Can the Covid-19 Crisis Lead to Reformation of the Evidence Generation System?

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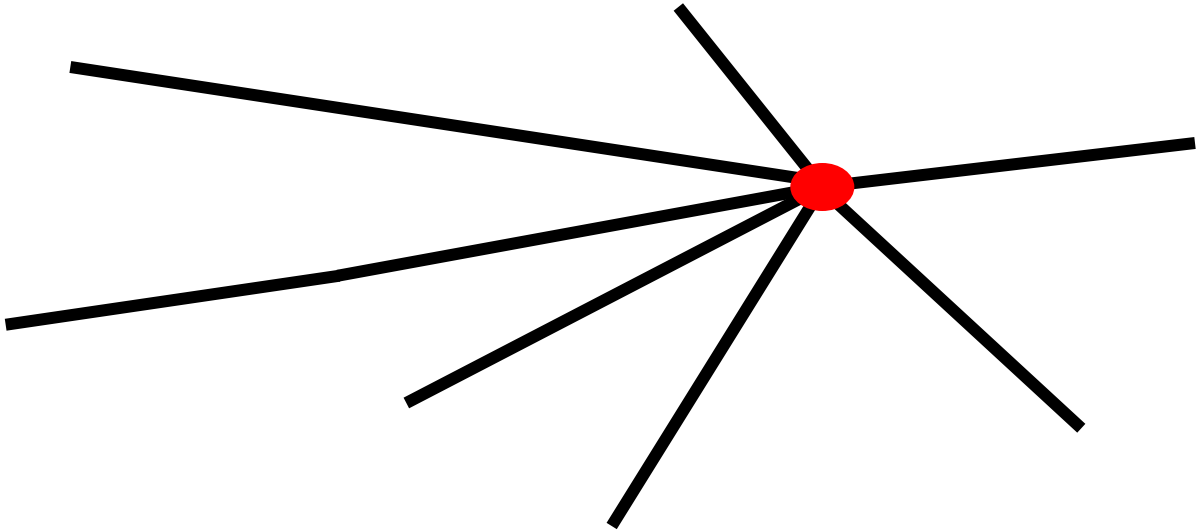
NIH Collaboratory Grand Rounds

May 1st, 2020

The Evidence Generation System

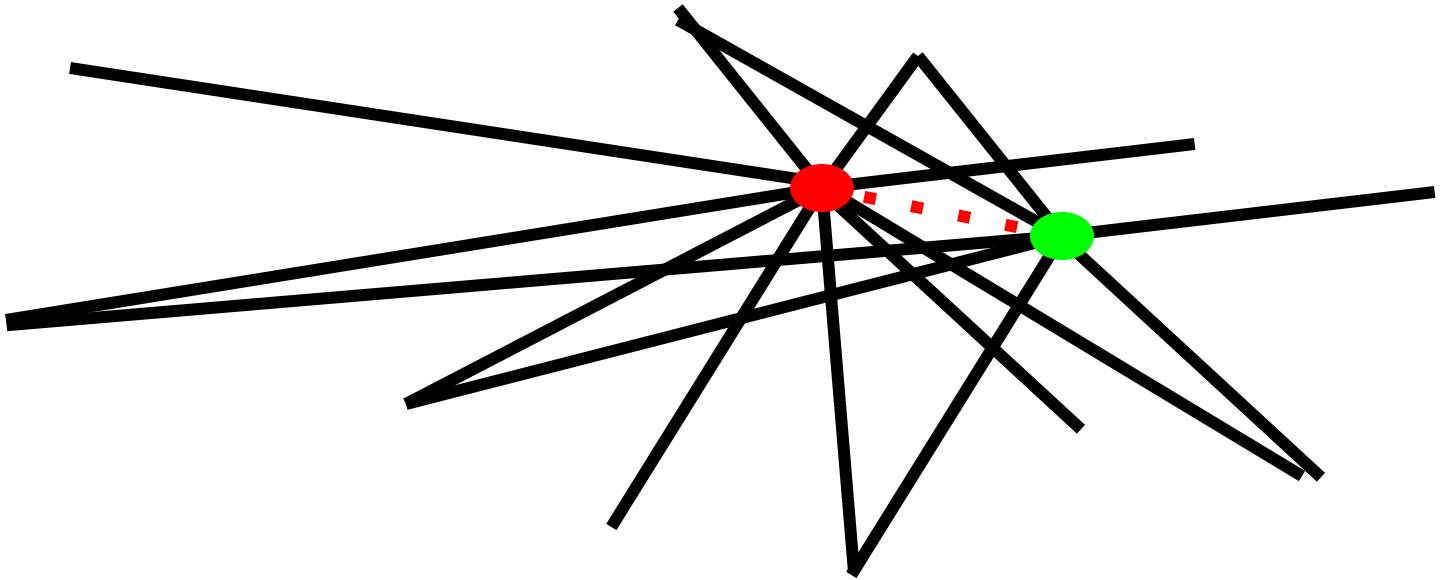
- Early in my career (1970's), I had access to one of the first databases that measured characteristics of patients undergoing cardiovascular procedures and followed them for life
- My chosen clinical role was acute cardiovascular care just as fibrinolysis and percutaneous intervention were invented—leading to a rapid evolution of databases, outcomes research, clinical trials
- Lessons were learned about linking evidence generation and clinical practice, well described in concepts of learning health systems
- Without reliable empirical evidence people/patients suffer from "eminence based" medical practice
- While progress has been made the system was falling far short of its capabilities, then COVID-19 hit
- **In the midst of this tragedy what are the opportunities that have been created to move the system to a better place?**
- **What are the main blockers of this system that we should seriously think about as our healthcare system is rebuilt?**

Typical NIH Network Academic Health Center Sites & Data Coordinating Center



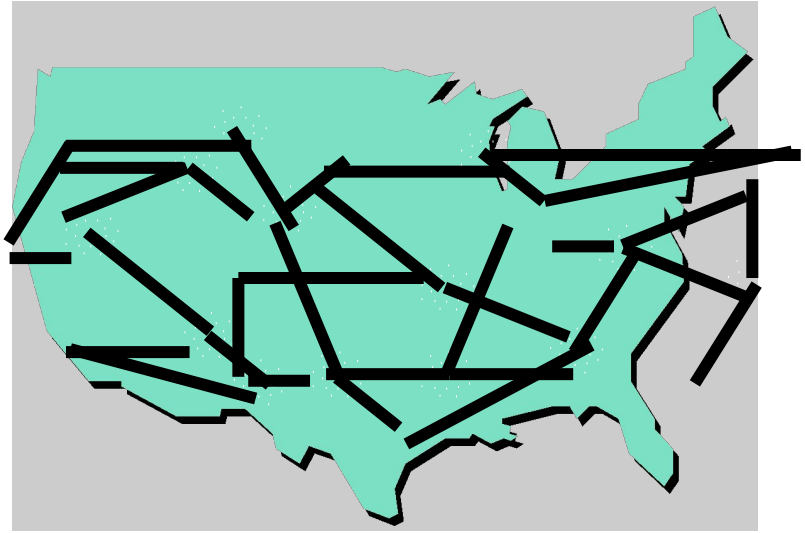
(circa 2005, Stephen Strauss in midst of CTSA planning)

