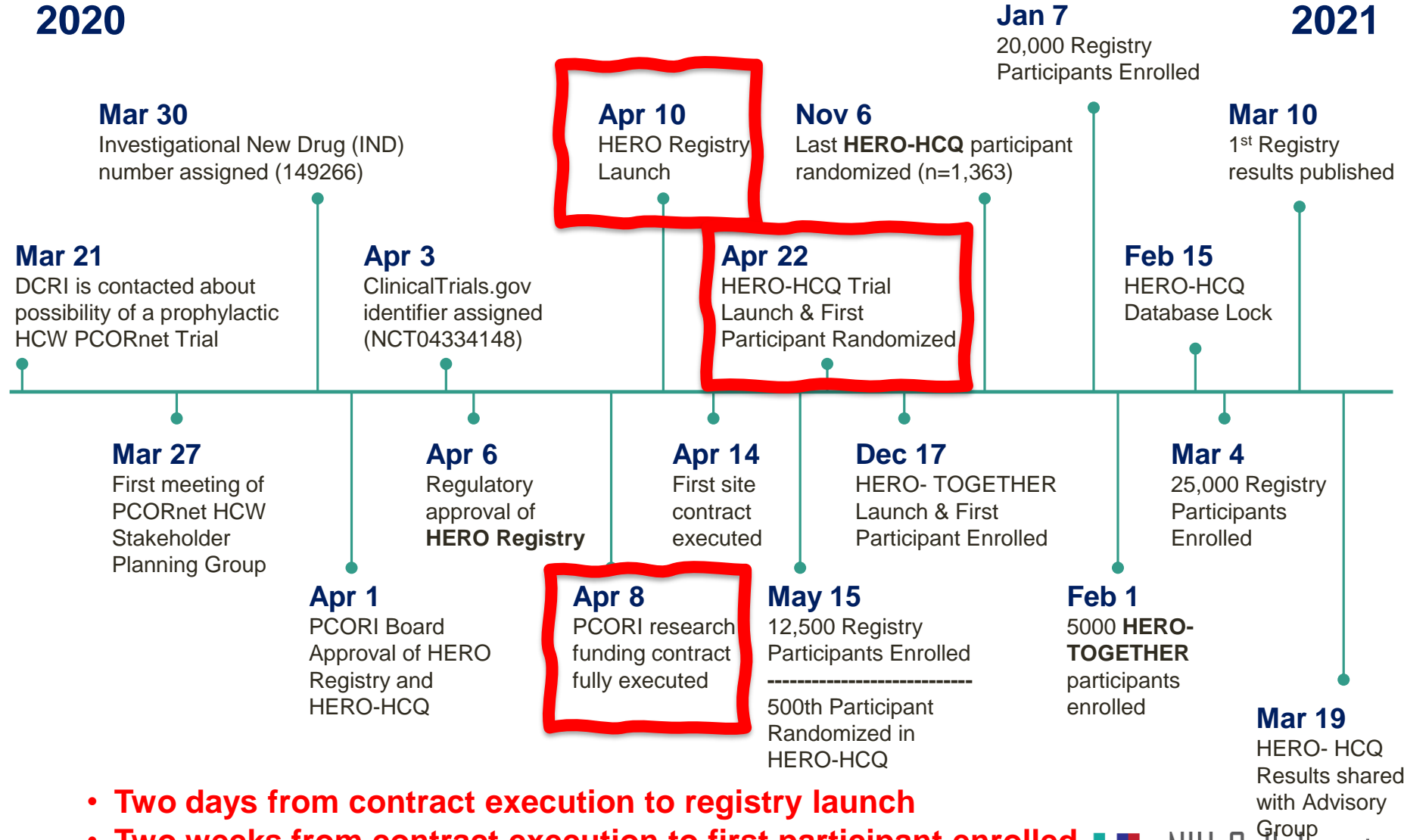
[To accompany H. R. 9176]

The Committee on Banking and Currency, to whom was referred the bill (H. R. 9176), to establish a system of priorities and allocations for materials and facilities, authorize the requisitioning thereof, provide financial assistance for expansion of productive capacity and supply, strengthen controls over credit, regulate speculation on commodity exchanges, and by these measures facilitate the production of goods and services necessary for the national security, and for other purposes, having considered the same, report favorably thereon with an amendment, and recommend that the bill as amended to pass.

One Year with HERO

March
2020

March
2021



- **Two days from contract execution to registry launch**
- **Two weeks from contract execution to first participant enrolled**

STUDY DESIGN & EXECUTION

In 2017...Prescient?

The NEW ENGLAND JOURNAL of MEDICINE

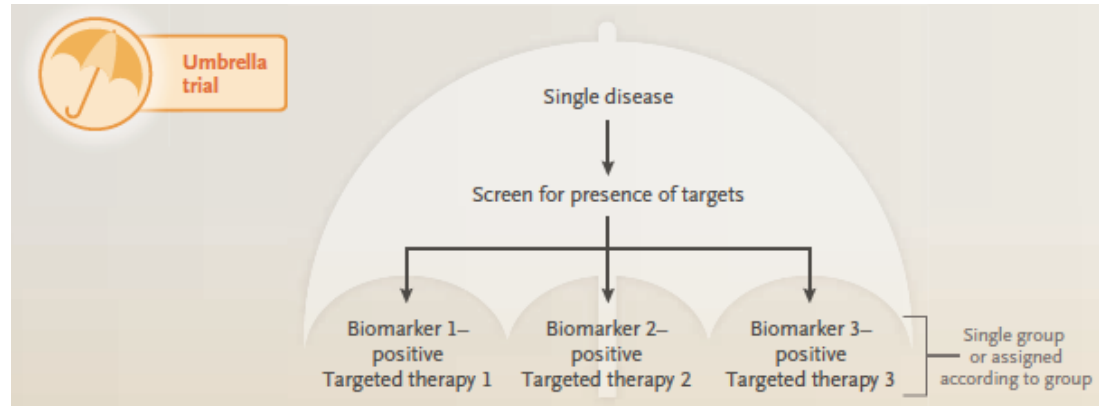
REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

