DESIGN FOR DIVERSITY

Designing studies for representativeness and generalizability

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Agenda

- Design for diversity
  - Preventing disparities
- Guidance
- Design approaches
- Systemic changes

Disclosures

Current grants and contracts to institution from

- NIH
- SCCM
- Novartis
- AstraZeneca
- Cytokinetics

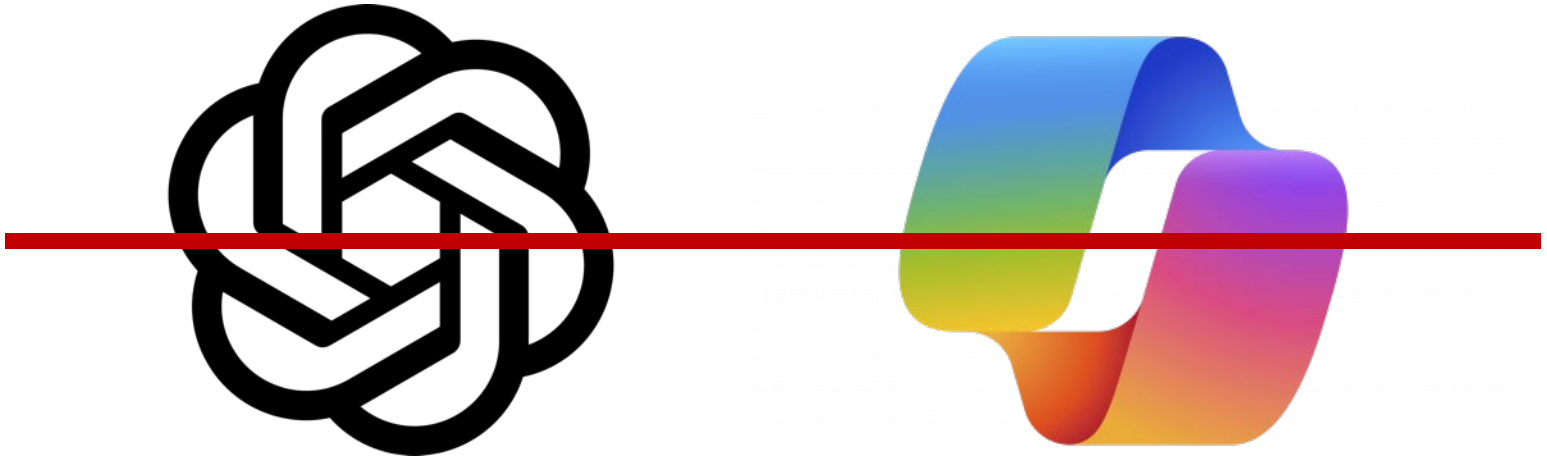
Stock options/consultancy

- Bioscape Digital
- Persistence Bio

Other commitments

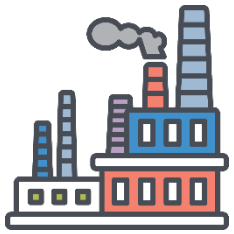
- Editor in Chief, Journal of Clinical and Translational Science
- Member of Data and Safety Monitoring Boards and External Advisory Boards, paid and unpaid
- Patents for risk stratification in septic shock held by CCHMC

Disclosures



Why design for diversity

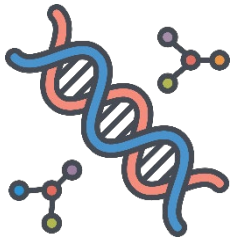
- Health disparities are factors that contribute to differences in health status and outcomes, e.g.



Environmental

Sociocultural

Behavioral



Biological

- A health disparity is
  - a **preventable** difference in health status and outcomes
  - adversely affects populations

Why design for diversity

We each have experiences with factors that contribute to disparities

- Exposure to stress and discrimination
- Lifespan
  - Changing biology through childhood
  - Work exposures and impacts
  - Comorbidities and aging
- Functional status
- Mental health
- Social drivers of health

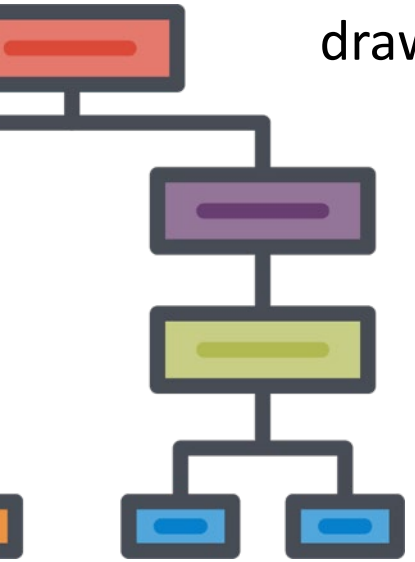
Why design for diversity

When we do not consider factors that change outcomes for some people differently to others, research can contribute to a **preventable** difference in health status and outcomes

Design for diversity

- A flawed evidence generation system compounds the problem
  - Evidence that is systematically biased
  - Evidence that systematically excludes at-risk populations
  - Evidence that ignores the contribution of lived context
- Popular solution:
  - **Let's measure and adjust for diversity variables**

