MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

HRA DEI Community Call: Promoting Diversity in Clinical Trials

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Health Research Alliance

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Health Research Alliance

Thank you for inviting me.

The Multi-Regional Clinical Trials Center (MRCT Center)

The MRCT Center is a research and policy center focused on addressing the conduct, oversight, ethics and regulatory environment for clinical trials.

Our Vision

Improve the integrity, safety, and rigor of global clinical trials.

Our Mission

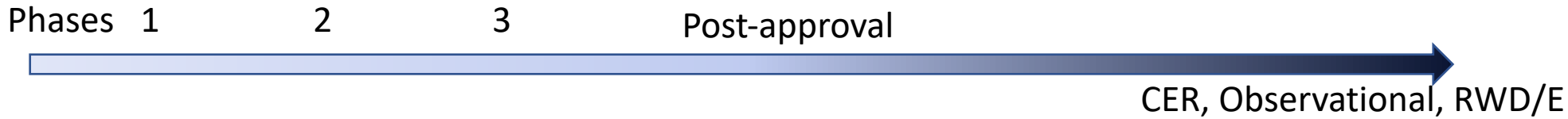
Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

Brigham and Women's Hospital
Founding Member, Mass General Brigham

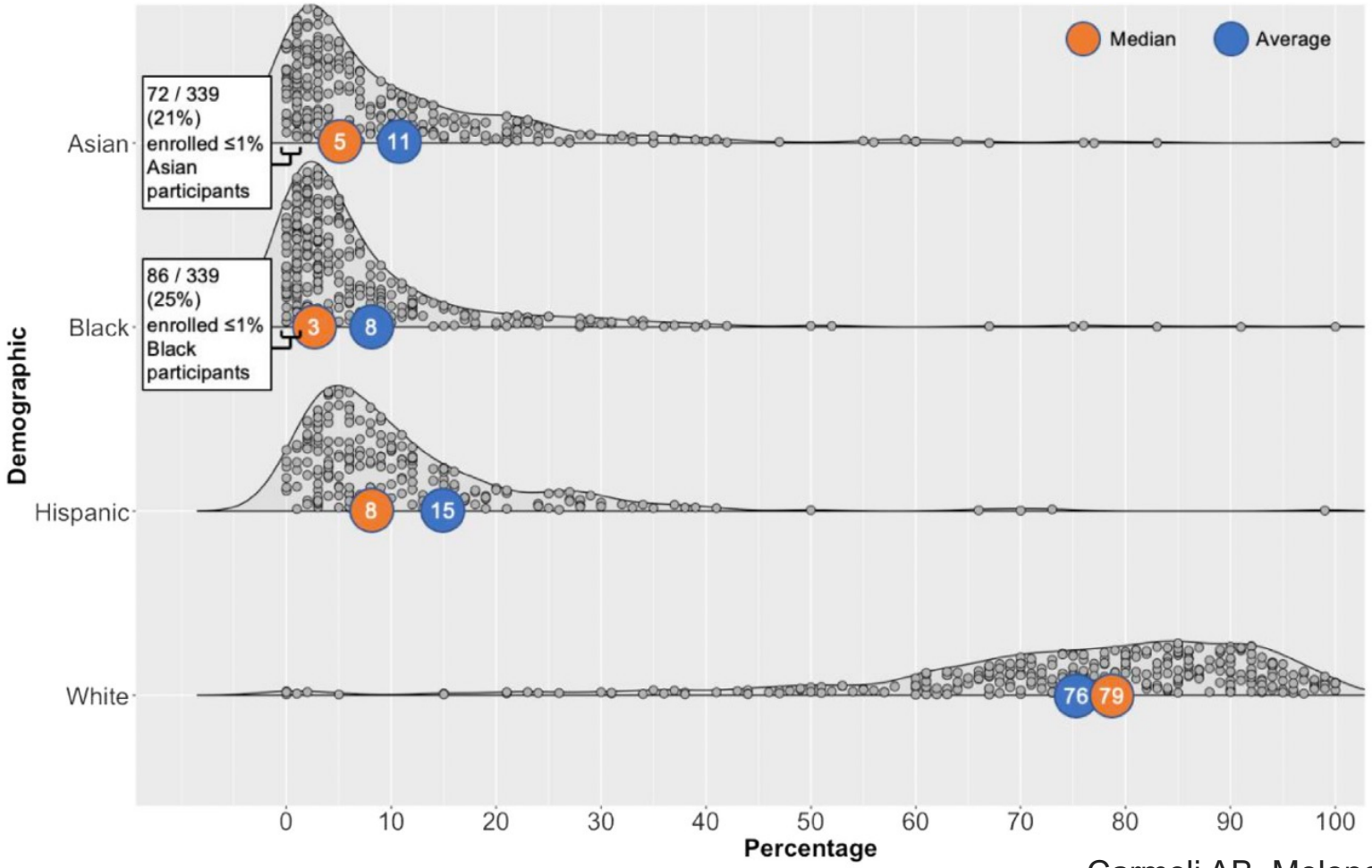
HARVARD UNIVERSITY

Importance of diversity and inclusion in clinical research

- Participant enrollment is often a challenge in clinical trials, and recruitment and retention of underrepresented populations in research can be particularly challenging.