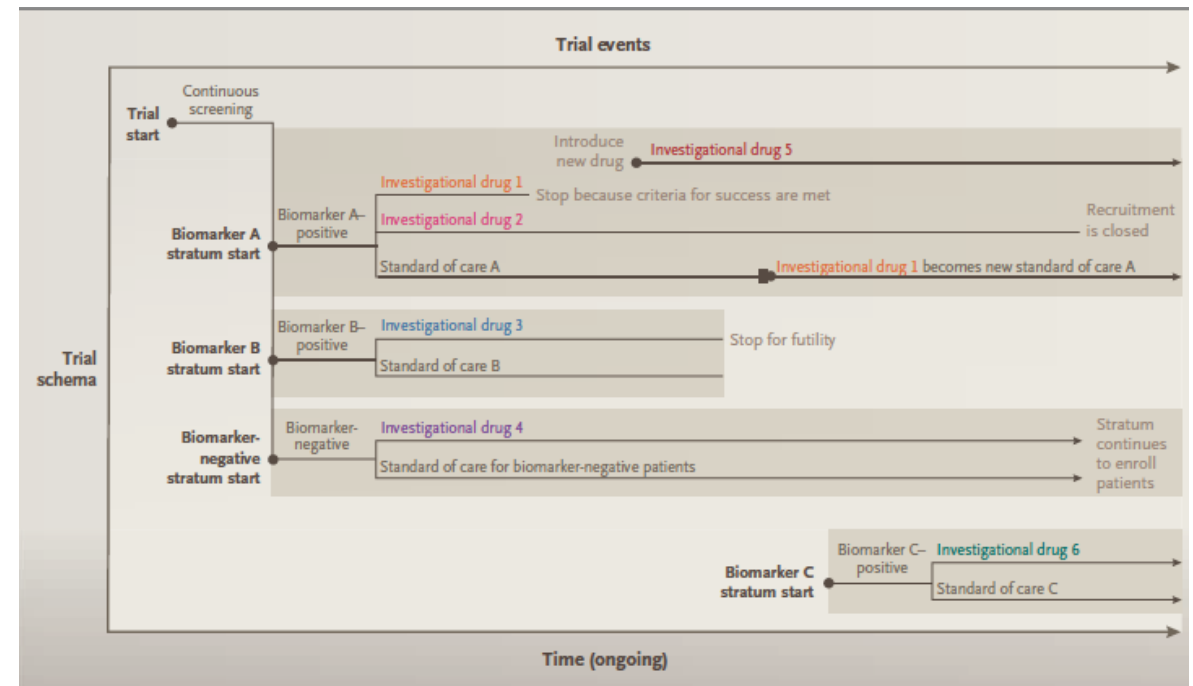
Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.



Platform Trial



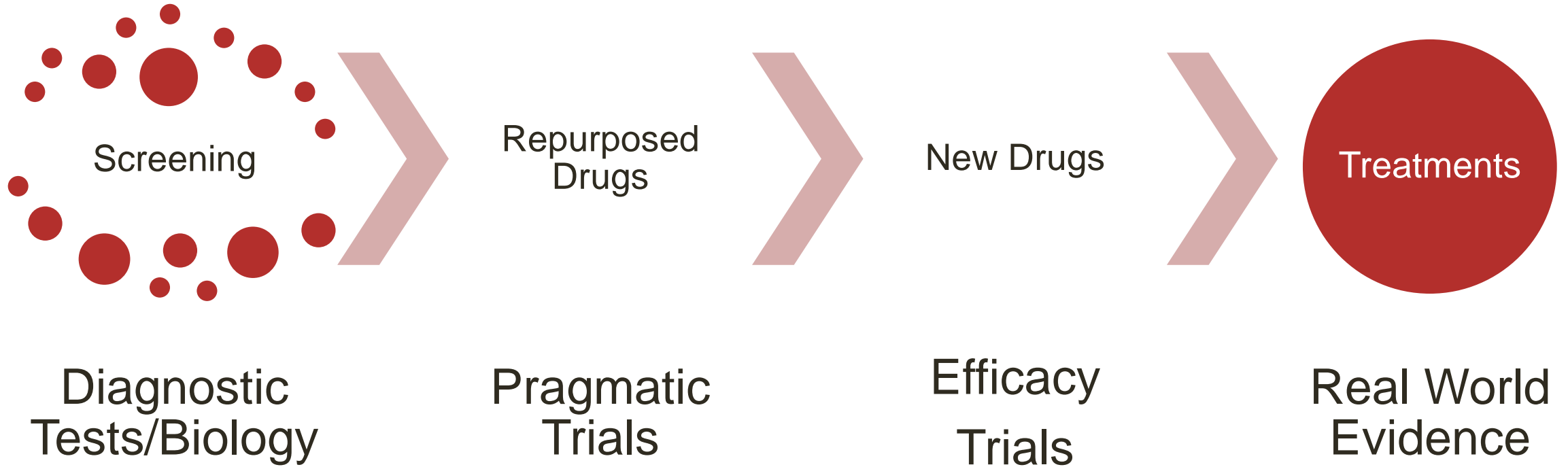
Just... 2% Challenge

31.3 Million
Covid Cases

562,000
Deaths

- On average 2%-4% of eligible participate in clinical trials
- For COVID-19, that could have been **~600K-1.2M** participants in a national, coordinated platform