Design for diversity



Clinical trials

Compare interventions to draw conclusions about their effect on outcomes

Find people

Enroll people

Randomize people

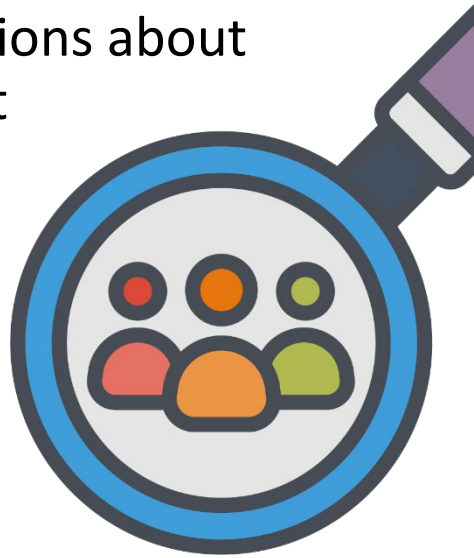
Do intervention

Collect data
(baseline, intervention, outcomes)

Compare groups

Observational studies

Assess factors associated with outcomes to draw conclusions about their likely effect



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When we add a variable…

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Adjust for diversity

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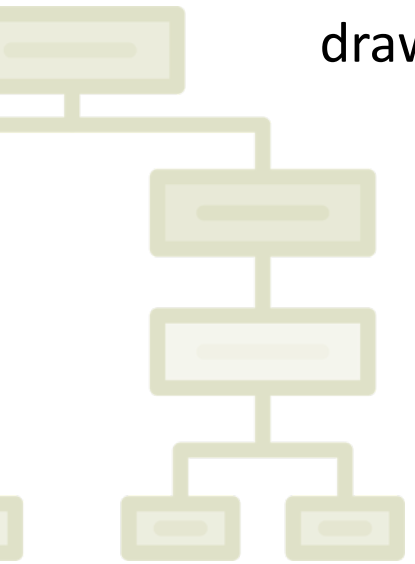

We often get the variable wrong or use it incorrectly

When the solution is design for diversity…

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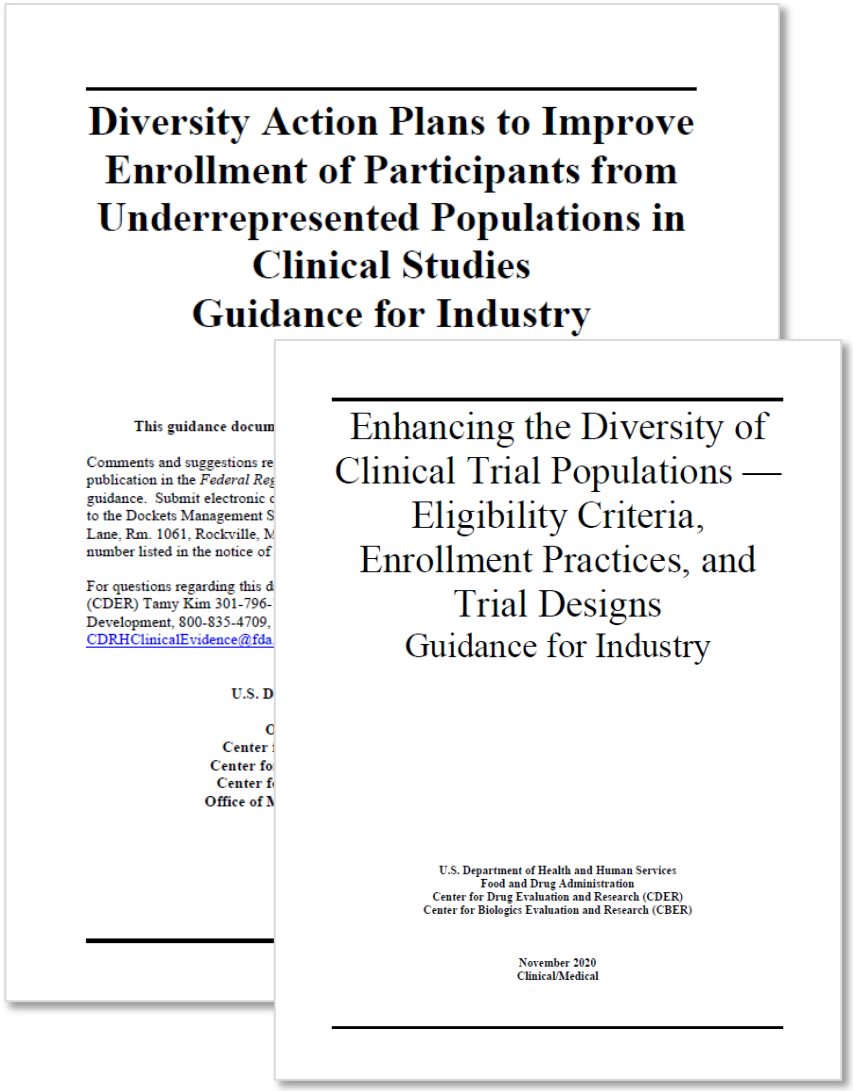
Compare groups