- Nevertheless, participation in clinical research should reflect the population affected by the condition or disease, or for whom the intervention is intended.
- Analyses of group differences in outcome among diverse populations can promote the identification of underlying biological and socially relevant factors that affect health, but only if data exist.
- Diversity in enrollment seeks fairness in the distribution of direct and long-term benefits of research.
- Diverse representation in clinical trials is not simply a matter of biology, but a matter of health equity and fairness.



FDA Drug Trial Snapshots 2015-2021



FDA approved 339 drugs and biologics from 2015 to 2021.

Of all FDA DTS reports:
21% included ≤ 1% Asian participants
25% included ≤ 1% Black participants

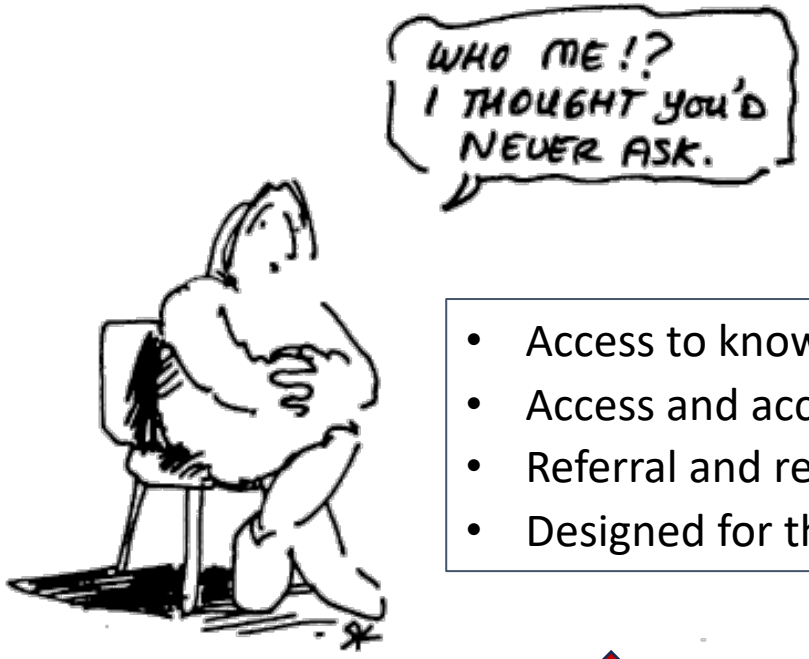
Blue: average weighted by enrollment
Orange: median

Carmeli AB, Meloney L, Bierer BE. Patterns. 2023 May 12;4(5).

