Equity and COVID-19 Research 101
Panelist Slides

This webinar was sponsored by the Harvard University Center for AIDS Research (CFAR), an NIH funded program (P30 AI060354),

In order: Adrianna Boulin, MPH (moderator) with Panelists Drs. Bisola Ojikutu, Atha Tsibris, Katy Stephenson, Julie Levison, Kenneth Mayer, and Boston Neighborhood Network Glenn Williams

HU CFAR COVID-19 Equity Research Initiative: A Webinar Series
Outline

Background
What is Research?
  • Past abuses
  • Responses to empower and protect participants
The Clinical Trial Process
  The nuts-and-bolts of how this works
    • What are the protections and the safety nets?
Types of Clinical Trials
  • Different phases based on how much we know
What should I be asking?
What is research?

“I don’t think I want to get involved in research – they’re just experimenting on people.”

Research - an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby contribute to knowledge.
Past abuses

Nazi medical atrocities – World War II

Tuskegee Syphilis Study

Jewish Chronic Disease Hospital Study

Tearoom Trade Study

Willowbrook Hepatitis Study
Responses to protect and empower

Tuskegee lead to a law in 1974, that formed a commission, that:
- identified key ethical principles
- developed guidelines for how research should be conducted

1. Respect for Persons – a moral requirement to acknowledge autonomy
2. Beneficence – An obligation to do no harm AND maximize benefits
3. Justice – The benefits of research are for all. No one group should bear the sole burden of figuring out if a treatment works.

It required the establishment of Institutional Review Boards (IRBs) at organizations receiving federal support for human subjects research.
Clinical trials are designed to answer a question, or sometimes multiple questions:

- Does a treatment work?
- Does it work better than the current treatment?
- Does it have side effects?

Step 1. Informed Consent – making an informed choice

_Guiding principle: participants decide what shall or shall not happen to them_

What should I expect from this informed consent process?

- Information
- Comprehension
- Voluntary Participation
Types of Clinical Trials

Look to see if a trial is Controlled, Blinded, and/or randomized.

• Controlled means there is a "placebo" group that gets a sugar pill. That group gets compared to the treatment group.

• Blinded means neither the participant nor the researcher know who got placebo or active treatment until the study ends.

https://www.youtube.com/watch?v=5zXuON7Rueo&feature=emb_logo
The Process, practically speaking

You hear about a study you're interested in, or a researcher and their team reaches out to you
   - you can speak first in person, or maybe over the phone
   • study principal investigator
   • study staff (a research assistant, a research nurse)

The researcher or her team tells you about the study and checks to makes sure you're “eligible”

   • Inclusion Criteria
   • Exclusion Criteria

You go through the informed consent process, get your questions answered and, if you agree to participate, sign the consent form.

The research team arranges study tests, study visits, and getting study drug
Who else is looking out for me?

Institutional Review Boards (IRBs)
- created after Tuskegee
- a review committee designed to protect the rights and welfare of research participants
- By Federal Regulation, IRB Approval is required for human research
- Each Hospital or University or Medical School will have their own IRB

As a researcher, what if I say “forget about the IRB – I’m doing my own thing….?”
- Suspension of some or all of a PI’s research
- Inability to use data or publish results
- Inability to receive funding from federal grants
- Termination of employment
- Loss of licenses
- Immediate shut-down of all research at an organization
For larger studies, they also have Data Safety Monitoring Boards (DSMB)

• The principal investigators don’t get to see the data during the study, but the DSMB does

• DSMB members are independent from the clinical study team. The study team agrees to abide by the decisions of the DSMB before the study starts.

• DSMB have the power to stop studies - either because a study drug is harmful, a study drug is fantastic, or if they don’t think they’ll ever be able to say if the study drug does anything (futility)
The Phases of Clinical Trials

Phases tell us how far along the development of a treatment is.

- **Phase 1** – small studies, emphasis on SAFETY evaluation, could be healthy volunteers, usually short trials.
- **Phase 2** – larger, designed for an early read of EFFICACY, may test different doses, participants will have the disease or condition of interest, last months to a year usually.
- **Phase 3** – Larger study size, done to answer the efficacy question: does this drug actually work?
- **Phase 4** – Post marketing surveillance studies after drugs are approved.
What should I be asking?