Draw meaningful conclusions relevant to all populations

Design for diversity

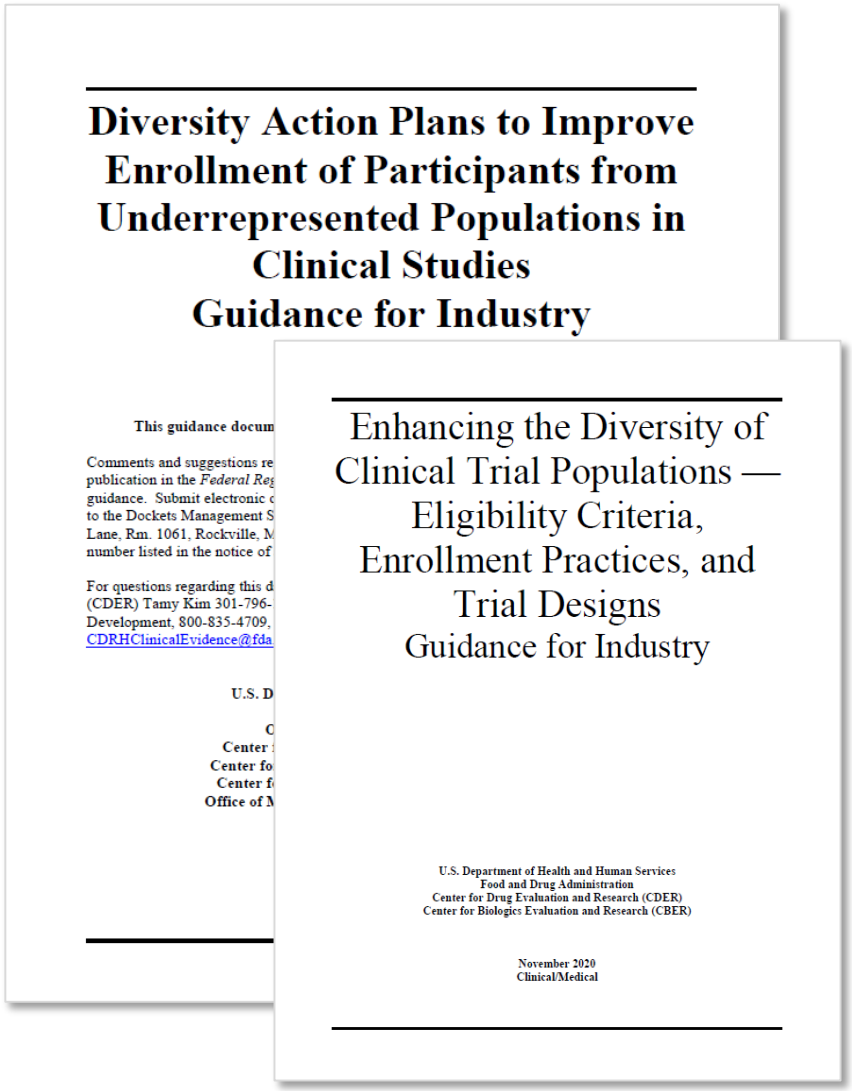
- By designing for diversity, we can
  - begin to address the generalizability of evidence
  - develop an understanding of factors that contribute to success or failure of interventions among diverse populations
  - remove the evidence generation system as a contributor to health disparities
- Diversity is not a choice
  - NIH targeted and planned enrollment tables
  - FDA guidance for industry
  - Social desirability

FDA Guidance



- Intended to
  - Ensure enough evidence to generalize to at-risk populations (pk/pd, efficacy, safety)
  - Prevent systematic errors (e.g., pulse ox)
- Early in the development process, but no later than end of phase 2, beginning of pivotal studies or when submitting development plan
- Applies broadly
- Goes beyond reporting on subgroups

FDA Guidance



- How the diversity variable is being assessed
- How the diversity variable will be analyzed
- Operational plans for recruiting and retaining a representative cohort
- Generate evidence when there is an expected impact of the diversity variable (i.e., when there is a plausible mechanism)
  - when no evidence exists to suggest effects of diversity, the cohort should be representative of the at-risk population
  - demographics of the geographic region will rarely reflect the at-risk population

Directionally sound, but we can do better

- Go beyond race, ethnicity, and gender
- Scrape beyond the surface to ensure diversity
  - Compensation
  - Language assistance
  - Location, transport
  - Community engagement
  - Minimizing burden

Involve participants in the design and conduct of the study

- Ensure rigorous measurement and analysis

Designing for diversity is an optimization problem

Historical optimization

- Objective measurement with rigorous assessments
- Control over the intervention
- Heavily constrained processes
- Obtain as much information as possible about the disease, mechanism of disease, and future proof everything by collecting specimens

Proposed optimization

- Objective measurement with rigorous assessments
- Control over the intervention
- Flexible processes
- Obtain the information needed to answer the clinical question and to inform about the disparities question

Designing for diversity is an optimization problem

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i.e., spend money to control the system

Proposed optimization

- Objective measurement with rigorous assessments
- Control over the intervention
- Flexible processes
- Obtain the information needed to answer the clinical question and to inform about the disparities question

i.e., spend money to make the system generalizable

Designing for diversity is an optimization problem

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Optimize for the researcher

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Optimize for the participant

Designing for diversity is an optimization problem

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Optimize for the researcher

EASY—because we are researchers

Proposed optimization

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Optimize for the participant

HARD—because we are not participants

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Optimize for the participant