What if you enrolled...600K or 1.2M



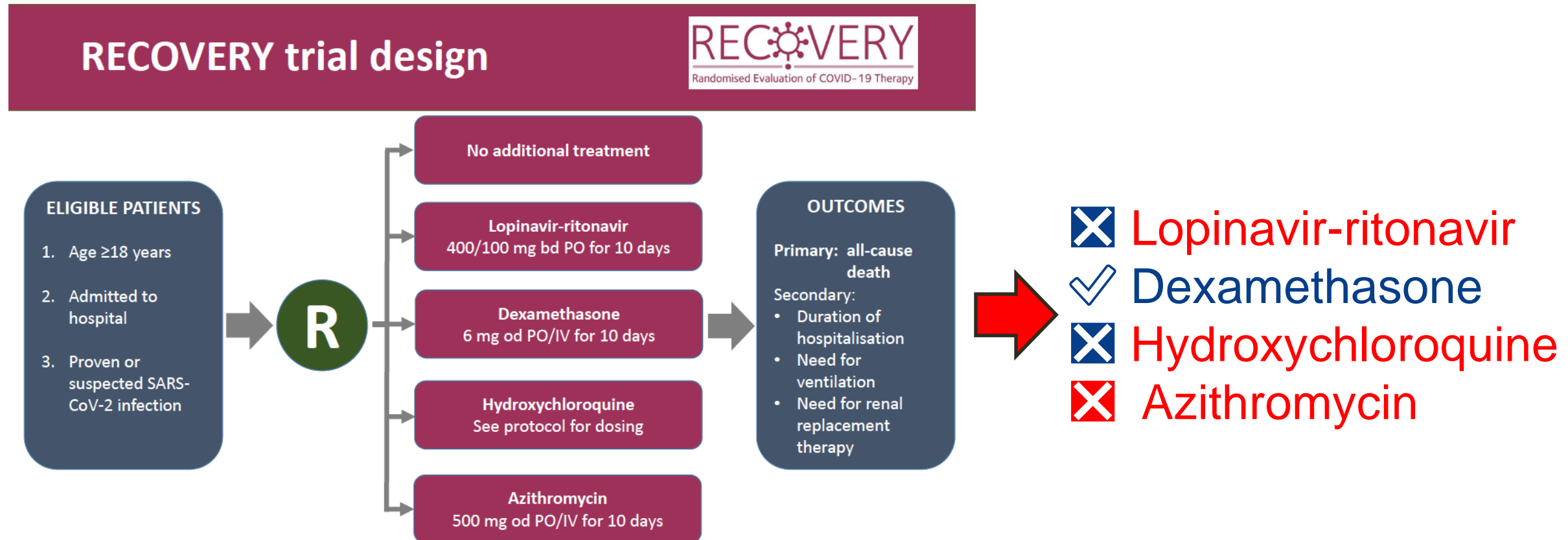
Instead....

We have few master protocols in U.S.

	All studies N=558	Industry N=242	NIH N=35	No external N=241	Other N=40
Master protocol, n/N (%)	14/558 (2.5%)	3/242 (1.2%)	6/35 (17.1%)	4/241 (1.7%)	1/40 (2.5%)

Data source: CTTI's database for Aggregate Analysis of ClinicalTrials.gov (AACT)
(<https://aact.ctti-clinicaltrials.org/>).