Interoperable Networks Share Sites and Data

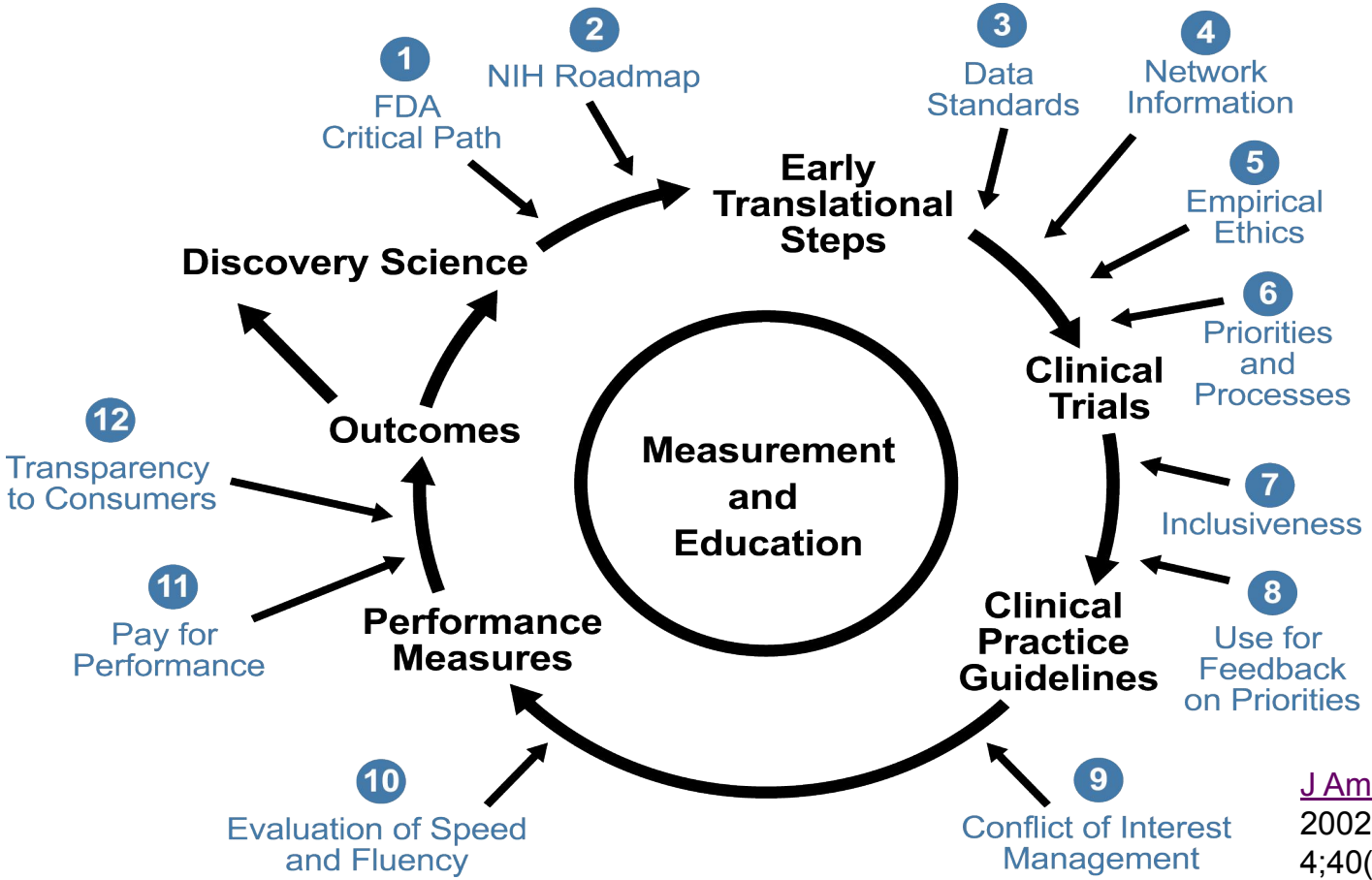


Integration of Clinical Research Networks

- Link existing networks so clinical studies and trials can be conducted more effectively
- Ensure that patients, physicians, and scientists form true “Communities of Research”



Generating Evidence to Inform Decisions



J Am Coll Cardiol.
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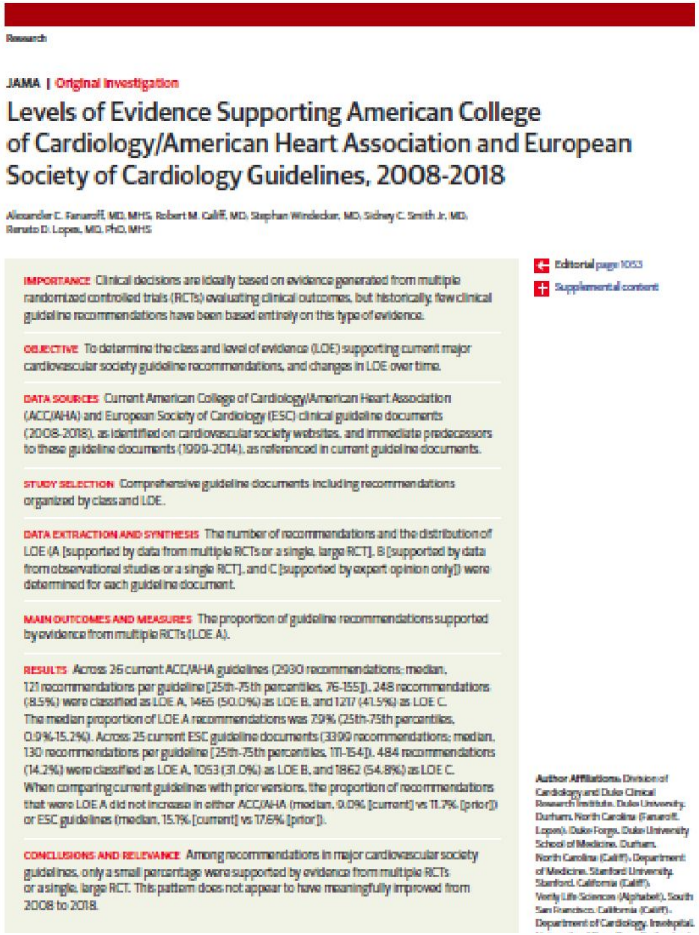

Research

JAMA | Original Investigation

Levels of Evidence Supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018

Alexander C. Fanaroff, MD, MHS; Robert M. Califf, MD; Stephan Windecker, MD; Sidney C. Smith Jr, MD; Renato D. Lopes, MD, PhD, MHS

Editorial page 1053
Supplemental content

IMPORTANCE Clinical decisions are ideally based on evidence generated from multiple randomized controlled trials (RCTs) evaluating clinical outcomes, but historically, few clinical guideline recommendations have been based entirely on this type of evidence.

OBJECTIVE To determine the class and level of evidence (LOE) supporting current major cardiovascular society guideline recommendations, and changes in LOE over time.

DATA SOURCES Current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) clinical guideline documents (2008-2018), as identified on cardiovascular society websites, and immediate predecessors to these guideline documents (1999-2014), as referenced in current guideline documents.

STUDY SELECTION Comprehensive guideline documents including recommendations organized by class and LOE.

DATA EXTRACTION AND SYNTHESIS The number of recommendations and the distribution of LOE (A [supported by data from multiple RCTs or a single, large RCT], B [supported by data from observational studies or a single RCT], and C [supported by expert opinion only]) were determined for each guideline document.

MAIN OUTCOMES AND MEASURES The proportion of guideline recommendations supported by evidence from multiple RCTs (LOE A).

RESULTS Across 26 current ACC/AHA guidelines (2930 recommendations; median, 121 recommendations per guideline [25th-75th percentiles, 76-155]), 248 recommendations (8.5%) were classified as LOE A, 1465 (50.0%) as LOE B, and 1217 (41.5%) as LOE C. The median proportion of LOE A recommendations was 7.9% (25th-75th percentiles, 0.9%-15.2%). Across 25 current ESC guideline documents (3399 recommendations; median, 130 recommendations per guideline [25th-75th percentiles, 111-154]), 484 recommendations (14.2%) were classified as LOE A, 1053 (31.0%) as LOE B, and 1862 (54.8%) as LOE C. When comparing current guidelines with prior versions, the proportion of recommendations that were LOE A did not increase in either ACC/AHA (median, 9.0% [current] vs 11.7% [prior]) or ESC guidelines (median, 15.1% [current] vs 17.6% [prior]).

CONCLUSIONS AND RELEVANCE Among recommendations in major cardiovascular society guidelines, only a small percentage were supported by evidence from multiple RCTs or a single, large RCT. This pattern does not appear to have meaningfully improved from 2008 to 2018.