HARD—because we are not participants

and if we were participants,
we would still be researchers

Aside: a design trick for observational research

Clinical trials	Observational studies
Compare interventions to draw conclusions about their effect on outcomes	Assess factors associated with outcomes to draw conclusions about their likely effect
Find people	Find people
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Do intervention	
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A design trick for observational research

Clinical trials	Observational studies
Compare interventions to draw conclusions about their effect on outcomes	~~Assess factors associated with outcomes to draw conclusions about their likely effect~~
Find people	Find people
Enroll people	Enroll people
Randomize people	Design as though you are randomizing people to the exposure of interest
Do intervention	
Collect data (baseline, intervention, outcomes)	Collect data (baseline, exposure, outcomes)
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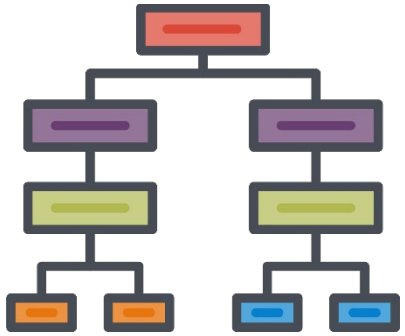
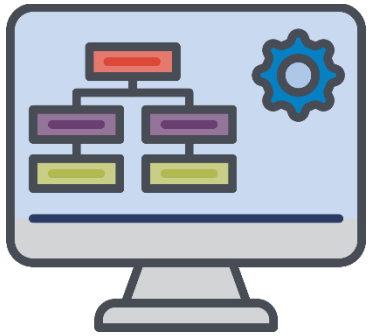
A design trick for observational research



Target trial

Trial emulation



Simulated trial

Optimizing for the participant

On comfort zones

Optimizing for the participant

Rigorous and flexible

Safe and practical

Complete and simple

CREATIVE FREEDOM IS A MYTH

(EMBRACE YOUR CONSTRAINTS)

Chocolate and caviar

Optimizing for the participant

Design from where the participant is

If it were me, why would I choose to be in the study?

What would help me give the study the best data possible?

Straightforward, but we are researchers first

Participants embedded in every part of the research team

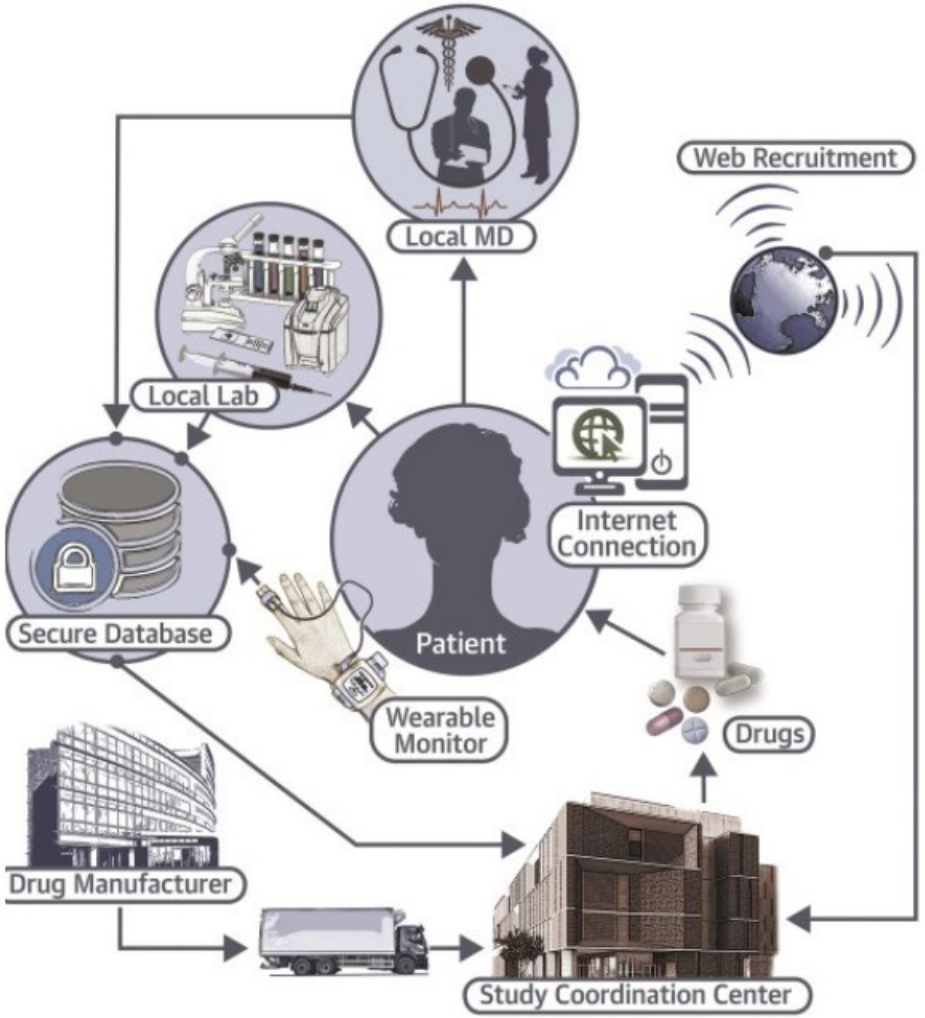
Hard, but effective

A journey through design for diversity

- Where are the patients/potential participants?
- What do their daily lives look like?
- How do they interface with the healthcare system?
- How might we best interact with people to tell them about the research?
- How do we communicate with them in understandable words and language?
- How do we go beyond the initial step of meeting people where they are and bring research into their lives, not the other way around?
- How do patients end up in the dataset and what is the information content of their data?
  - i.e., all of the above

For retrospective studies

Ah-ha – the decentralized trial



G.A. J Am Coll Cardiol Basic Trans Science. 2021;6:384-387.

