Generating Real-World Evidence to Enhance Knowledge during COVID-19

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Context, opportunity, and the challenge of real world evidence
High quality evidence is scarce

<15% of guideline recommendations are supported by high quality evidence, a statistic without meaningful change from 2008 to 2018

It takes ~17 years for evidence to make its way to practice
The cost and complexity of high-quality research is rising

Real-world definitions from FDA

- **Real World Evidence (RWE)** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD).

- Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.
Real-world definitions from FDA

Real world data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- Electronic health records (EHRs)
- Claims and billing data
- Data from product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

Many potential uses of RWD/RWE

<table>
<thead>
<tr>
<th>Traditional Randomized Trial Using RWD Elements</th>
<th>Trials in Clinical Practice Settings</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RWD to assess enrollment criteria / trial feasibility</td>
<td>eCRF + selected outcomes identified using EHR/claims data</td>
<td>RCTs Leveraging RWD</td>
</tr>
<tr>
<td>RWD to support site selection</td>
<td>Mobile technology used to capture supportive endpoints (e.g., to assess ambulation)</td>
<td>RCTs with pragmatic design elements using claims/EHR data</td>
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</tbody>
</table>

- Single arm study using external control
- Increasing reliance on RWD

Adapted 2019 RWE Margolis/FDA Public Workshop
**21st Century Cures Act**

FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:

- Approval of new indication for a drug approved under section 505(c)
- Satisfy post-approval study requirements

Program will be based on a framework issued by December 2018 that describes priority areas, remaining challenges and potential pilot opportunities that the program will address.

Draft guidance to be issued by 2021

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**What we had learned by 2019**
What we had learned by 2019

The world of RWE development is dynamic and changing rapidly

What is impossible today may become easy tomorrow
Any given technology or data approach may soon become obsolete

What we had learned by 2019

The world of RWE development is dynamic and changing rapidly

Incentives are often misaligned
What we had learned by 2019

The world of RWE development is dynamic and changing rapidly

Incentives are often misaligned

The evidence base for evidence generation in the real world is nascent

Commit to evaluate | Report what works AND what doesn’t

Understanding the capabilities of sites and health systems is essential (data, IT, research)

Type, format, and structure of RWD (EHR, claims) used for care delivery, population health management, and research

Personnel resources – informatics, data science, IT, coordinators, investigators

Provide training and education around best practices for leveraging RWD
What we had learned by 2019

Understanding the capabilities of sites and health systems is essential (data, IT, research)

Developing RWE is hard work and slow going

Generating RWE during the COVID-19 crisis
We can move quickly when time is of the essence

HERO Program: Overview
Uniting our healthcare community to protect the health and well-being of America’s frontline workers
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

We Need to Protect our Healthcare Workers

- Ongoing international concerns of risks to Health Care Workers (HCW)
- Reported rates of HCW conversion to COVID-19 positive status reported (~20%)
- >9000 healthcare workers infected in US
- Need to protect frontline HCW from clinical infection or becoming transmission vectors
- High risk individuals in ICU, ER, EMS, SNFs – but other groups may be at risk as well
- No existing – proven – prophylactic therapy
  - Therapies could help, but could also harm
- Stress and burnout are serious concerns, as is the lack of personal protective equipment

Questions and Answers Needed for Hydroxychloroquine

**Benefits**
- Decades of experience
- First approved 04/18/1955
- In a class of medications that was first used to prevent and treat malaria.
- Primary use in high risk inflammatory diseases (Lupus, RA)
- Preferred agent in pregnancy with SLE
- Anti-viral activity
  - In-vitro viral suppression
  - Small studies with viral suppression

**Risks**
- Serious side effects are rare and associated with longer exposure.
- Most common: nausea and diarrhea
- Less common: rash, hair changes, and muscle weakness.
- Rarely anemia
- Small studies with QT prolongation typically in setting of multiple agents and higher risk individuals

An Accelerated Timeline

- Mar 19: RTC recommends a prophylactic HCW PCORNet Trial
- Mar 27: First meeting of PCORNet HCW Stakeholder Planning Group
- Mar 25: First meeting of PCORNet Protocol Advisory group
- Mar 30: Investigational New Drug (IND) number assigned (149266)
- Apr 1: PCORI Board Approval of HERO registry and trial
  - First PCORI Advisory Panel meeting
- Apr 6: IRB approval of HERO registry
- Apr 8: PCORI research funding contract fully executed
- Apr 10: HERO Registry Launch
- Apr 14: First site contract executed
- Apr 22: First participant randomized
- Apr 27: 50th participant randomized

March 2020 - May 2020
The HERO Program

- Will enroll thousands of HCWs into a living registry
  - To understand the impact of COVID 19 on HCW health, well-being, stress, PPE availability, and other to-be-defined modules
  - To build a community to support and engage HCW
  - To answer questions – related to COVID19 and not – important to HCWs
  - To understand preferences about participation in future trials

- Will randomize 15,000 at-risk HCWs into a trial to determine if hydroxychloroquine can prevent COVID19 infection