1. What are you studying and why is it important?
2. Will this research directly benefit me?
3. What are the risks to participating in your study? If this is a phase 2 or phase 3 study, were there side effects seen that I should know about?
4. How are you minimizing the risks to me from participating in your study?
5. What are your expectations of me?
6. Are you collecting my genetic information?
7. What happens if you discover something that you can make $$$ from using my samples?
# COVID-19: Spectrum of Symptoms

<table>
<thead>
<tr>
<th>Mild COVID-19</th>
<th>Severe COVID-19</th>
<th>Critical COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 out of 100 people</td>
<td>14 out of 100 people</td>
<td>5 out of 100 people</td>
</tr>
<tr>
<td>• Fever</td>
<td>• Shortness of breath</td>
<td>• Respiratory failure</td>
</tr>
<tr>
<td>• Cough</td>
<td>• Low oxygen levels</td>
<td>• Life support machines</td>
</tr>
<tr>
<td>• Muscle aches</td>
<td>• Pneumonia</td>
<td>• Intensive care unit</td>
</tr>
</tbody>
</table>

Interested in COVID-19 Studies?
617-735-4610
cvrtrials@bidmc.harvard.edu
COVID-19: Standard of Care in March 2020

Mild COVID-19
- Self-isolation
- Tylenol for fevers
- Drink lots of fluids
- Cough medicine

Severe COVID-19
- Oxygen
- Sometimes antibiotics
- Medicine to prevent blood clots
- Help to lie on stomach
- Close monitoring

Critical COVID-19
- Mechanical ventilation
- Blood pressure support
- Sedation
- Dialysis
- Diabetes control
- Increased medicine for blood clots
- Heart monitoring
- Positioning on stomach

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COVID-19 Treatment Research

• Standard of Care
  – Includes treatment that is already proven to help
  – Research always adds to the standard of care; never takes it away

• Antiviral Medicine
  – Therapies that kill the virus that causes COVID-19
  – Examples: Tamiflu, Valtrex

• Anti-inflammatory Medicine
  – Therapies that quiet the immune response that may make COVID-19 worse
  – Examples: Steroids

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Example of Trials in May at BIDMC

- **Antiviral:**
  - Remdesivir, RNAp inhibitor
  - Favipiravir, RNAp inhibitor
  - Selinexor, nuclear export inhibitor
  - Lopinavir, protease inhibitor
  - DAS181, sialic acid inhibitor

- **Anti-inflammatory:**
  - Hydroxychloroquine
  - Sarilumab, IL6r inhibitor
  - Leronlimab, CCR5 inhibitor
  - Ibrutinib, BTK inhibitor
  - Abatacept, CTLA4 inhibitor
  - Losmapimod, p38 MAPK inhibitor

- **Trials:**
  - HCQ vs. LPV vs. PL
  - Remdesivir Open Label
  - Losmapimod vs. PL
  - HCQ vs. PL
  - Conv. Plasma
  - Favipiravir vs. PL
  - DAS181 vs. PL
  - Sarilumab vs. PL
  - Selinexor vs. PL
  - iNO vs. PL
  - Ibrutinib vs. PL
  - tPA vs. PL
  - Leronlimab vs. PL
  - Methylprednisolone. vs. PL
  - High Titer Anti-C19 Plasma vs. PL, & Plasma Donation
  - Abatacept Open Label
  - Remdesivir Emerg. Use
  - 11 May 20
Good Results: Remdesivir and Dexamethasone

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COVID-19 Research Experience: Personal Lessons

- I assumed patients knew more about the experimental drugs than they did
- I underestimated how many people would not speak English
- I did not expect so many people would decline research all together
COVID-19: Standard of Care in July 2020

Mild COVID-19
- Self-isolation
- Tylenol for fevers
- Drink lots of fluids
- Cough medicine

Severe COVID-19
- Oxygen
- Sometimes antibiotics
- Medicine to prevent blood clots
- Help to lie on stomach
- Close monitoring
- Remdesivir
- Steroids

Critical COVID-19
- Mechanical ventilation
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Because of COVID-19 Clinical Trials!

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Vaccines

Kenneth H. Mayer, M.D.

Equity and COVID-19 Research 101
July 1, 2020
What is a Vaccine?

- A substance that teaches the body how to recognize and protect itself against a disease-causing agent, e.g. a virus or bacterium.
- Vaccines may be inactive microbes, or parts of a microbe that elicit an immune response.
- Most licensed vaccines against other diseases are 70–99% effective.
TIME TO DEVELOP A VACCINE
Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine

- Typhoid: 1884 - 1955, 105 years
- Polio: 1908 - 1948, 47 years
- Pertussis: 1906 - 2006, 42 years
- Rotavirus: 1973 - 2006, 33 years
- HPV: 1984 - 2006, 22 years
- Hepatitis B: 1953 - 1981, 16 years
- Measles: 1953 - 1963, 10 years
- HIV: 1983 - 1989

Source: AVAC AIDS Vaccine Handbook
How Vaccines Might Work

Different ways a COVID-19 vaccine may work
- Designed for people who are **NOT** infected
- If effective, would reduce risk of infection
- Or, could reduce the ability of the organism to multiply after infection
- This might prevent people who acquire COVID-19 after vaccination from getting sick
- If someone has very early COVID-19 infection, a vaccine could also prevent the development of disease
How Is A Vaccine Developed?
Vaccine Trial Stages

• Phase I: safety assessment, small numbers of low risk people
• Phase II: early assessment of immunogenicity may involve somewhat riskier persons, but not designed to show efficacy
• Phase III: efficacy trial, large numbers of high risk persons, with placebo-control. Everyone needs standard of care prevention package
• Phase IV: refinement post-demonstration of efficacy, e.g. trials in subpopulations (youth?)
How Do Preventive Vaccines Work?