- Recruit via social media/the web
- Collect baseline data at a local lab, in home visit or on the web
- Use eConsent and a central IRB
- Mail the intervention to the patient or otherwise deliver the intervention remotely
- Follow the patient via wearables, PROs, home visits, local labs, or EHR
- At the end, send them compensation for their time

The myth and promise of decentralized trials

Myth:

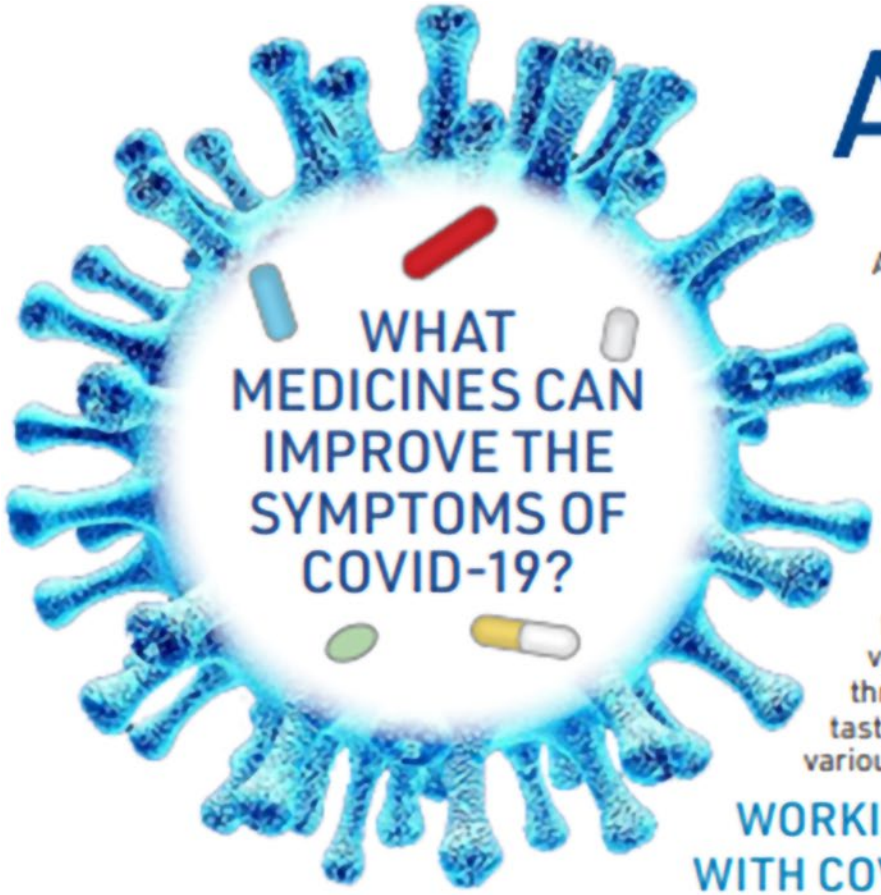
- By making everything virtual, all physical barriers to enrollment are removed, and everyone will sign up
- It is a cheap solution to solving the diversity problem
- The data will be poor, the FDA won't accept it, and participants will be harmed

Promise:

- If we do it badly, the data will be poor, the FDA won't accept it, and participants will be harmed
- If we build it for them, they won't come
- We don't quite know what we are doing yet
- If we build together, we can achieve success on the optimization problem:

  Quality information about what works for all people at risk

Lessons from ACTIV-6



ACTIV-6

ACTIV-6 is a nationwide study to test medicines that are already approved for other diseases to see if they can help people with mild to moderate COVID-19 feel better faster and stay out of the hospital. ACTIV-6 is part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program.

WHO CAN PARTICIPATE? Adults age 30 or older with COVID-19 symptoms, a positive test within the last 10 days, and at least two symptoms of the illness for seven days or less. Symptoms include fatigue, difficulty breathing, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, and/or new loss of sense of taste or smell. You may be excluded from the study for various reasons.

WORKING TOGETHER TO HELP PEOPLE WITH COVID-19 FEEL BETTER FASTER.

WHAT ARE THE STEPS IN THIS STUDY?

1 SIGN UP ONLINE

People can participate from anywhere in the US. After signing up online, by web or phone, you will get an email or text message within a day with a link. That link will take you to the registration survey.

2 ABOUT THE MEDICINES

This study is testing several different medicines. You will be selected by chance to get either a medicine you are eligible for or a placebo. Learn about the medicines here.

CLINICAL STUDIES AND PLACEBOS

Participants in this study take either a study medicine or a placebo. A placebo is a medication that has no active ingredients and will have no effect on you. When some people take medicines and others take placebos, that lets researchers figure out if a medicine is useful or not.