The Work We've Done

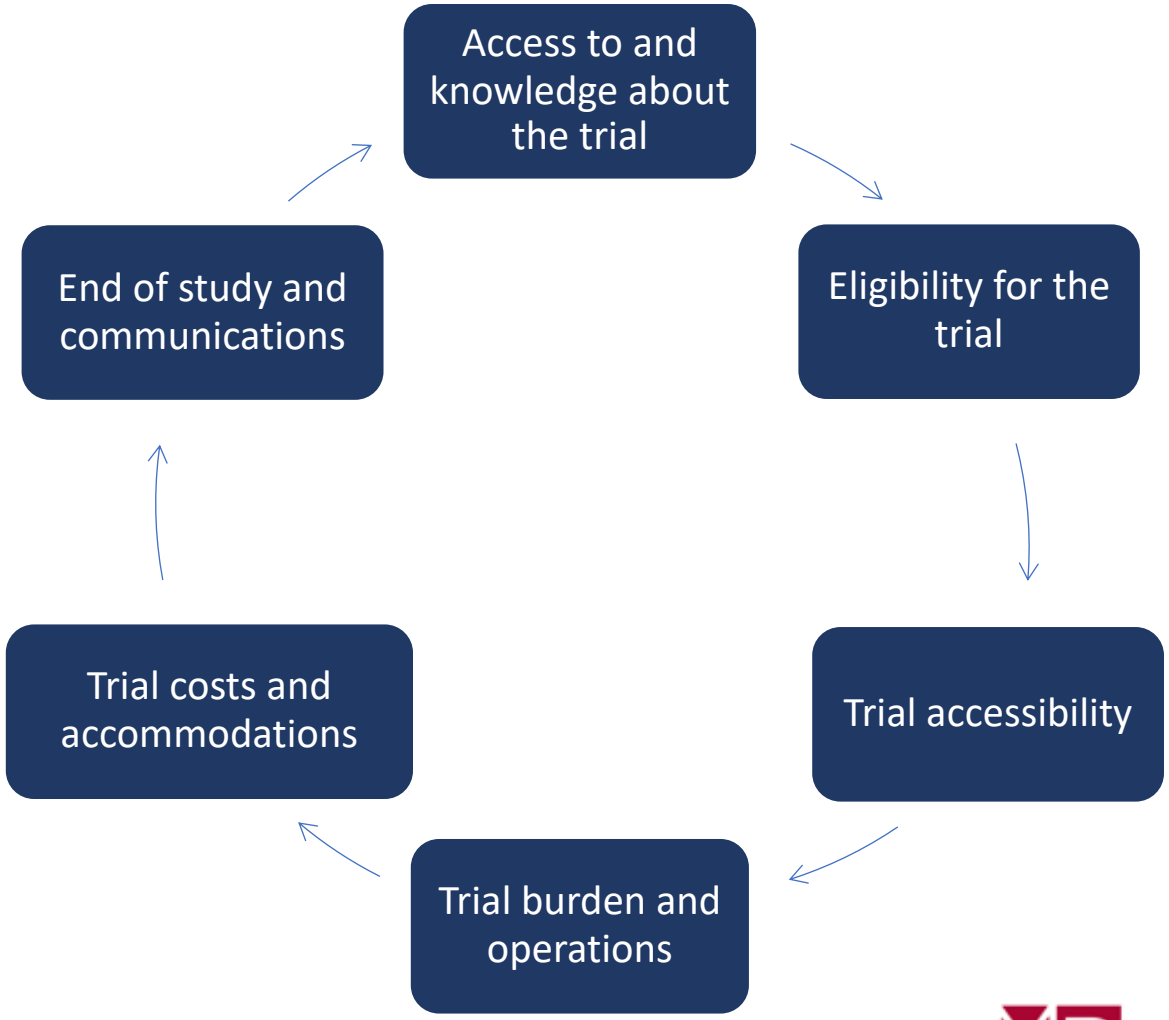
https://mrctcenter.org/diversity-in-clinical-trials/

Individuals must be invited



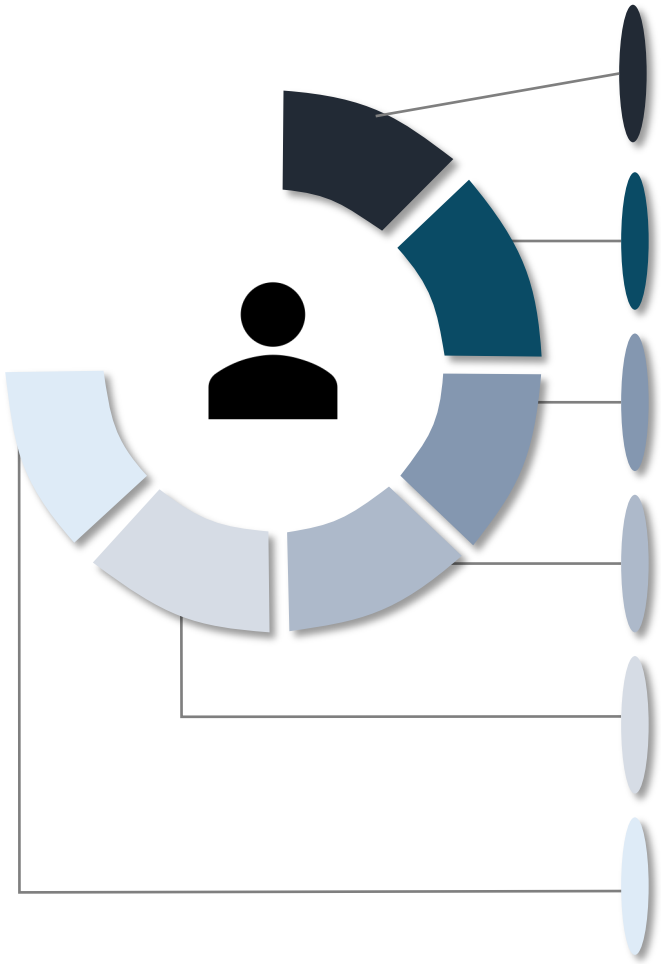
- Access to knowledge & choice
- Access and accessibility to trial
- Referral and resources
- Designed for the patient

Participant pool
Enrollment



From: http://www.aral.com.au/ari/p-ywadsworth98.html

Moving to inclusion: ↑ engagement and ↓ burden



Participant- and community-engagement

Patient, community partnership, input to study question, conduct, communications

Study Design and Plan: Traditional, hybrid, decentralized

Data minimization, mobile-enabled (e.g., eConsents), remote monitoring, geo-mapping

Design for inclusion

Accessible, health literate, translation, ↑ eligibility, recruitment, navigators, payment