A Real Learning Healthcare System: United Kingdom



REMAP

RANDOMIZED

Allow CAUSAL inference

EMBEDDED

Align with care; leverage the EHR

MULTIFACTORIAL

Multiple treatments and subgroups

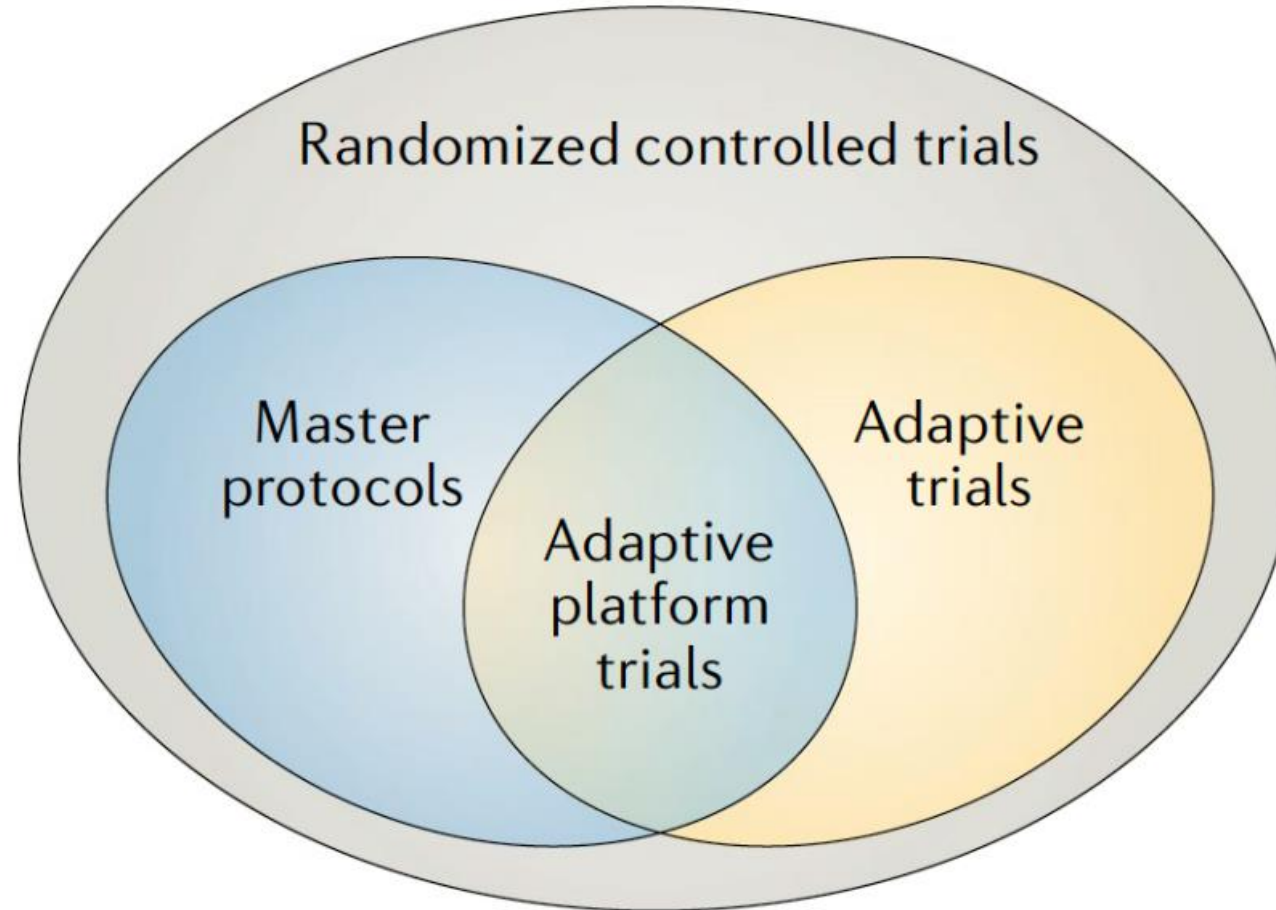
ADAPTIVE

Match odds of success to odds of assignment

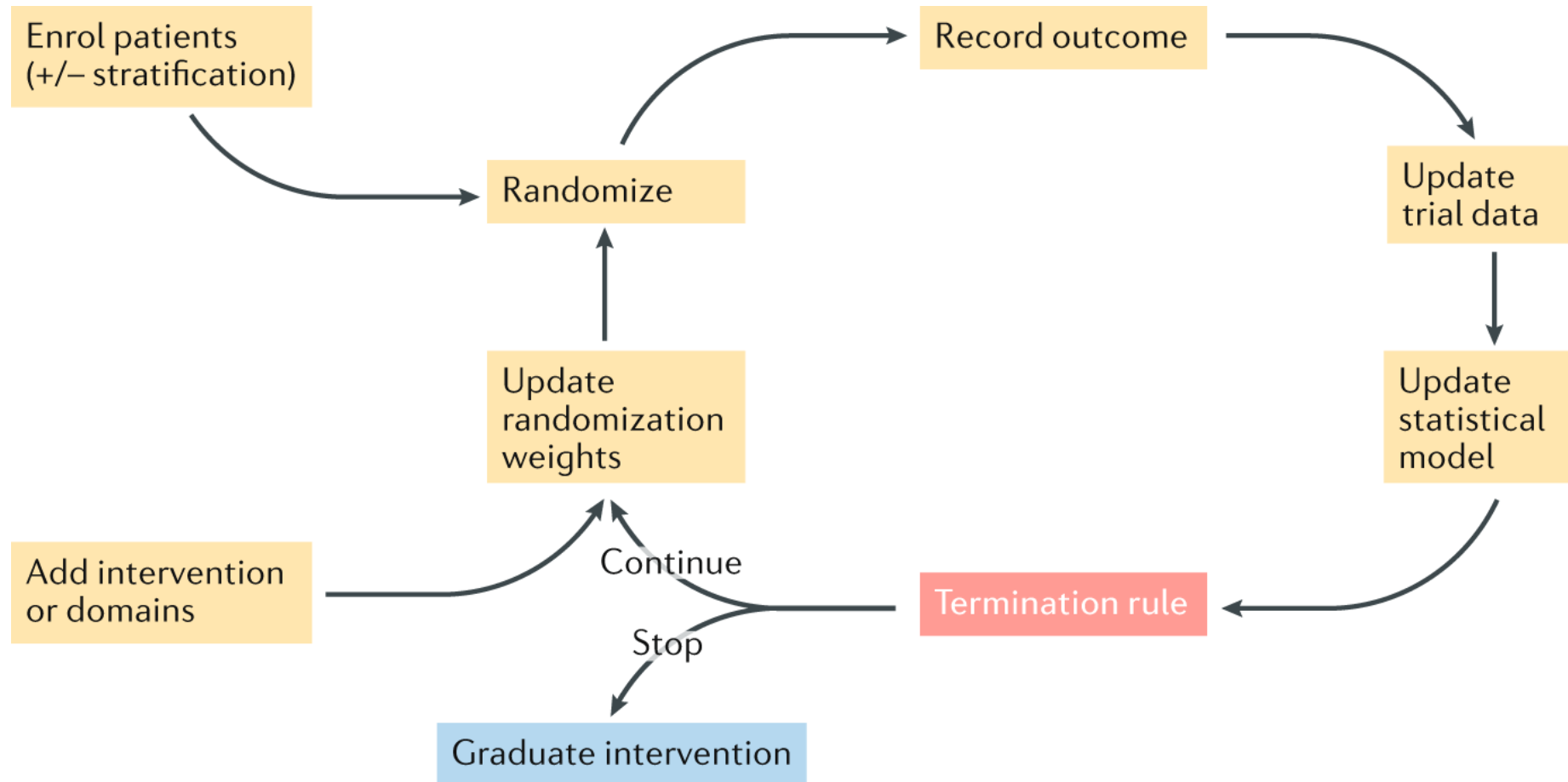