3 CHOOSE THE MEDICINES YOU WOULD WANT TO TRY

Participating in this study involves: **1)** choosing which medicines you'd be willing to take, **2)** taking the medication assigned to you, and **3)** keeping track of your symptoms by using online surveys. No one, including you, will know if you're taking a medicine or a placebo.

Your chance of taking a medicine instead of a placebo depends on how many medicines you are willing to try and are eligible for:

Choose 1, your chance is 50% (1 out of 2)

Choose 2, your chance is 67% (2 out of 3)

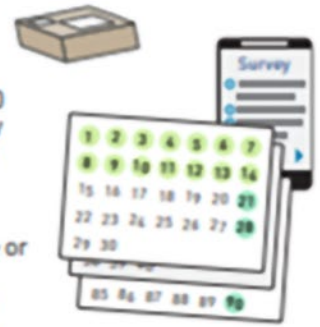
Choose 3, your chance is 75% (3 out of 4)

4 RECEIVE AND TAKE YOUR MEDICATION, COMPLETE DAILY SURVEYS

Your medication will be mailed to your home at no cost, and then you will start taking it according to its instructions.

You will be asked to answer a short (5 to 10 minutes) survey on a secure website every day for 14 days, and follow-up surveys on days 21, 28 and 90.

If you still have symptoms after 14 days, you'll take a daily survey until they're gone or you reach day 28. If you feel worse at any time, you should seek medical care as you normally would and notify the study team during the next survey.



There are no in-person visits involved with this study. You can stop participating in the study at any time.

5 GET YOUR REWARD

You will receive gift cards on the 28th and 90th day that total $100.

ACTIV-6

Successes

- Emphasizing how people feel
- Letting go of failed technical solutions
- Minimized participant burden for data collection
- Thousands of patients enrolled
- Answers to whether seven different repurposed drug regimens work for COVID-19
- Information relevant to FDA, policy makers, providers

Lessons

- It took considerable effort to achieve diversity, but with constant monitoring and attention it can be done
- Disparities in the mail system, and how they contribute to disparities in health
- Systemic barriers to creating equal access based on language and ability

The data science bit

- Most people think of data science as using information that exists
- The interface between **data generation** and **data use** is critical

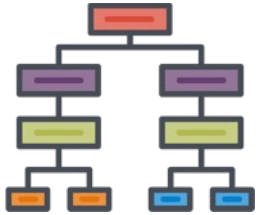
Making systems that work to bring in the right information is one part of the puzzle

Making systems that use the information appropriately is equally critical

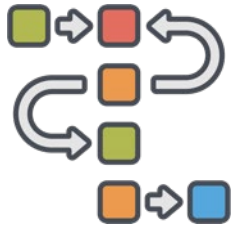
Bringing in the right information

Interface

Language



Design



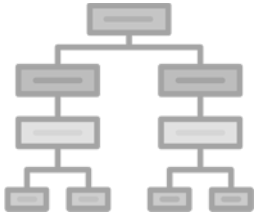
Process

Many things in research are designed around a white, English-speaking person (often male)…