Resourced

Digital and data access, technology, help, financial neutrality, insurance independent

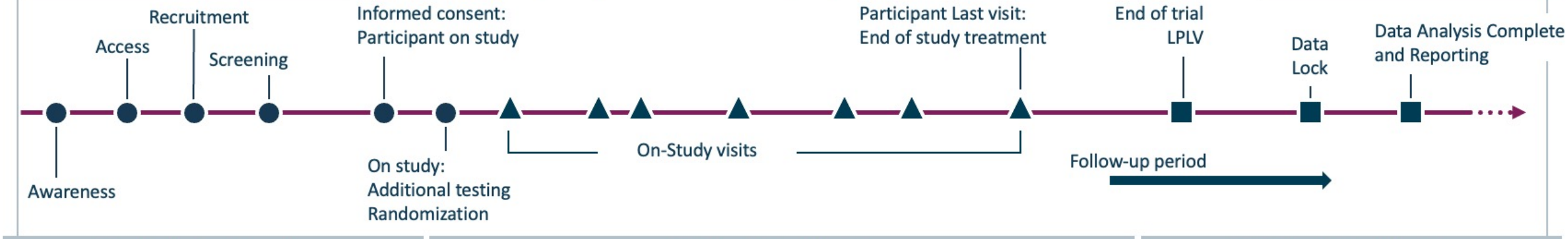
Confidentiality and Communications

Privacy, confidentiality, security, connectivity

End of study

Results return, transitions of care (participant), continued engagement (community)

DIVERSITY, EQUITY, & INCLUSION (DEI) STUDY LEVEL CONSIDERATIONS



Pre-Study Considerations

- ❑ Form and nurture partnerships with underserved communities. Engage with community physicians, patients, and others (e.g., cultural ambassadors) to inform the study question, design, and conduct.
- ❑ Develop health-literate communications and support educational activities to enhance diverse participant awareness, access, recruitment and retention (e.g., translation of study materials, participation in local health fairs, engage with community health centers).
- ❑ Establish processes to minimize burden (e.g., protocols for payment, flexible appointments, accommodations, translation services). Consider if decentralized/hybrid trials would be an appropriate option to reduce burden.
- ❑ Create/adapt a standard mechanism to collect, record, and track demographic and non-demographic variables of participants screened, offered, and consented into study.
- ❑ Develop objective screening approaches and systematically collect and record reasons for screen failure.
- ❑ Periodically analyze/evaluate screen failure data.

On-Study Considerations

- ❑ Document the basis of the decision for excluding participants from a trial.
- ❑ Devise a simple, honest, and clear informed consent process for participants that is conducted in a health-literate, culturally- and linguistically-appropriate manner.
- ❑ Provide translation services of the informed consent form and/or interpreter services for individuals with limited or no English proficiency, as applicable.
- ❑ Apply accessibility principles to study documents and provide accommodations for people with disabilities as required.
- ❑ Allow flexible strategies that enable participants and their caregivers to adhere to the expectations of the study (e.g., amenable clinic hours, locations, virtual visits; provision of childcare, eldercare, and food during study visits; transportation assistance; appropriate reimbursement and compensation).
- ❑ Offer regular, open, and respectful communication through the platform of participant preference (i.e., phone, text, email, virtual meeting, etc.) to foster participant understanding.
- ❑ Establish a monitoring and evaluation system to ensure timely interventions if actual enrollment does not meet expected enrollment or if the actual enrollment does not reflect the expected demographic(s) intended for the study.
- ❑ Monitor retention to study by demographic and non-demographic factors.
- ❑ Put practices in place that provide continuous education, support, and outreach to participants and their communities.
- ❑ Train all staff interacting with participants and their caregivers in principles of respectful communications, bias, and cultural humility.

Post Study Considerations

- ❑ Plan for data analyses that includes sub-group analysis and examination for heterogeneity of treatment effects as applicable to the study.
- ❑ Provide clear communication around end-of-study expectations, including transitions of care, potential later outreach, timing of further communications.
- ❑ If the study involved an investigational product, anticipate continued access to the investigational product for participants who are benefitting from the treatment and have no other equivalent options for treatment
- ❑ Return aggregate and, to the extent possible, individual study results in health literate and understandable language to study participants.
- ❑ Return aggregate results, if applicable, to the community in a culturally- and linguistically-appropriate manner to the community.
- ❑ Conduct post-study survey of participants to learn what worked well and areas for improvement.
- ❑ Review study performance for lessons learned and to help plan future studies.