PLATFORM

Perpetual enrollment; continuous learning

Adaptive Platform Trials

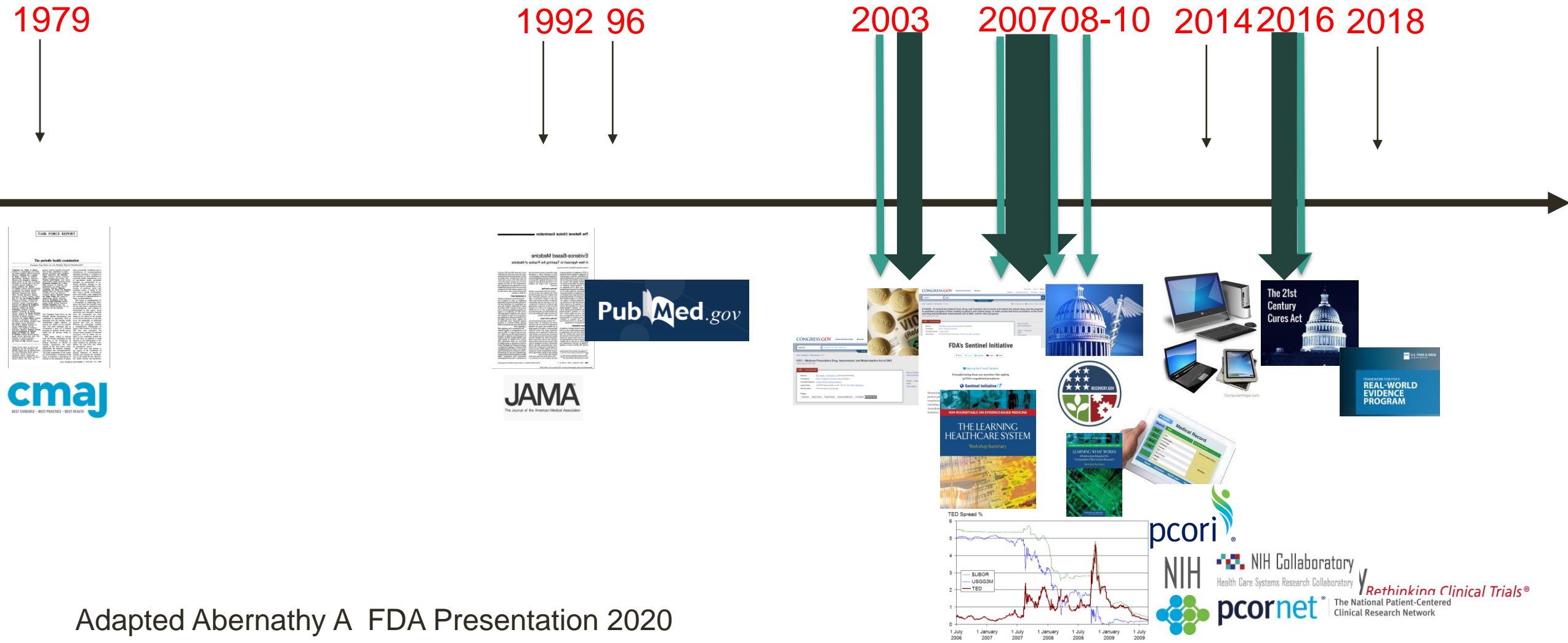


Learning and Evolving



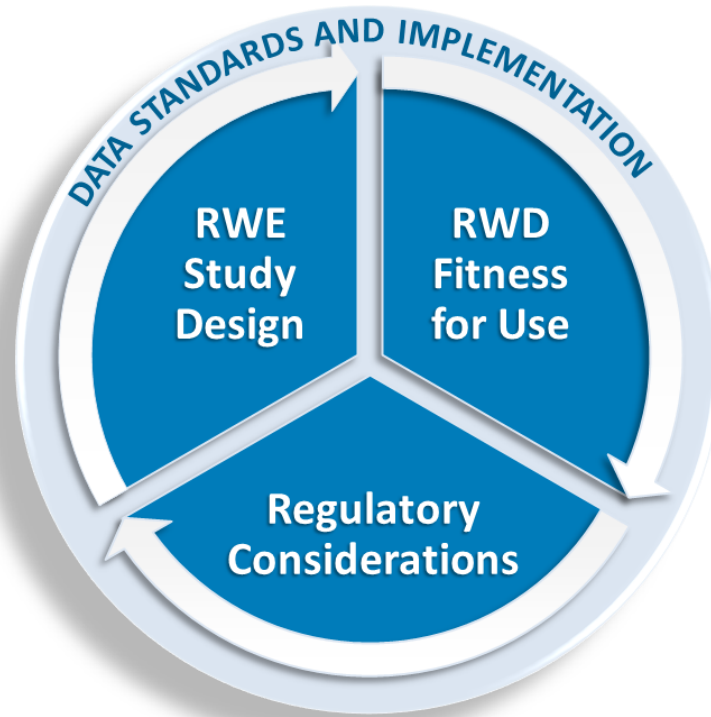
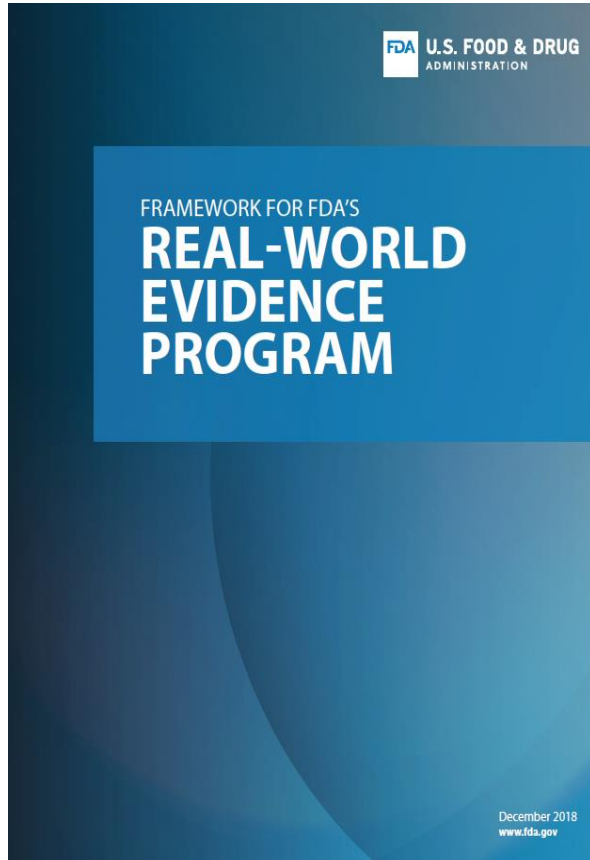
DATA

Acceleration of Real World Data



Adapted Abernathy A FDA Presentation 2020