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Across 26 current ACC/AHA guidelines, 8.5% of recommendations were LOE A

Across 25 ESC guidelines, 14.2% of recommendations were LOE A

This pattern does not appear to have meaningfully improved from 2008 to 2018

Fanaroff AC, Lopes RD, et al. JAMA 2019;321:1069

Our National Clinical Research System is Well-intentioned But Flawed

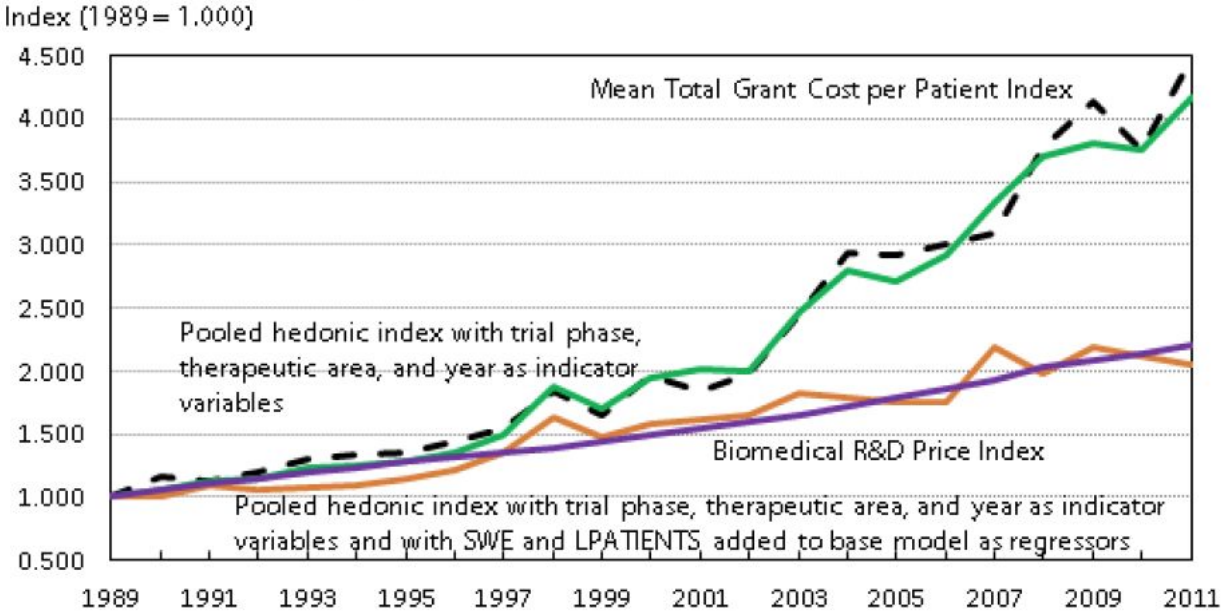
- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great **except**:
  - Too slow, too expensive, and not reliable
  - Doesn't answer questions that matter most to patients
  - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.

Tricoci P et al. JAMA 2009;301:831-41

Trial Hyperinflation

Figure 3. Mean Total Grant Cost per Patient Index, Biomedical R&D Price Index, and pooled hedonic indexes, 1989–2011



Source: Authors' calculations based on Medidata Solutions, Inc.'s, PICAS® database.

Berndt E, Cockburn I. Monthly Labor Review, June 2014

SOUNDING BOARD

Transforming Evidence Generation to Support Health and Health Care Decisions

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Nancy De Lew, M.A., Karen B. DeSalvo, M.D., M.P.H., Christine Dymek, Ed.D., Victor J. Dzau, M.D., et al.

December 15, 2016
N Engl J Med 2016; 375:2395-2400
DOI: 10.1056/NEJMsb1610128

Table 1. Key Principles and Foundational Elements for an Evidence-Generation System to Support a Learning Health System.*

Core Principle	Foundational Elements	Examples
Organize operational systems that create effective research networks embedded in practice and bring them together	Broad stakeholder participation in prospective, randomized, controlled trials and observational studies Regulatory approaches that facilitate practice-based systems for surveillance and research Support for adequate time commitment for clinicians to engage with patients to ensure mutual understanding and appropriate informed consent Efficient systems to handle contracting and liability A new paradigm for evidence generation in which clinical care and research are closely aligned	AHRQ Primary Care Practice-Based Research Networks[14] include groups of primary care clinicians and practices that are focused on community-based health care research and translation of research findings into practice The National Patient-Centered Clinical Research Network (PCORnet)[15] combines Clinical Data Research Networks that are based in health care systems with Patient-Powered Research Networks run by patients, advocacy organizations, and research partners interested in sharing health data and participating in effectiveness research
Establish robust frameworks for autonomy, privacy, confidentiality, and security	A system in which patients and consumers are valued, integral participants in the development of evidence to inform care Robust procedures that ensure data security and protect confidentiality Efficient systems to keep patients and potential study participants informed about research opportunities and ensure appropriate informed consent Balance of individual autonomy with public health needs	The All of Us Research Program[16] is a data-driven enterprise supporting cutting-edge research that prioritizes responsible data sharing to ensure privacy and foster participant engagement The Million Veteran Program[17] is a partnership in which volunteering veterans receiving care in the VA system participate in studies about how genes affect health through the creation of a database comprising genetic data and information, stored and shared with authorized researchers under strict procedures designed to ensure privacy and confidentiality, to enable research on health conditions, including those related to military service
Adopt common approaches to configuring, storing, and reusing digital health care data with appropriate informed consent and privacy protections	Interoperability among systems that capture, store, and exchange health care data Development of common standards and terminology for prospective data collection Continuous effort to curate data to produce high-quality data sets for analysis with the use of common data models Streamlined randomized, controlled trials and high-quality observational studies that leverage existing digital health and health care data to create efficiencies	The ONC Shared Nationwide Interoperability Roadmap[18] is a stakeholder-driven effort to coordinate policy and technical efforts to achieve the interoperability of health information technology for a national research and health care data system The CMS Virtual Research Data Center[19] provides timely access to Medicare and Medicaid program data and facilitates analysis within the CMS secure environment
Develop and test new methods to reliably answer research questions	Dissemination of information from pilot programs that provide proof of concept for efficient, scalable, randomized, controlled trials, cluster-randomized trials, and observational studies Improvements in statistical and epidemiologic methods to better leverage increasing amounts of existing health care data Continued development of approaches to observational comparisons of treatments and empirical analysis of which methods are best for which types of research questions Approaches that promote further integration of clinical care and research	The FDA Sentinel System[20] expands the FDA postmarketing surveillance capabilities by aggregating claims data on >100 million U.S. residents to actively gather information about the safety of regulated medical products once they reach the market The National Academy of Medicine Clinical Effectiveness Research Innovation Collaborative[21] facilitates information exchange and knowledge sharing among researchers and health system leaders
Ensure development of new approaches that facilitate efficient study design and conduct	Streamlined and harmonized processes that eliminate barriers to efficient research while ensuring needed safeguards Systems for high-quality and efficient ethics review (institutional review boards) and contracting Development of approaches to assure the quality of research results that make better use of analytic approaches to increase efficiency	NIH HCS Research Collaboratory[22] brings together multiple large, integrated health systems to use existing data in pragmatic clinical trials to build infrastructure, methods, knowledge, and capacity for pragmatic research at the health care system level NCATS Clinical and Translational Science Awards Program[23] is a national consortium of >60 large academic health centers that seeks to foster and enhance the efficiency, quality, and effect of clinical and translational research

* AHRQ denotes Agency for Healthcare Research and Quality, CMS Centers for Medicare and Medicaid Services, FDA Food and Drug Administration, HCS Health Care Systems, NCATS National Center for Advancing Translational Sciences, NIH National Institutes of Health, ONC Office of the National Coordinator for Health Information Technology, and VA Department of Veterans Affairs.