Bringing in the right information

Interface

Language



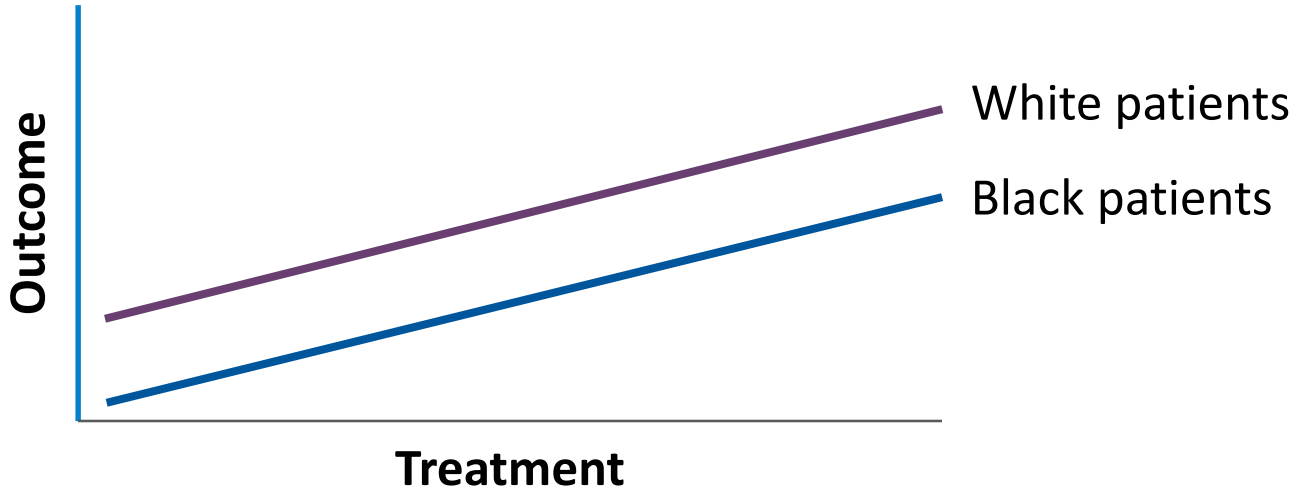
Design

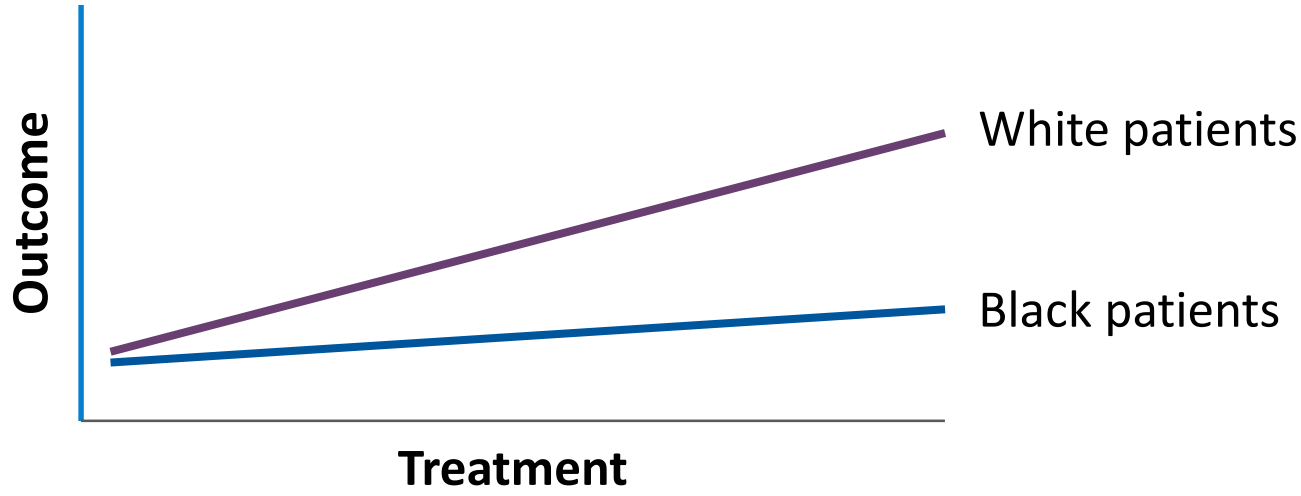
Process

Many things in research are designed around a white, English-speaking person (often male)…

But assuming we solved that, what do we do with the data?

Heterogeneity of effects — Where is there a disparity?





A call to ditch the ordinary subgroup analysis

Does the effect differ based on group membership?

$\neq$

What is the effect in the subgroup?

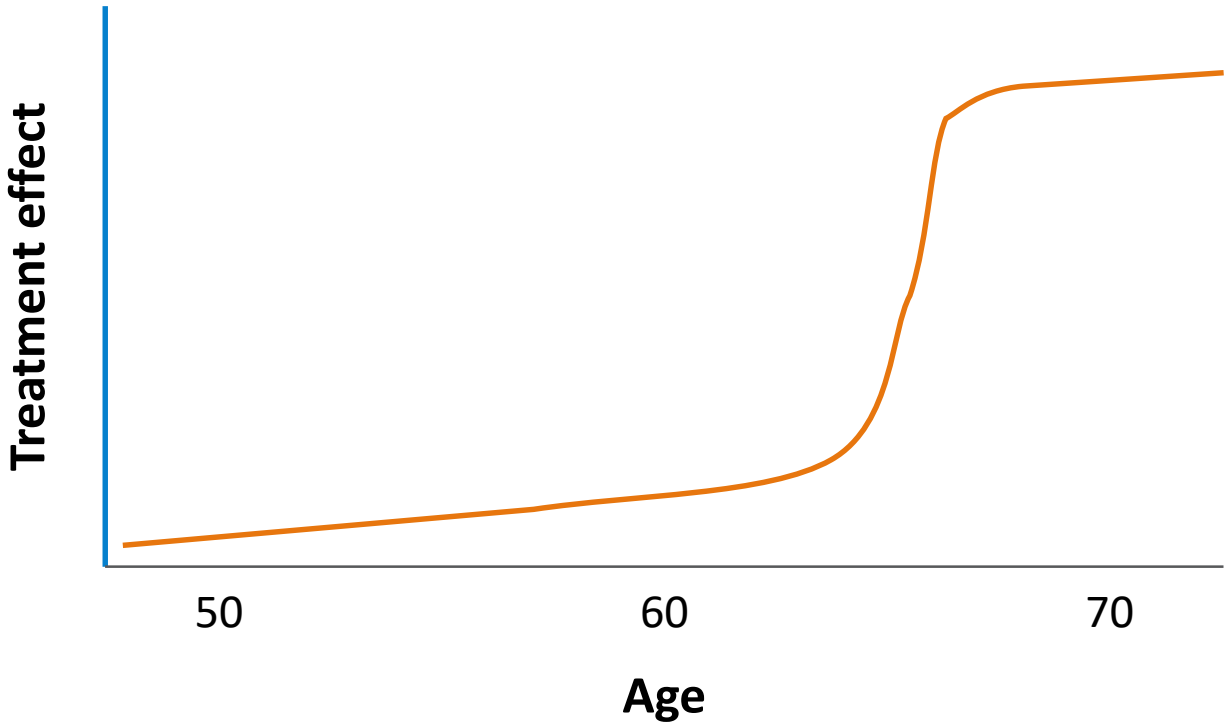
Focus on interaction terms

A call to ditch the ordinary subgroup analysis

Moreover

groups are not binary AND not all groups have meaning

What is the potential cause of the disparity?