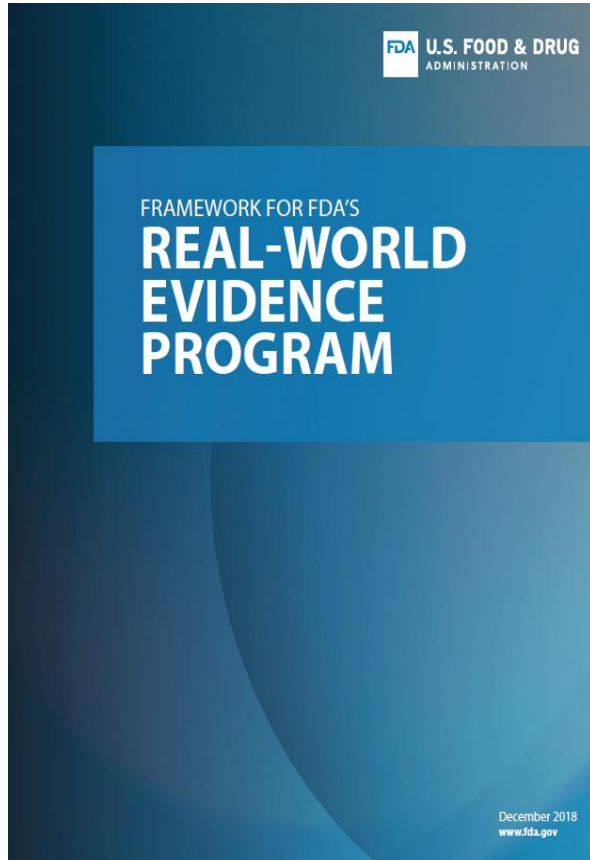
FDA RWE Framework



Key Issues

- Are the RWD **fit for use**?
- Will the **trial or study design** used to generate RWE provide adequate scientific evidence to answer the regulatory question?
- Will the study conduct meet **regulatory requirements**?