Organize Operational Systems that Create Effective Research Networks Embedded in Practice and Bring them Together

- Broad stakeholder participation in prospective RCTs
- Regulatory approaches that facilitate practice-based systems for practice and research
- Support for adequate time commitment by clinicians to engage with people/patients to ensure mutual understanding and appropriate informed consent
- Efficient systems to handle contracting and liability
- New paradigm for evidence generation in which clinical care and research are closely aligned

Establish Robust Frameworks for Autonomy, Privacy, Confidentiality and Security

- A system in which patients and consumers are valued, integral participants in the development of evidence to inform care
- Robust procedures to ensure data security and protect confidentiality
- Efficient systems to keep patients and potential study participants informed about research opportunities and ensure appropriate informed consent
- Balance of individual autonomy with public health needs

Adopt Common Approaches to Configuring, Storing and Reusing Digital Health Data with Appropriate Informed Consent and Privacy Protections

- Interoperability among systems that capture, store and exchange health care data
- Development of common standards and terminology for prospective data collection
- Continuous effort to curate data to produce high-quality datasets for analysis with the use of common data models
- Streamlined randomized, controlled trials and high quality observational studies that leverage existing digital health and health care data to create efficiencies

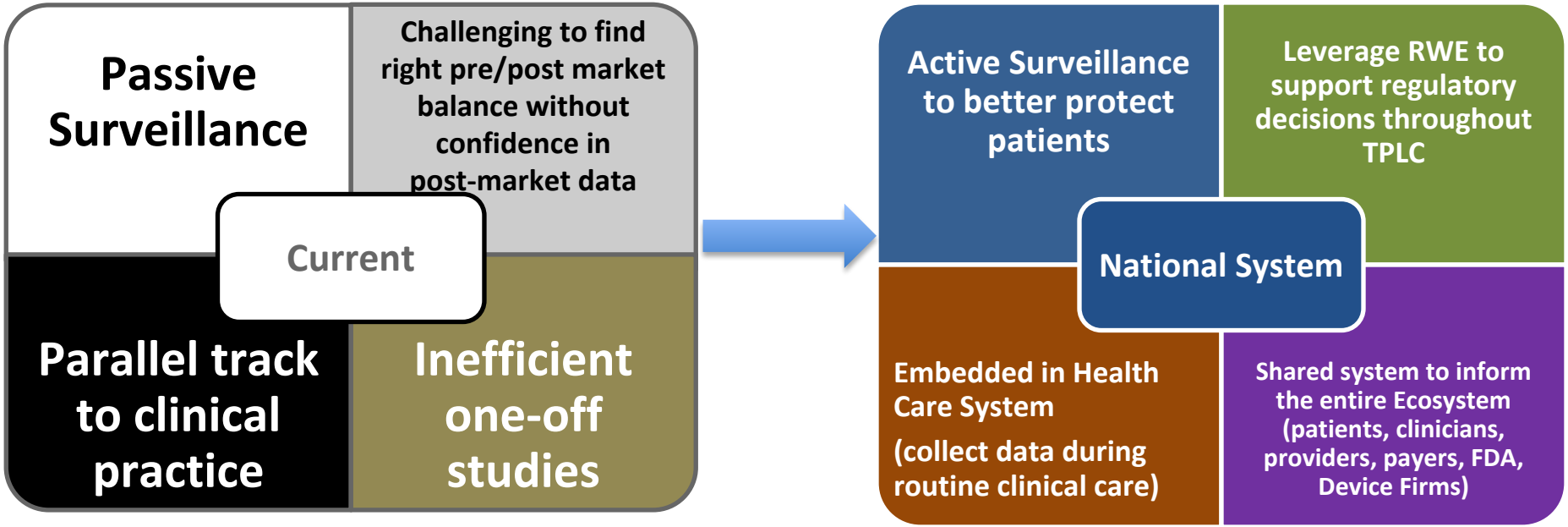
Develop and Test New Methods to Reliably Answer Research Questions

- Dissemination of information from pilot programs that provide proof of concept for efficient, scalable, randomized, controlled trials, cluster randomized trials and observational studies
- Improvements in statistical and epidemiological methods to better leverage increasing amounts of existing health care data
- Continued development of approaches to observational comparisons of treatments and empirical analysis of which methods are best for which types of research questions
- Approaches that promote further integration of clinical care and research

Ensure Development of New Approaches that Facilitate Efficient Study Design and Conduct

- Streamlined and harmonized processes that eliminate barriers to efficient research while ensuring needed safeguards
- Systems for high quality and efficient ethics review and contracting
- Development of approaches to assure the quality of research results that make better use of analytic approaches to increase efficiency

National System Paradigm Shift



Policy efforts underpinning RWE push

Cures provisions (Sec. 3022)

- Requires FDA to establish a program to evaluate the potential use of real world evidence to:
  - Help support the approval of new indications for an approved drug
  - Help support or satisfy post approval study requirements

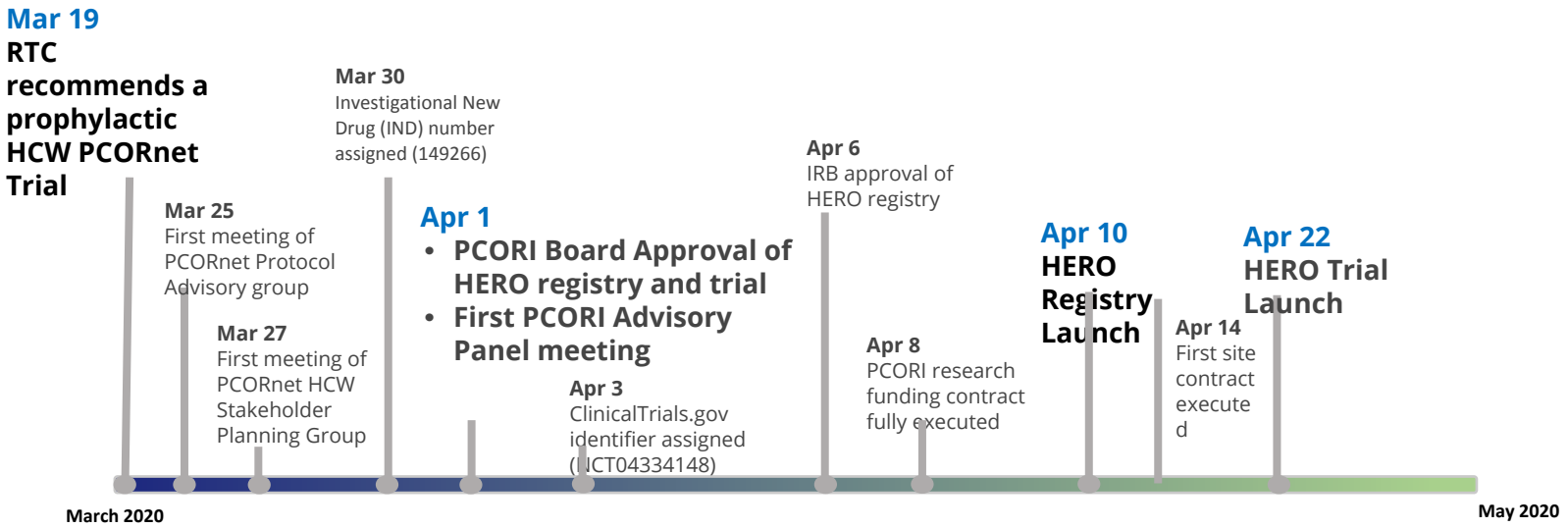
PDUFA RWE provisions

- Tracks with Cures Act
- Requires FDA to establish a program to evaluate the potential use of real world evidence to:
  - Help support the approval of new indications for an approved drug
  - Help support or satisfy post approval study requirements

Reinforcing of a Learning Health Care System:

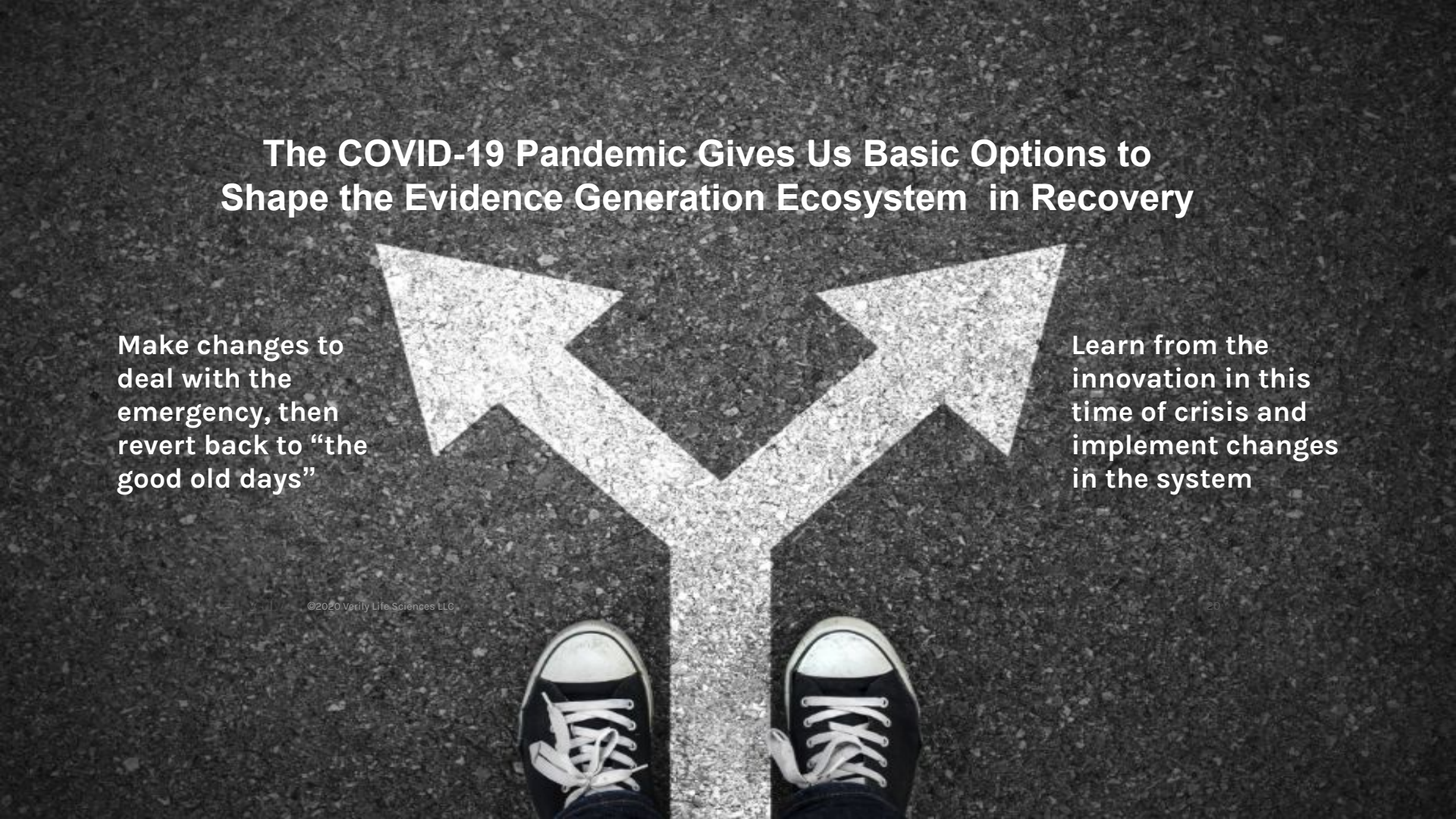
- Doesn't change approval standards, rather it better supports and enables use of data and evidence on outcomes that are hard to get from traditional RCTs (e.g., outcomes that are too costly, too small populations with particular clinical features, too long follow-up needed, diff impact in diff clinical settings, etc.)
- Learning from real-world patient experiences can support better informed health care decision-making by a range of stakeholders

Research Timelines Change in a Pandemic



PCORI's vision for PCORnet was a national infrastructure designed to find a faster more powerful way to conduct CER to improve the nation's health and health care

The COVID-19 Pandemic Gives Us Basic Options to Shape the Evidence Generation Ecosystem in Recovery



Make changes to deal with the emergency, then revert back to "the good old days"

Learn from the innovation in this time of crisis and implement changes in the system

Against Pandemic Research Exceptionalism:

- Problematic Beliefs
  - Some evidence now, even if flawed, seems preferable to expending greater resources on more demanding studies whose benefits only materialize later
  - Key features of rigorous research, like randomization or placebo comparators, conflict with clinicians' care obligations.
  - Expectation that researchers and sponsors are generally free to exercise broad discretion over the organization and design of research
    - **"the goal of research ethics and policy is to use regulations reporting guidelines, and other social controls to align research conduct with the public interest"**
- Five Conditions of Informativenss and Social Value
  - Importance
  - Rigorous design
  - Analytical integrity
  - Report completely, promptly and consistently with prespecified analyses
  - Feasibility
    - "**studies must have a credible prospect of reaching their recruitment target and being completed within a time frame where evidence is still actionable"**

London and Kimmelman Science , 23 April 2020

Urgent Questions Need Ready Collaborations...

- **The Patient-Centered Outcomes Research Institute (PCORI) has long invested in PCORnet,® the National Patient-Centered Clinical Research Network to be research ready**

- **Thus with PCORI funding and PCORnet infrastructure, the Healthcare Worker Exposure Response & Outcomes (HERO) program quickly organized to help**

Consent, Regulatory, and Ethics Review

The Good

- Templated consent and alternative forms of consent work
- Ethics review can be rapid
- Central IRB can work
- FDA can expedite reviews
- **“Single IRBs and e-consent are things I think we'll be able to use more readily, since there will be relatively little counter pressure. We just needed the activation energy that COVID research provided.”**
- **“E-consent can work under the most trying conditions, so it can certainly work in more ordinary times.”**
- Data monitoring committees can consider and respond to emerging information from other trials.

The Bad

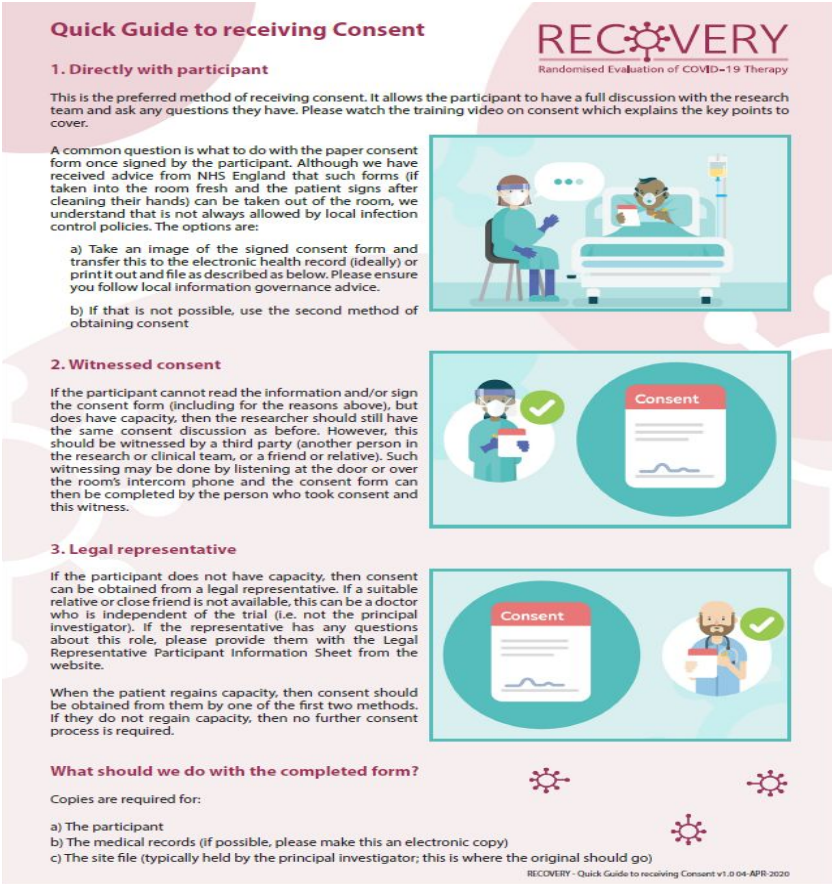
- We don’t have an objective measurement of how well alternative forms of consent worked
  - Results from usual consent process are not so good
  - Are the innovative approaches better or worse?
- **Dropping of regulatory standards can be dangerous (all the bad serology tests on the market)**

Simple 2 page information sheet & 1 page form

Option for witnessed consent

- If participant cannot read or sign for themselves
- If infection control procedures do not allow ICF out of the ‘red zone’

Option for legal representative if patient lacks capacity



Quick Guide to receiving Consent

RECOVERY
Randomised Evaluation of COVID-19 Therapy

1. Directly with participant

This is the preferred method of receiving consent. It allows the participant to have a full discussion with the research team and ask any questions they have. Please watch the training video on consent which explains the key points to cover.