MRCT Center's Clinical Research DEI Toolkit & Case Studies

https://mrctcenter.org/diversity-in-clinical-research/tools/toolkit/

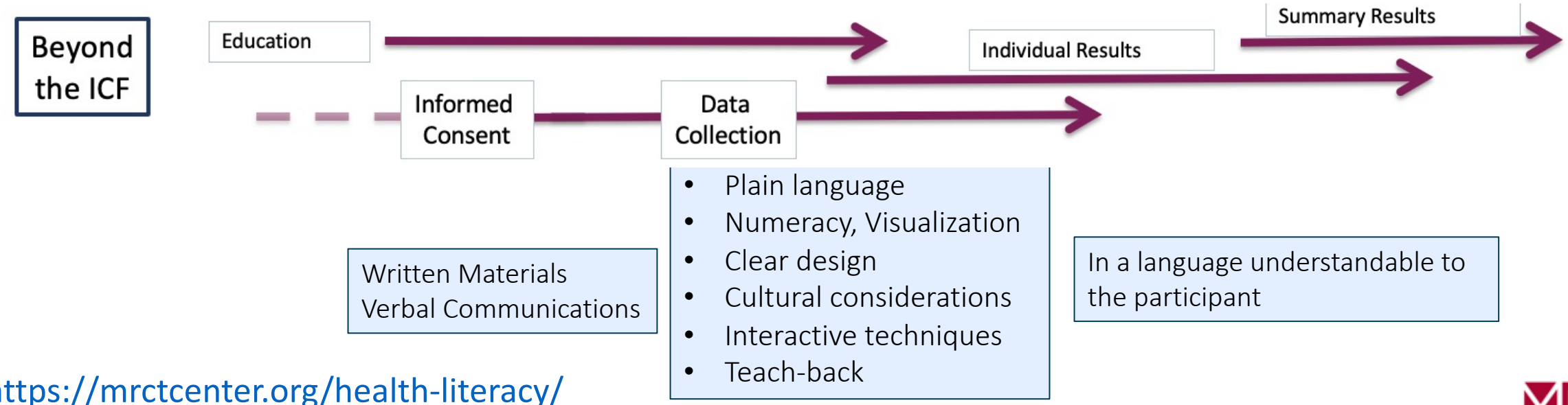
- Audience: Sponsors, CROs, PIs and study teams
- Tools directed at different time points in the design and conduct of a clinical trial
  - Overview documents
  - Participant & Community Engagement
  - Participant awareness, knowledge, access
  - Workforce training and development
  - Data variables, collection and reporting
  - Study design, conduct, and implementation
  - Stakeholder commitments
  - Case studies (therapeutic and programmatic)

- Downloadable, editable → adaptable

Health Literacy and Communication

- The listener does not have “poor literacy,” and is not responsible for making sense of the information.

- The communicator is responsible for sharing information that is understandable to the listener.
- The listener should be comfortable communicating any lack of understanding.



https://mrctcenter.org/health-literacy/

Health literacy beyond the ICF

Injection Guide for Study Drug or Placebo
Panel A (Days 1-5) and Panel B (Days 6-10)

Instructions for Use

Study Drug or Placebo Injection

Each vial contains 1 mL of study drug or matching placebo. The volume removed from the vial determines the dose administered. The study staff will tell you how much to inject from each vial.

Important Information

- **Refrigerate kit box: Do Not Freeze.**
- **Vials should only be used one time.**
- **Only uncap the vials that you are preparing to inject.**
- **Only inject the volume instructed by study staff. Do not inject the entire contents of either vial.**
- **Always use a new site-provided syringe/needle for each injection.**

Step 1: Prepare Vials

- Remove 2 vials from the kit box and return kit box to the refrigerator.
- Allow vials to come to room temperature for at least 15 minutes.
- Vials should then be inverted a minimum of three times.
- Wash your hands with soap and water.

Step 2: Prepare Syringe

- Remove the cap from one of the vials and wipe the top of the vial with an alcohol swab.
- Open a new syringe and needle.
- By pulling back on the plunger, draw air into the syringe up to the mark of the volume to be injected and then slowly inject the air into the vial.
- Keep the needle in the vial and turn the vial upside down. Make sure that the needle tip is well below the surface of the liquid in the vial.
- With the tip of the needle in the liquid, pull slowly back on the plunger to get the right volume into the syringe.
- Check the syringe for air bubbles. If there are bubbles, hold both the vial and syringe in one hand, and tap the syringe with your other hand. The bubbles will float to the top. Push the bubbles back into the vial, then pull back to get the right volume of study drug/placebo.
- When there are no bubbles, take the syringe out of the vial. Put the syringe down carefully so the needle does not touch anything.

Step 3: Injection

- Clean an injection site that is about 2-3 inches away from your belly button on your abdomen with a new alcohol swab. Let dry thoroughly.
- Hold the syringe in the hand that you will use to inject study drug. Use the other hand to pinch a fold of skin at the cleaned injection site.
- Use the injection technique shown to you by the study staff.
- After the needle is inserted and while pinching the skin, pull the plunger back slightly. If no blood appears, steadily push the plunger all the way down until the study drug is injected. **Note:** If blood enters the syringe, remove the syringe, clean and prepare another spot on your abdomen and using the same syringe/needle, inject the product.
- Leave the syringe in place for about 6 seconds after injecting (the pinch may be released) and remove. After the needle is removed, you can apply light pressure with clean gauze or cotton ball but, do not rub the site.
- Place used syringe/needle (do not re-cap the syringe) in a sharps disposal container provided by site.