By teaching the body to recognize and fight a pathogen

- Vaccine carries something that ‘looks and feels’ like the pathogen
- The body reacts by activating the immune system and creating antibodies or killer cells and a memory response
- Upon exposure to the actual pathogen, antibodies and killer cells are waiting to respond and attack

*Note: This is general definition, not specific to HIV vaccines*
Preventive HIV vaccines are designed to elicit two arms of the immune system – **humoral** and cellular

1. **Humoral immunity**
   - Primary action of humoral arm is creating antibodies: Y-shaped proteins produced by B cells in response to a pathogen to prevent infection.
   - Antibodies have multiple functions: attaching to and helping destroy pathogens, keeping the pathogens from entering host cells (neutralization), and calling other cells into action (sensitization).
Immune Responses

Preventive HIV vaccines are designed to elicit two arms of the immune system – humoral and **cellular**

(2) **Cellular immunity**

- Two types of T cells: Cytotoxic T lymphocytes (CTL) and T-helper cells
- T cells recognize virus-infected cells, coordinate the immune response (helper cells) and kill the infected cells (CTLs)
How Are Vaccines Typically Made?

- **Live attenuated vaccines** (examples: Sabin polio vaccine, measles, mumps, and rubella)

- **Whole killed virus vaccines** (example: influenza, rabies and Salk polio vaccine)

Note: This is general vaccine development, not specific to HIV vaccines.

Courtesy of HIV Vaccine Trials Network
How Are HIV Vaccines Made?

- Examples of recombinant vaccines:
  - DNA vaccines
  - Vector vaccines (viral and bacterial)
  - Subunit vaccines

- Do not contain HIV – only synthetic copies of fragments of HIV that will create an immune response but cannot cause HIV infection
Developing a COVID-19 Vaccine Will Be Difficult, but Doable

- New pathogen with great transmission efficiency and high levels of morbidity
- Animals have been protected against SARS-CoV-2 challenge after getting a vaccine
- Animals transfused antibodies appear protected
- People who get infected with other coronaviruses appear to have some level of protection for several years post-infection
Repurposing NIH’s AIDS Clinical Trials Infrastructure

- NIAID
- VTEUs
- ACTG (UCLA)
- HPTN (FHI360)
- HVTN (Fred Hutch)
- CRS
- CRS
- CRS
COVID-19 Prevention Network

Candidate COVID-19 vaccines

Platform 1

Platform 2

Platform 3

Platform 4

Platform 5

Harmonized efficacy trials

Collaborating clinical trials networks

Collaborating labs
1. Defining COVID infections from vaccination
2. Quantitative immune responses to spike and spike epitopes
3. T-cell responses

Data and Safety Monitoring Board

Between-trial statistical group for correlates of protection

NIH/COVID Network-supported infrastructure
bNAb studies also getting underway focusing on outbreaks (e.g. nursing homes, meat packing plants)
For the first two COVID-19 vaccine trials, sites have been selected.
CoVPN Website (live 7/7/20)

WORKING TO PREVENT SARS-CoV-2

Who Are We?
The COVID-19 Prevention Network (CoVPN) was formed by the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health to respond to the global pandemic. Using the infectious disease expertise of their existing research networks and their global partners, NIAID has directed the networks to utilize their expertise to address the pressing need for vaccines and monoclonal antibodies against the SARS-CoV-2 virus. The CoVPN is comprised of the partners listed below.

Our Mission:
To Conduct Phase 3 Efficacy Trials for COVID-19 Vaccines and Monoclonal Antibodies. CoVPN will work to develop and conduct studies to ensure rapid and thorough evaluation of United States government-sponsored COVID-19 vaccines and monoclonal antibodies for the prevention of COVID-19 disease.
Today's research studies have safeguards in place to protect the safety and well-being of participants.

In the U.S., several organizations are responsible for vaccine research ethics:
- Institutional Review Boards
- Office of Human Research Protection
- U.S. Food & Drug Administration (FDA)

All participants in NIH-funded trials have a Bill of Rights and Responsibilities
Clinical Trial Resources

Julie Levison, MD, MPhil, MPH, FACP
Assistant Professor of Medicine, Harvard Medical School
Division of General Internal Medicine and the Mongan Institute,
Massachusetts General Hospital
Toolkit for Research Participant Empowerment

- Why is the research being done?
- What is expected of me if I agree to participate in the research?
- How will I benefit from the research?
- Could the research hurt me?
- What will the researcher do with my information?
- Will the research cost me anything? (e.g. time away from work, transportation, need for child care)
- How long will the study last?
- What happens if I decide to leave the study early?

Levison, July 1, 2020

https://catalyst.harvard.edu/services/rsa/