A common question is what to do with the paper consent form once signed by the participant. Although we have received advice from NHS England that such forms (if taken into the room fresh and the patient signs after cleaning their hands) can be taken out of the room, we understand that is not always allowed by local infection control policies. The options are:

a) Take an image of the signed consent form and transfer this to the electronic health record (ideally) or print it out and file as described as below. Please ensure you follow local information governance advice.

b) If that is not possible, use the second method of obtaining consent

2. Witnessed consent

If the participant cannot read the information and/or sign the consent form (including for the reasons above), but does have capacity, then the researcher should still have the same consent discussion as before. However, this should be witnessed by a third party (another person in the research or clinical team, or a friend or relative). Such witnessing may be done by listening at the door or over the room’s intercom phone and the consent form can then be completed by the person who took consent and this witness.

3. Legal representative

If the participant does not have capacity, then consent can be obtained from a legal representative. If a suitable relative or close friend is not available, this can be a doctor who is independent of the trial (i.e. not the principal investigator). If the representative has any questions about this role, please provide them with the Legal Representative Participant Information Sheet from the website.

When the patient regains capacity, then consent should be obtained from them by one of the first two methods. If they do not regain capacity, then no further consent process is required.

What should we do with the completed form?

Copies are required for:

a) The participant
b) The medical records (if possible, please make this an electronic copy)
c) The site file (typically held by the principal investigator; this is where the original should go)

RECOVERY - Quick Guide to receiving Consent v1.0 04-APR-2020

Simple 2 page information sheet & 1 page form

Option for witnessed consent

- If participant cannot read or sign for themselves
- If infection control procedures do not allow ICF out of the ‘red zone’

Option for legal representative

- If patient lacks capacity

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

Hospital: **Patient Name:**

1. Information about the study has been provided to me: I confirm that I have read and understood the Participant Information Leaflet (V1.0 13-Mar-2020) I have had the opportunity to consider the information and ask questions. These have been answered satisfactorily.

2. Voluntary participation: I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

3. Access to study data about me: I give permission for relevant sections of my medical notes and information collected during the study to be looked at, in confidence, by authorised individuals from this hospital, the University of Oxford, and regulatory authorities to check that the study is being carried out correctly.

4. Access to my medical information: I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided to the study coordinating centre both during and for up to 10 years after the scheduled follow-up period. I understand that information that identifies me will be passed securely to such bodies to make this possible and that I can opt out of this at any time by writing to the coordinating centre team.

5. Data stored on computer: I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

6. Agreement to take part: I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

..... PRINTED name of participant	..... Signature	...../...../..... Today's date
..... PRINTED name of person taking consent	..... Signature	...../...../..... Today's date

**1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes*

Recruitment and Consent

Recruitment methods

- IRB-approved advertisements
- Social & conventional media
- Care provider recommendation
- Peer recommendation

Consent

- E-consent to cover baseline and follow-up data capture
- **HCQ Trial (and potentially other studies) will require additional consent**

Healthcare Work Engagement is Key

- Seat on HERO Steering Committee
- Dedicated Healthcare Worker Sub-committee
- Seat on DSMB
- Specific outreach plans, including the HERO to HERO video challenge

Guidance Documents

Contains Nonbinding Recommendations

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on March 27, 2020

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic

Version 2 (27/03/2020)

Key changes from v1 (20-03-2020): additional clarification on obtaining informed consent; link to methodological guidance on statistical considerations in relation to COVID-19 pandemic; advice on IMP stocks, safety reporting, conduct of audits; temporary halts

The European Medicines Agency (EMA), Good Clinical Practice (GCP) Inspectors Working Group, the Clinical Trials Facilitation and Coordination Group (CTFG, a working group of the Heads of Medicines Agency (HMA)), the Clinical Trials Expert Group (CTEG, a working group of the European Commission representing Ethics Committees and National Competent Authorities) and the European Commission (EC) acknowledge the impact of COVID-19 on the health system and broader society, and the impact it may have on clinical trials and trial participants[1]. Extraordinary measures may need to be implemented and trials adjusted due to e.g. trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks. Therefore, EMA, EC and HMA strongly support the efforts of the GCP Inspectors' Working Group for developing a harmonised EU/EEA-level guidance to mitigate the negative effects of the COVID-19 pandemic on the conduct of clinical trials.

The situation is evolving, and pragmatic actions may be required to deal with the challenges of conducting research, and in ensuring the rights, safety and wellbeing of participants. The points mentioned below are intended to provide guidance for all parties involved in clinical trials during this time.

Due to the urgency, this guidance is issued without prior public consultation. The sponsors should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Sponsors and investigators need to take into account that there might be specific national legislation and guidance in place[2], which they should consult and which can be used to complement this guidance, or, with respect to particular matters may take priority over these recommendations. This document is however seeking to include most of the current guidance across Member States with the aim to serve as an EU-level harmonised set of recommendations. Hence, this guidance is agreed by the Clinical Trials Expert Group (CTEG) of the European Commission supported by the EMA, the Clinical Trials Facilitation and Coordination Group (CTFG) of the Heads of Medicines Agencies (HMA) and the GCP Inspectors' Working Group coordinated by the EMA.

The word « participant » is used in this text as a synonym for the term "subject", defined in Directive 2001/20/EC as " an individual who participates in a clinical trial as a recipient of the investigational medicinal product or a control".
[1] Links to national recommendations can be found at CTFG website (https://www.hma.eu/ctfg.html)

Contracts and Liability

The Good

- When all sides want to get the research done, contracts and liability provisions get done quickly

The Bad

- The consequences of errors because of the frenetic activity may not be known
- Many practices and health systems are losing large amounts of $$; where this will settle out is not known
- **“Organizations have stepped up, which is great, but this is not a viable long-term business model”**
- **“The idea of a trial being a profitable source of revenue for an institution is not healthy. Can we alter the pricing model and move away from price per patient?”**

Digital, Virtual and Hybrid Trials

The Good

- Many protocol visits have been switched from clinic to virtual visits
- Patient reported outcomes are replacing or being combined with in-person clinic visits
- Data, including adverse events, are being collected directly from participants
- Coincident conversion of clinical care to “telemedicine” sets a possible framework for integration of research and clinical care
  - **“This is a central governing idea for the future. I am far from sure how we achieve integration of research and clinical care”.**

The Bad

- Standards unclear
- When the dust settles, unclear which approaches are most successful
- **“Virtual care can increase access (to both health care and research), but some people will be left behind”**

Design and Operational Features

- Rapid, large registry of healthcare workers – enrollment open to all
  - To understand healthcare worker burnout, stress, and other experiences
  - To facilitate enrollment in HERO-HCQ and future trials and understand preferences for participation
- Healthcare workers eligible for the HERO-HCQ trial will work at one of the 40 PCORnet sites participating in the trial
  - Pre-screened within the registry, and referred to their local participating site
  - Site will confirm healthcare worker status, randomize onsite, and provide month supply of study drug
  - Complete enrollment within 4-6 weeks/site (10 total for trial)
- Trial participants will have weekly web-based check-ins for symptoms, side effects, exposure history, quality of life, through week 8. Call center rescue for missed check-ins.
- Baseline and end of study swab-checks for viral shedding
- Baseline and end of study serum for future testing for sero-conversion

Interoperability and Access to Health Records

The Good

- People can get their health records by law and direct them to whom they wish
- Health system data lakes/warehouses are ubiquitous
- The ingredients are there—but putting them together remains a problem
  - **“Another central governing idea. Perhaps it’s not about the technology, which should be “invisible”. Rather, it’s about the individual participant experience.”**
- PCORnet and the NIH Collaboratory indicate that high quality research can be done using EHRs shared or federated across systems

The Bad

- Getting EHRs downloaded in manageable form for research purposes is an elusive goal
- Health systems continue to block data despite legal requirements and public purpose
- **Understandable concern about privacy-we have not resolved the trade-offs as a society**
- **“The technical capability has been there for a while, but human nature was the barrier. A crisis led to some changes in human behavior - at least for a while.”**

Data Integration

The Good

- Data can be integrated across systems in an increasing number of countries
- Several dominant common data models: OMOP, Sentinel, PCORnet
- FHIR standards advancing
- Sentinel has been going for a long time
- NIH Collaboratory has succeeded in using EHR data in
- ADAPTABLE provides proof of concept for PCORnet federated data strategy