How to give yourself the study medicine

Panel A (Days 1-5) and Panel B (Days 6-10)

Study medicine

Each bottle holds 1 mL of active drug or placebo.

The study staff will tell you how much medicine to use each time (this is called your dose). Only give yourself the dose the study staff told you. Do not use all the medicine in the bottle.

The study staff will tell you how much to inject from each bottle.

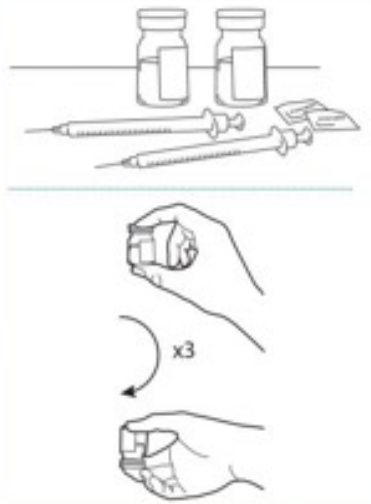
Important safety information

- Refrigerate the kit box – Do not freeze.
- Only use each bottle 1 time.
- Use a new syringe and needle each time.
- Only uncap the bottles when you use them.

Steps to give yourself the study medicine

Get ready

1. Gather your supplies:
   - 2 syringes
   - 2 bottles of medicine
   - 2 alcohol swabs
2. Take out 2 bottles from the kit box and put the kit box back in the refrigerator.
   - Let the bottles sit on the counter for at least 15 minutes to get to room temperature.
   - Turn the bottles upside down and then right side up at least 3 times.
3. Wash your hands with soap and water.



https://mrctcenter.org/health-literacy/

Merck & Co., Inc. example with input from Health Literacy Media

Translation. US regulation: "…in language understandable…"

- Common Rule and FDA both require "information that is given to the subject or the representative shall be in language understandable to the subject or the representative."

  [1]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guide-informed-consent#content

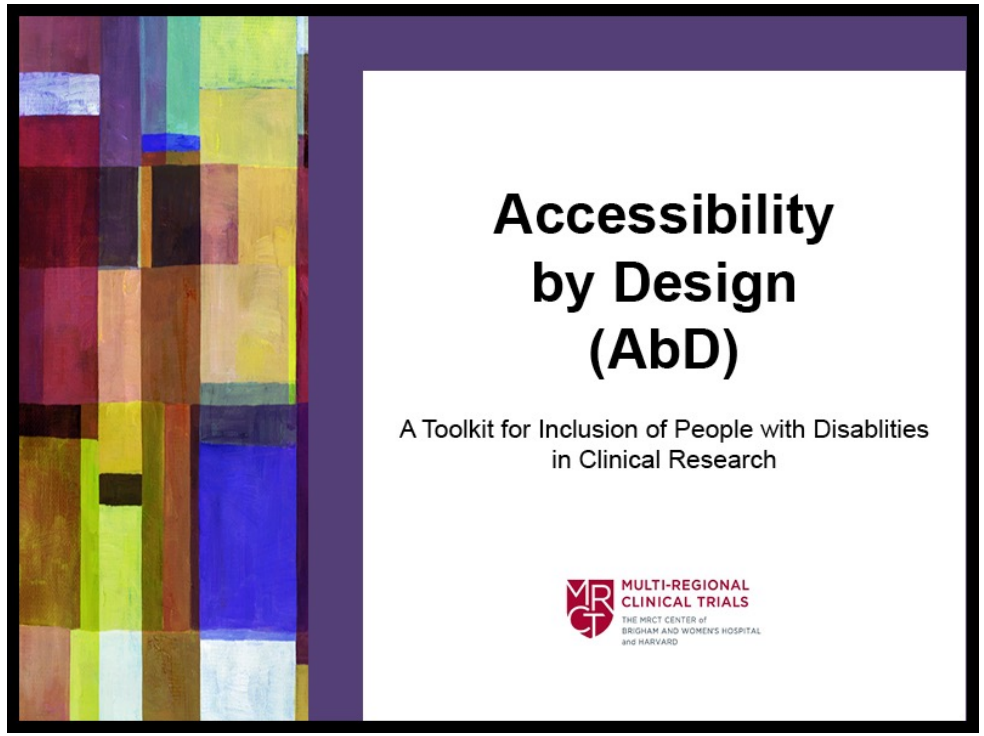
- Of all interventional trials for adults with one site in US registered between 1/1/2019 and 12/1/2020, approximately **19%** required the ability to read, write, and/or speak English or be a native English speaker*

Routine exclusion on the basis of language is discriminatory.