Registry Objectives

1. Create a community of HCWs who may be at risk of COVID-19 infection
2. Identify HCWs interested in engaging in upcoming clinical trials related to COVID-19 and obtain preferences and willingness regarding participation
3. Create a dataset of basic clinical and environmental COVID-19 risk factors and clinical and emotional outcomes for analysis
**Trial Aims**

**Primary:**
- To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in healthcare workers (HCWs)

**Secondary:**
- To evaluate the efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs
- Evaluate safety and tolerability of HCQ

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**Registry and Trial Study Flow**

[Diagram showing the trial flow from Any HCW to HERO Registry, through HCW Risk and Willing to Randomize, to Randomization into Hydroxychloroquine or Placebo, with objectives for primary and secondary outcomes, and exploratory objectives including SARS-CoV-2 seroconversion and COVID-19 infectious complications in participants taking HCQ.]
heroesresearch.org

Uniting our healthcare community to protect the health and well-being of America’s frontline workers

We can move quickly when time is of the essence

Consent, regulatory, and ethics reviews
Contracts
Meaningful engagement of patients, families, and caregivers
Clinician engagement
Transition from in-person to virtual
Data integration
The need for high standards of quality remains

RESEARCH ETHICS: COVID-19

Against pandemic research exceptionalism
Crises are no excuse for lowering scientific standards

Conditions of informativeness and social value

• Importance
  Trials should address key evidence gaps

• Rigorous design
  Studies should be designed so that positive and negative results inform.

• Analytical integrity
  Prespecified protocols, prospective registration

• Complete, prompt, consistent reporting

• Feasibility
  • Credible prospect of completion in a time frame where evidence is still actionable
Coordination and collaboration are essential

COVID-19 Evidence Accelerator

To sign up for updates on the COVID-19 Evidence Accelerator, click here

The COVID-19 Evidence Accelerator is an initiative launched by the Reagan-Udall Foundation for the FDA in collaboration with Friends of Cancer Research (Friends) to provide a unique venue for major data organizations, government and academic researchers, and health systems to gather and design quick-turnaround queries and share their results.

The Accelerator will bring together the country’s leading experts in health data aggregation and analytics in a unified effort to share insights, compare results, and answer key questions about COVID-19 treatment and response as quickly as possible.

Urgency and Action: Since the beginning of the pandemic, data scientists around the country have been engaged in an intense effort to capture real-world data and rapidly deploy data analytics to help answer key questions related to the management of COVID-19 patients. While over time each of these individual efforts will likely develop into valuable insights, by banding together we can collectively accelerate and maximize the utility of this information in the near term. To do this effectively, a core set of common data elements are being developed that will allow any willing data collection effort to embed these data elements into their on-going work in a uniform way to allow for rapid aggregation and analysis.

Combining efforts will make the findings more robust and accelerate answers. https://www.focr.org/covid19
COVID-19 Evidence Accelerator

• Developing key research questions that multiple organizations and teams can address simultaneously.
  • Among hospitalized patients with COVID-19...
    • Characterize COVID-19 patient populations treated with hydroxychloroquine +/- azithromycin vs control
    • Characterize hydroxychloroquine +/- azithromycin treatment (e.g., timing in COVID-19 illness trajectory; monotherapy vs co-prescription; dose)
    • Characterize safety signals with hydroxychloroquine +/- azithromycin vs control, including by subpopulations (e.g., age, diabetes, COPD)

• Share findings from interested data partners on critical questions

The Living Textbook of Pragmatic Clinical Trials

www.rethinkingclinicaltrials.org
COVID-19 Grand Round Series

- **April 3, 2020**: “Innovative Support for Patients with SARS-COV-2 Infections Registry (INSPIRE): Participant-Centered, Rapidly-Deployed, Digitally-Enabled Research”
- **April 10, 2020**: “Hydroxychloroquine for the Early Treatment of COVID-19 in Hospitalized Adults: A Multicenter Randomized Clinical Trial”
- **April 17, 2020**: “The HERO Program: PCORnet® at Work to Create a Healthcare Worker Community for Rapid Cycle Evidence”
- **April 24, 2020**: “The RECOVERY Trial: A UK National Platform Trial of Potential Treatments for Patients Hospitalised With COVID-19”
- **May 1, 2020**: “Can the COVID-19 Crisis Lead to Reformation of the Evidence Generation Ecosystem?”
- **May 15, 2020**: “Optimizing Learning While Doing: The REMAP-CAP Adaptive Platform Trial”
- **June 5, 2020**: “PCORnet COVID-19 Common Data Model Design and Results”
- **More to come...**

https://rethinkingclinicaltrials.org/grand-rounds-hub/

From real world evidence to policy
- Plan for augmenting evidence at product approval or in emergency use authorization by building on existing networks
- Provide Federal funding to assure broad participation in key postmarket studies that meet benchmarks for speed and quality
- Link payment to implementing virtual postmarket registries and aligned studies

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- **Facility policies** to help mitigate transmission risk:
  - changing the culture to decrease the obligation to work when sick would be a start
  - sick leave and benefits.

- **State/Federal policies**
  - Increase Medicaid reimbursement to support translation to temporary hazard pay

- **Family strategies**
  - Temporary shift of unpaid care work to capable, non-essential employees or other members of LTC workers’ social network
Thank you

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