The Bad

- Standards… so many to choose from…
- For many clinical trials, EHR and claims data based on usual care leave many key items unknown, particularly for measurement that need to be done on a timely basis
- **“Let’s not forget data governance. We’ve known all along that there’s nothing technically complicated about data linkage—it’s all about trust and control. Agreements re data that are being linked for RECOVERY in UK were worked out over a weekend and the data are already flowing. It took us years to get to “probably” in XXXXX.”**
- **“I'd add in "The Bad" column the fact that there are effectively no standards on data quality / data curation. This is a much greater problem, when the data are separated from the patient. Many opportunities to recognize errors when the patient is in the room (actually 5'9" tall, not 4'9") are not applicable when all we have is the data. Even PCORnet data are a considerable work in progress. ”**

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Simple on-line form completed by research nurses

- Which treatments did the patient receive
- COVID-19 test result
- Discharge status & date
- Use of ventilation

Linkage to national data sources

- Vital status, death certificate
- Coded hospital episode statistics (diagnoses, procedures)
- Intensive Care audit data, SARS-CoV-2 PCR laboratory results
- Primary care, national outpatient prescribing data

Permission to follow-up via record linkage for up to 10 years

Involvement of People/Patients/Families/Carers

The Good

- PCORI refunded!
- HERO will provide an important grounds where the participants are health care workers
- Platforms are developing that can involve patients and families in communities for both rare and chronic diseases

The Bad

- Most studies are not truly patient/people centered
- Optimal methods remain elusive
- **Disparities accentuated by the pandemic**
- **Great concern that in the recovery, disparities will increase even further**

HERO
IS HERE TO HELP

Join the HERO mission

It's a difficult time for healthcare workers on the COVID-19 front lines.

Caring for patients in uncertain times + **Protecting themselves and their families**

In response, we invite healthcare workers to unite in a mission – the HERO Registry.

Be part of a national response to address the problems our healthcare heroes face in real time—and over time.

What is the HERO Registry?

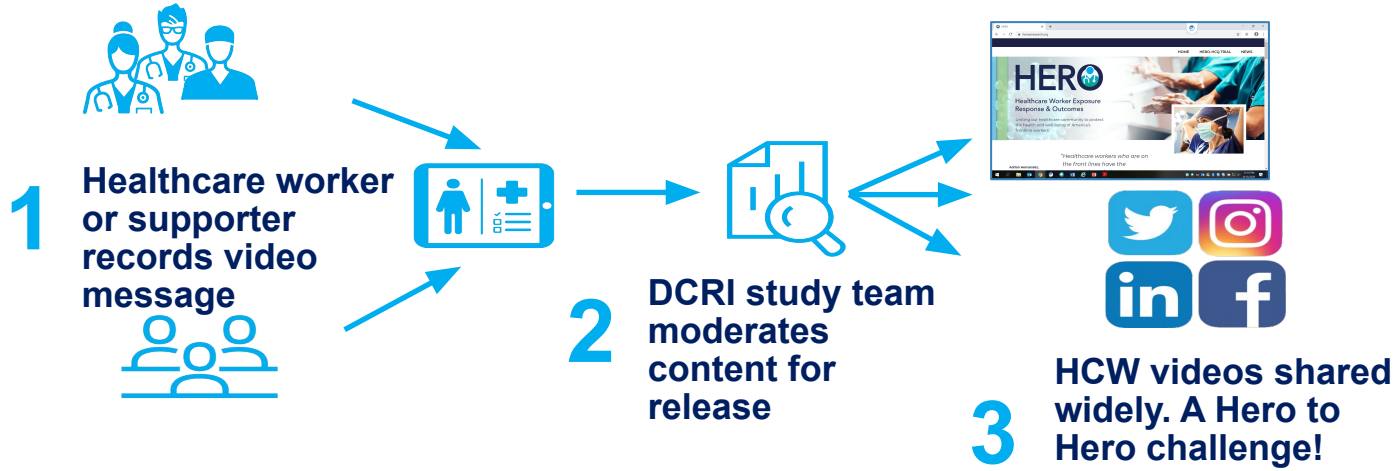
HERO will engage healthcare workers in a research community to understand their experiences and interests.

We will track critical health outcomes associated with caring for patients with COVID-19, such as emotional distress, burnout, and well-being.

We will help speed clinical studies that address unmet needs for healthcare workers, such as an upcoming study of hydroxychloroquine's effectiveness in preventing coronavirus infections

Together, healthcare workers can ENGAGE to help find the answers that will PROTECT and IMPROVE the health and well-being of America's front line.

HERO Stories to build and unite our research community…



Novel Outcomes & Safety Assessment

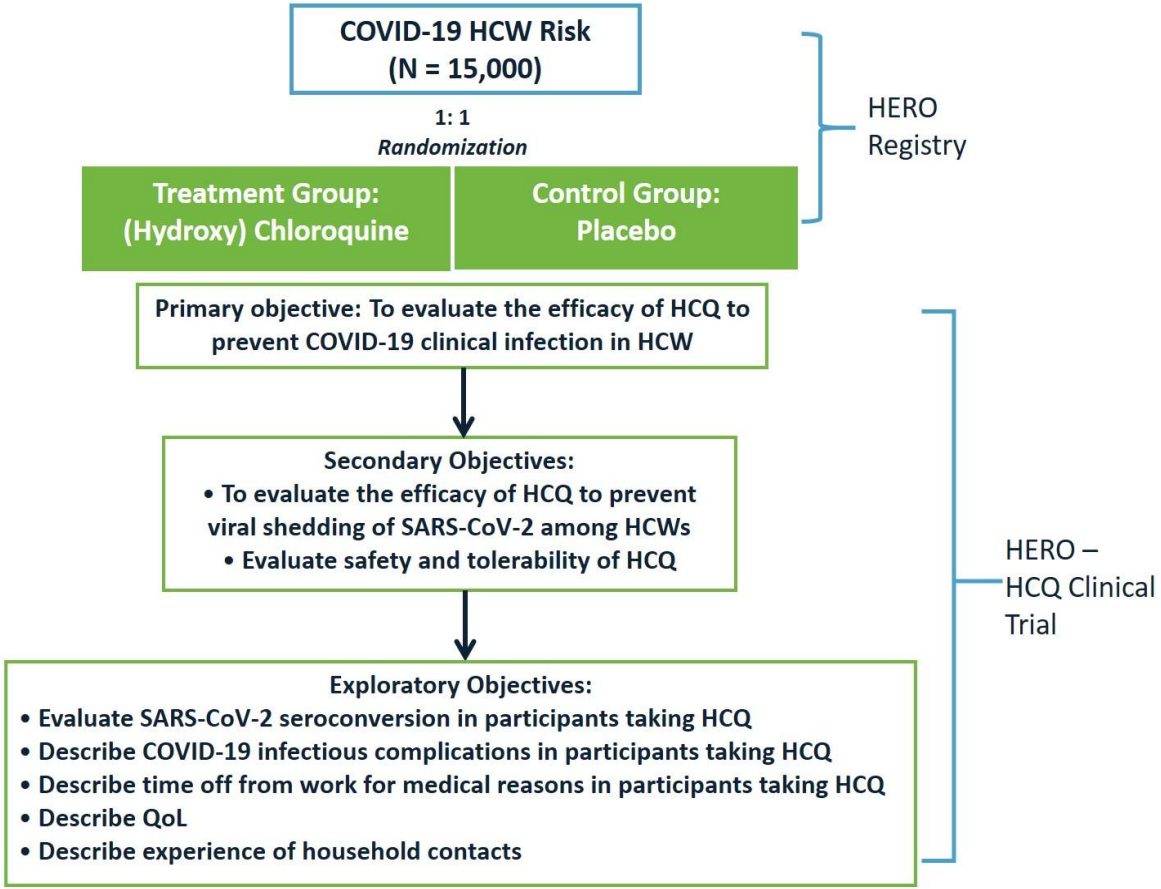
The Good

- Major innovation and creativity has occurred
- FDA guidance very responsive to need to change methods in midst of crisis
- Quality by design is essential guide (https://www.ctti-clinicaltrials.org/projects/quality-design)
- Conversion of clinic-based tests to digital measurement of outcomes in many trials
- HERO and RECOVERY using EHR based outcomes
- Useless adverse event reporting and excessive in person documentation being dropped