*Muthukumar AV, Morrell W, Bierer BE. Evaluating the frequency of English language requirements in clinical trial eligibility criteria: a systematic analysis using ClinicalTrials. gov. PLoS medicine. 2021 Sep 14;18(9):e1003758.

The Accessibilty by Design (AbD) Toolkit

AbD toolkit website: https://mrctcenter.org/diversity-in-clinical-research/tools/abd_toolkit/



- Preparing for AbD : General Considerations
- Implementing AbD: Communication Accessibility
- Implementing AbD: Physical Accessibility
- Innovating AbD: Newer Strategies for Inclusion
- Upholding AbD: Accountability and Advocacy

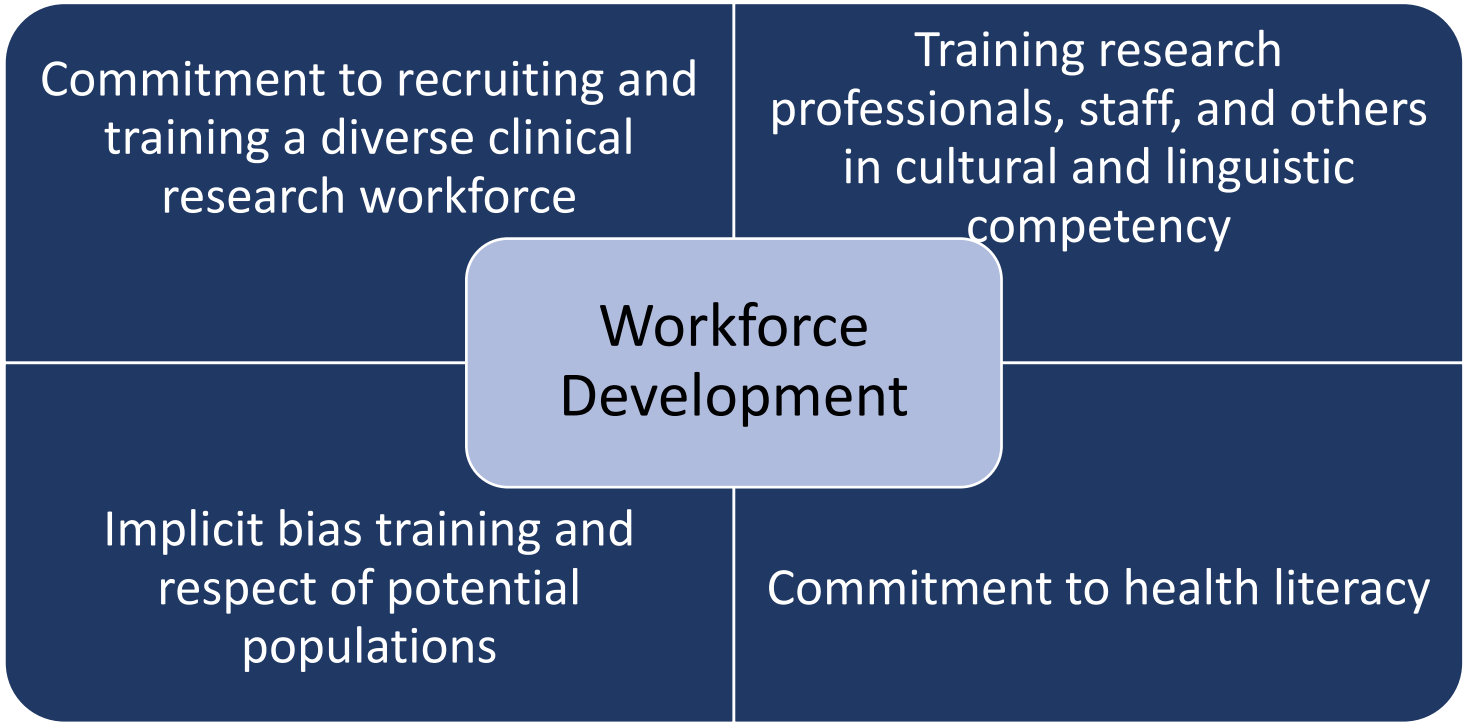
Integrating Supported Decision-Making into the Clinical Research Process

Barbara E. Bierer, Ari Ne'eman, Willyanne DeCormier Plosky, David H. Strauss, Benjamin C. Silverman & Michael Ashley Stein

https://doi.org/10.1080/15265161.2021.1980141

https://www.nature.com/articles/s41591-022-02035-3

Minimum expectations of workforce development



Inclusive of

- Clinicians
- Investigators
- Research team members
- Referring physicians
- Sponsors
- CROs/AROs
- Patient recruitment vendors
- Participant navigators