To address disparities, assess the right diversity factor

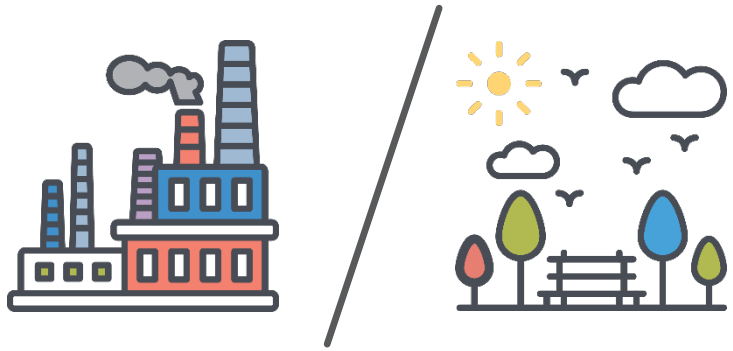
- When evaluating a pulse oximeter, is it **skin tone** or **self-reported race**?
- For understanding the impact of a care strategy, is it **race** or **access to care**?
- In an asthma trial, **are outcomes influenced by environment**?

Design for diversity means thinking about what might perturb the relationship between treatment and outcome

i.e., mechanistic thinking

Designing for diversity

- Central to guidance is the concept of reasoned mechanisms
  - Biological differences
  - Sociocultural differences
  - Behavioral differences
  - Environmental differences



- Central to design should be reasoned mechanisms
  - How do I ensure my study cohort represents the diversity of factors that will influence the effect of exposures of interest?
  - How do I measure the diversity factors?

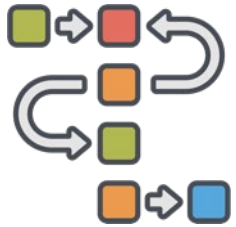
Back to practicalities

- FDA guidances emphasize reducing participant burden
- **Who** is predefined

What

When

Where



How

are the things we can change

Everything is a tradeoff

Rigor of a data point –v– generalizability

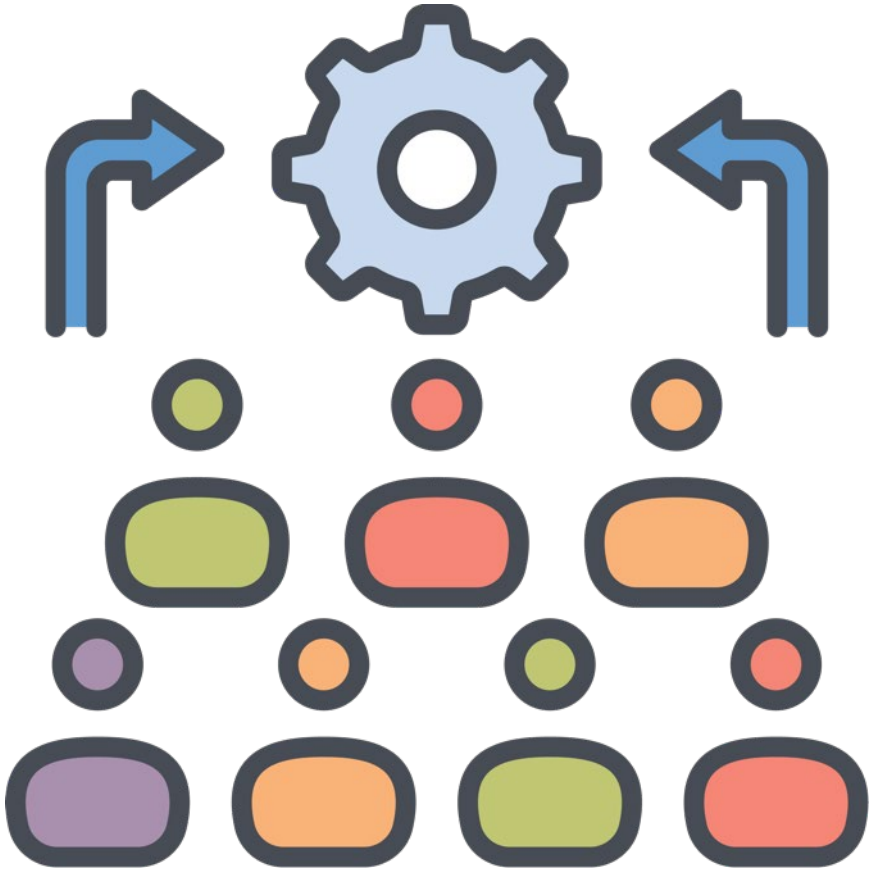
Ease of recruitment –v– generalizability

Simple for the research team –v– generalizability

Cost control –v– generalizability

Impact of the science –v– ???

The need for systemic change



- Is it possible to **implement** design for diversity without a diverse workforce?
- How can we influence monolithic infrastructures centered on decades of rules and processes?

Mitigating health disparities

In optimizing design for diversity we begin to mitigate the contribution of clinical research to health disparities