The Bad

- No assurance that outcomes chosen are "valid"
- Are important safety events being missed?
- **"We might remind ourselves of the important differences between "reliability" and "validity". Understanding these terms better may help us build needed bridges between the science of safety/efficacy/dose trials and the science of implementation and dissemination research"**

Design


COVID-19 HCW Risk
(N = 15,000)
1: 1
Randomization
Treatment Group:
(Hydroxy) Chloroquine
Control Group:
Placebo
HERO
Registry
Primary objective: To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in HCW
Secondary Objectives:
• To evaluate the efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs
• Evaluate safety and tolerability of HCQ
Exploratory Objectives:
• Evaluate SARS-CoV-2 seroconversion in participants taking HCQ
• Describe COVID-19 infectious complications in participants taking HCQ
• Describe time off from work for medical reasons in participants taking HCQ
• Describe QoL
• Describe experience of household contacts
HERO –
HCQ Clinical
Trial

Clinicians

The Good

- Heroesresearch.org
- RECOVERY platform trial
- Broad awareness of the risk in not having the answers
- **“Clinicians involved in pragmatic trials don’t all have to complete GCP training!”**

The Bad

- Much frustration and concern about support
- Risk that when chronic phase of epidemic hits, the system will be overwhelmed by chronic disease + Covid
- **“On the other hand, willingness to work collaboratively will likely settle back to something like its original state”**
- **“How often do clinical trials in ambulant patients really need a physician on the front line?Leave these poor people alone and let them get on with caring for patients”**

Analytical Methods

The Good

- Structured approach to observational treatment comparisons is advancing, led by FDA
- Growing awareness that observational studies cannot provide reliable answers to many questions about therapeutic effectiveness
- **“The value of randomization is undermined by poorly designed and underpowered trials”.**
- **Dr. Fauci!**

The Bad

- Way too many bad observational studies with claims about treatment effect that are outrageous or misleading
- Bad studies can be amplified by the press or social media
- Value of randomization can be undermined by poorly designed or resourced trials
- **“Yesterday’s news on 1043 patient NIH trial of remdesivir is a case in point. Extreme confidence on days recovery. All things considered I’d say quite high confidence on mortality (I did a back of the envelope and got risk ratio 95% CI 0.50 >0.71>1.03 and 90% CI 0.53>0.71>0.97)To read the media it seemed the mortality opportunity was zero. But Wall St hedge funds did the same math I did, and that’s why stocks went up”**

Meta-organization of studies/questions

The Good

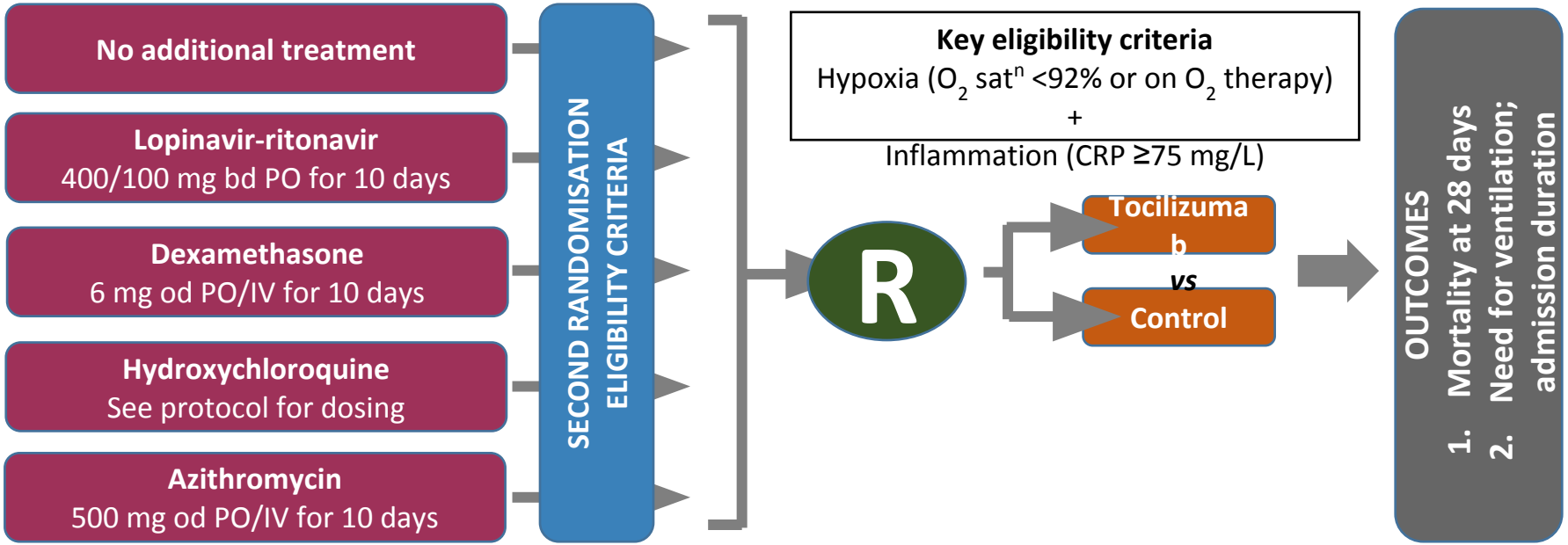
- Efforts to organize at multiple levels show awareness of the issue
- NIH – Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV)
- WHO-SOLIDARITY Trial evaluating multiple therapies
- RECOVERY Trial—highly organized with adequate power

The Bad

- Little evidence of prioritization of studies at the individual institutional level and across institutions
- Far too many small, under-resourced studies unlikely to answer important questions
- Many hundreds of Covid-19 trials registered in clinicaltrials.gov; nearing 100 Hydroxychloroquine trials

RECOVERY

Randomised Evaluation of COVID-19 Therapy



Dissemination

The Good

- Rapid public dissemination is common
- Pre-prints are taking off, leading to earlier dissemination
- Twitter has become a major source of medical knowledge and opinions about that knowledge-almost ”real time”

The Bad

- Pre-prints often look different than the final publication or never appear in peer-reviewed publications
- Press sometimes seizes on gossip, erroneously posted data and pre-prints; too often raises false hope in the public
  - Hydroxycholoroquine
- Politicization of science
- The other side of twitter is its domination by “twitteraties”
- **“Rapid communication of findings is somewhere in the middle, I think. I expect the speed of peer review to return to baseline. But sharing of non-reviewed / pre-reviewed results is likely to increase. That will be a mixed blessing.”**

Purposefulness

The Good

- COVID-19 brings a powerful purpose
- Historically trials go better with a powerful purpose and community
  - MRC trials of tuberculosis treatment 1946
  - ACTG trials from 1987
  - GUSTO-I | ISIS-2
  - Val-HeFT
  - Tamoxifen adjuvant trials
- Trials that simultaneously address a big medical/health problem and deliver improvements in methodology provide added purpose

The Bad

- We've lost our sense of purpose for many trials we do
- Many trials are done:
  - "Because a sponsor pays for it and it keeps the lights on.."
  - "Because the CRO competed for it and offers major financial incentives"
  - "Because someone says "the FDA requires it" which is rarely true and never quite that simple"
- Professional organization of trials in health systems often driven by optimizing finances
- **"As long as trials are done "for profit" (meaning the people doing the trial do so solely for professional or financial gain), the sense of purpose may be muted"**

Purpose
Bill Gates April 30th, 2020

"If you use January and February properly and did community testing, you didn't have to go through this horrific economic cost," Gates said on CNN's global town hall. "Tools can be developed enough that an epidemic like this one could have been stopped at very small numbers."

What is Most Important to Move the Evidence Generation Ecosystem in the Right Direction?
My Short List

- Evaluate what has worked and what hasn't worked in the changes that have been made in response to the crisis
- Allocate significant part of recovery funding to transition issues in evidence generation--especially at the interface of medicine and public health
- Do everything possible to fix the "purposefulness issue"
  - Create methods for deciding the most important questions
  - Reward behavior that gets important questions answered quickly
- Develop inclusive networks
  - Inclusive of or driven by people/patients with the health/medical problems of interest
  - Incentives for clinicians & investigators that lead to reliable and faster evidence generation (balance financial focus with purpose)
  - Automate mapping of EHR data beyond individual systems, including general standards and specific terminology

The effective use of digital information (EHR, telehealth, apps, PROs) should free up effort to fix the human components that are holding us back