FDA RWE Framework



Key Issues

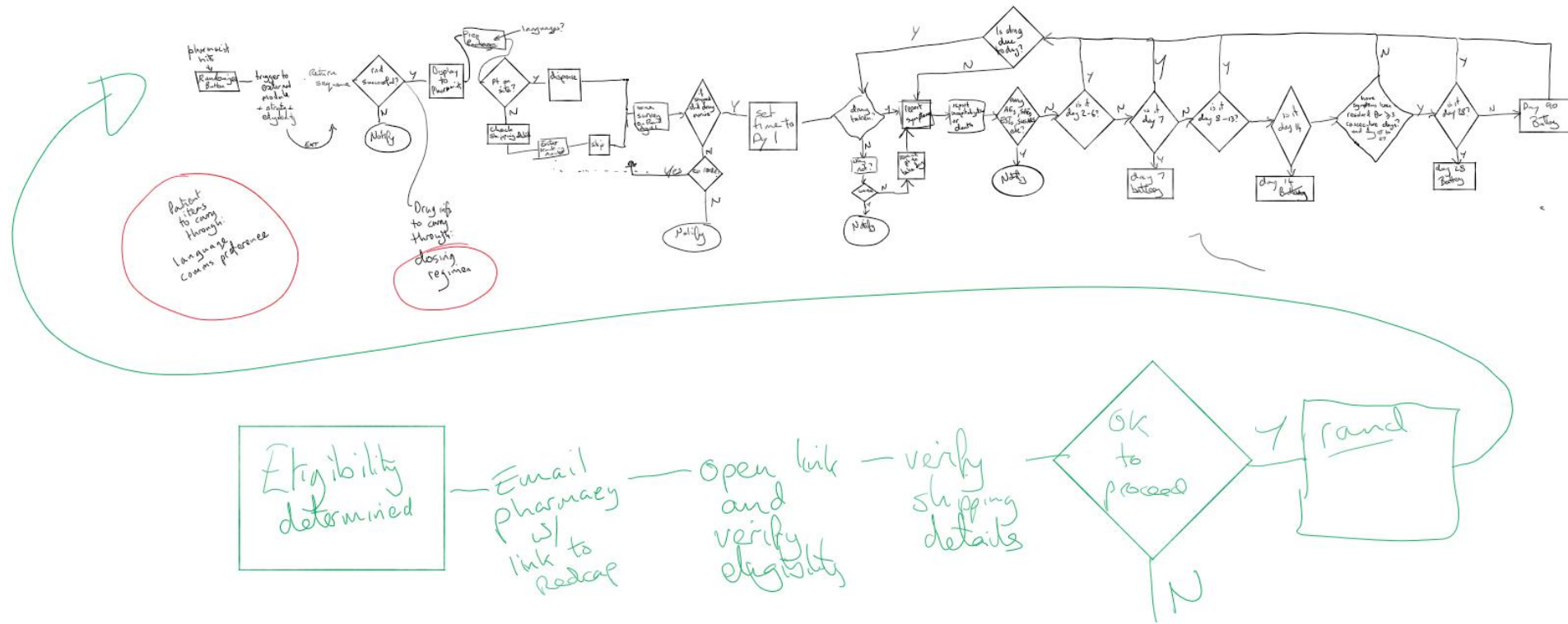
Are the RWD **fit for use**?

Will the **trial or study design** used to generate RWE provide adequate scientific evidence to answer the regulatory question?

Will the study conduct meet **regulatory requirements**?

- Can you trust, trace and replicate?

Case for Making Data Smarter *in Real Time*: TREAT NOW



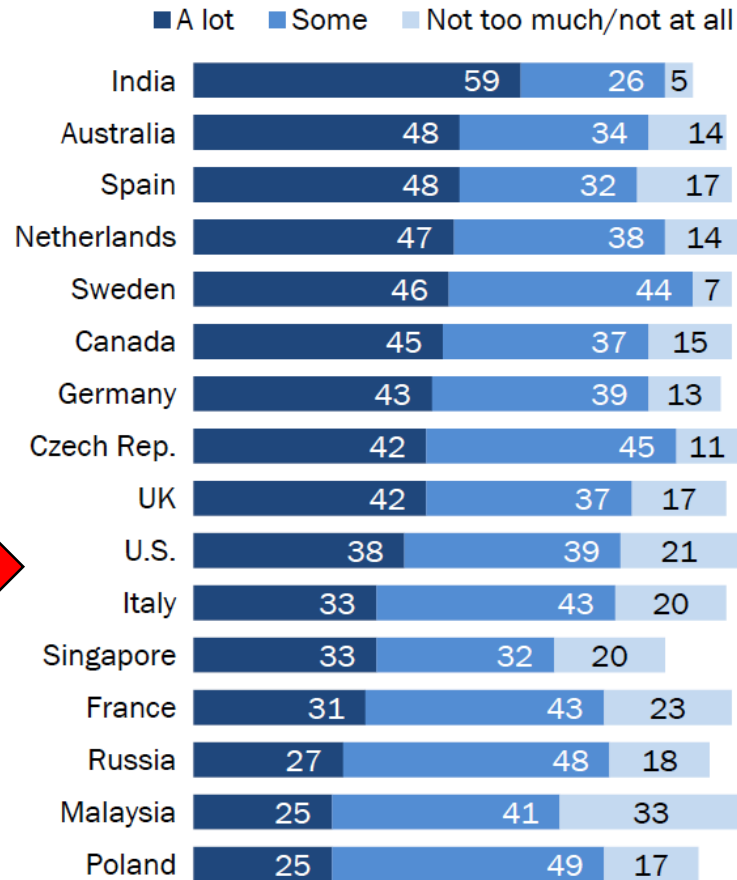
At every step and with every data form, it is essential to think through the possible failures and how the technology can trap them to maintain trial integrity

IN REAL TIME

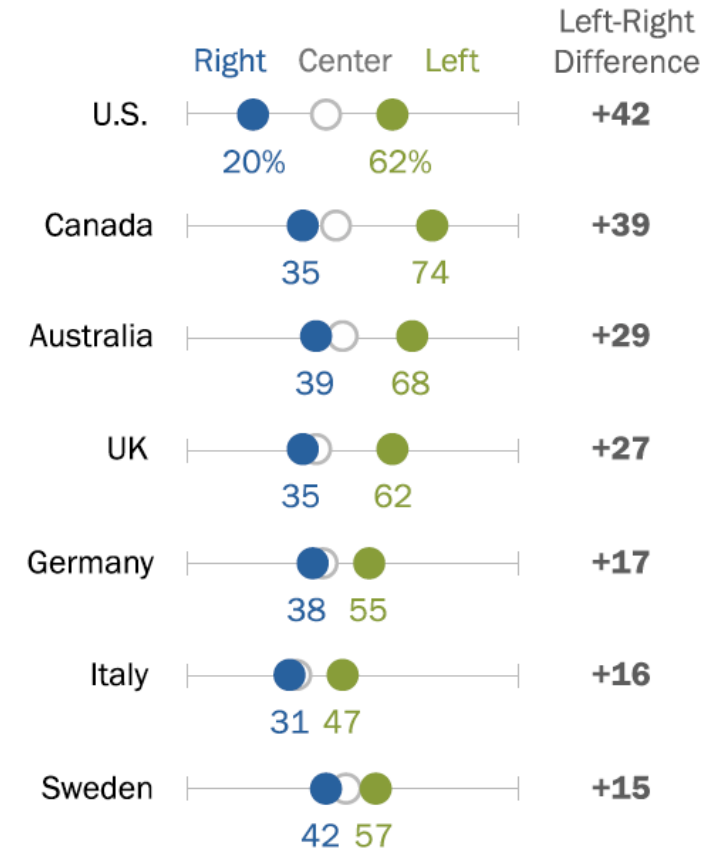
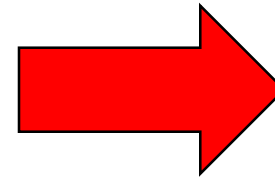
DISSEMINATION

Trust in Science

Trust in Science



Political Views and Trust in Science



What is easier to use?

A. Data from yesterday

B. Data from tomorrow

Completed COVID19 Studies: Observational vs. Prospective Trials

medRxiv

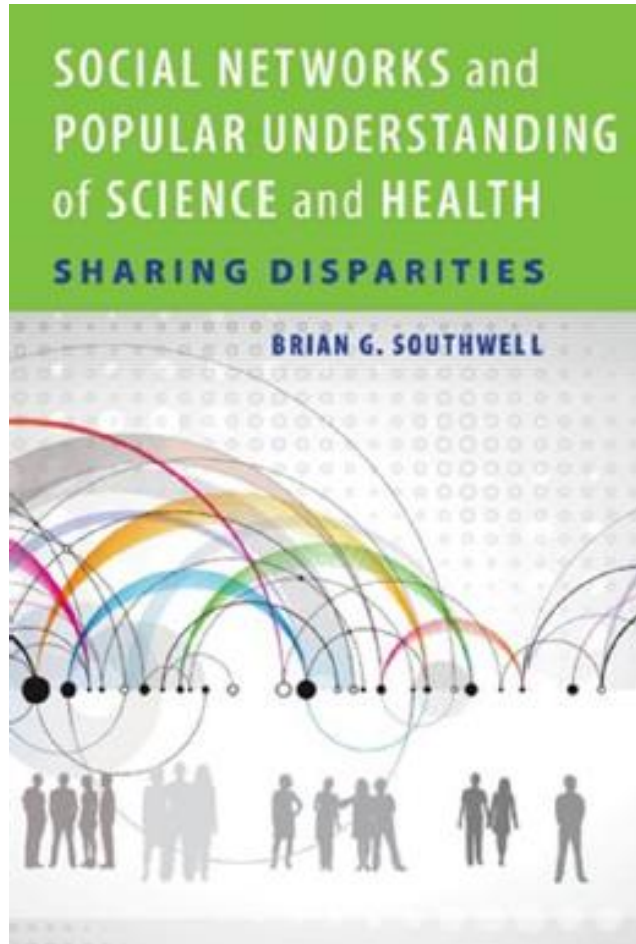
THE PREPRINT SERVER FOR HEALTH SCIENCES

8,973



26

Preventing Gossip, Misinformation, Misunderstanding



- Bias towards acceptance
- Discomfort of uncertainty
- Lack of corrective information
- Information is a relationship currency
- Emotions allows inaccurate information acceptance

Brian Southwell, PhD NIH Collaboratory Grand Rounds July 15, 2019

Weeks, B.E. (2015). Emotions, partisanship and misperceptions. *Journal of Communication* 699-719

Conclusions

- No doubt...we can do better next time:
 - Administratively
 - Smart study designs
 - Purposeful data
 - Rapid, yet careful dissemination
- To do so,
 - Need a PANDEMIC RESPONSE PRODUCTION ACT
 - Leverage national system(s) of care
 - AVOID unnecessary bureaucracy
 - AVOID individualism (the thousand flowers...)
- And maybe....
 - Some of this will help common, chronic health conditions or crises