Invest in

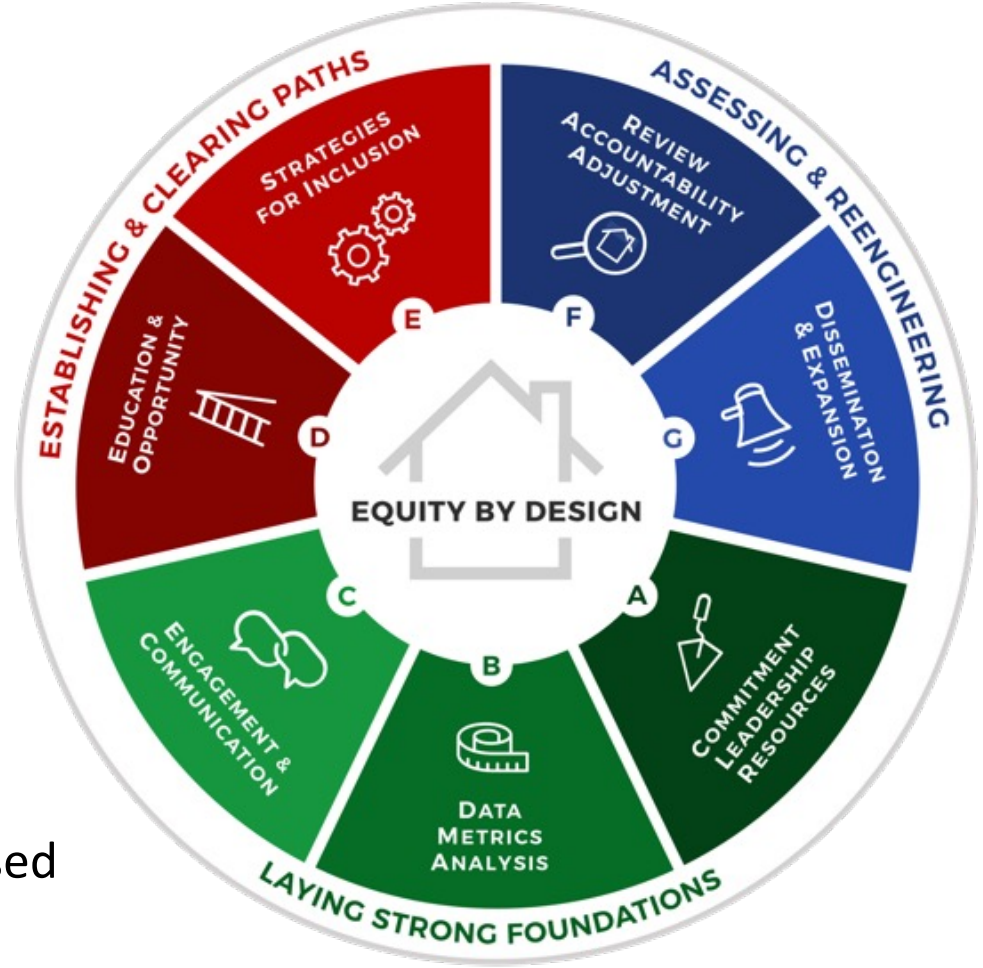
- Talent development
- Training

Assessments and improvements should be data-driven, tracking predefined metrics.

Accountability

How do we hold ourselves accountable?
How do we improve?
How do we know how we are doing?

Equity by Design (EbD): Metrics Framework



Built in layers

- 7 key themes
- Quantitative and qualitative metrics
- Each metric has levels of detail that can be accessed

https://mrctcenter.org/diversity-in-clinical-research/tools/ebd-metrics-framework-and-user-guide/

Diversity Convergence Project:

A National Framework for Achieving Diversity in Clinical Trials

National Action Plan: Priority Goals and Collective Actions

- Public Awareness and Communication
- Community Engagement and Investment
- Site Enablement
- Workforce Diversity
- Design for Equitable Access to Trial Participation
- Funding, Resources, and Support
- Comprehensive and Consistent Data
- Accountability

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CLINICAL TRIALS TRANSFORMATION INITIATIVE

NATIONAL ACADEMIES Sciences Engineering Medicine

MILKEN INSTITUTE FasterCures

Accountability: Funders

Is there a roll for funders?

- Direct funding or provision
- Indirect (as a condition of grant award)

Accountability: Funders

YES

National Action Plan: Priority Goals and Collective Actions

- Public Awareness and Communication
- Community Engagement and Investment
- Site Enablement
- Workforce Diversity
- Design for Equitable Access to Trial Participation
- Funding, Resources, and Support
- Comprehensive and Consistent Data
- Accountability

Possible roles and actions: Funders

Public Awareness and Communication

Provide access to information to patients, potential participants, and communities:
- About their rights as research volunteers
- About clinical trials in general
- About disease-specific possible trials

Provide and align patient and participant navigators
Plan and support community health and health research activities

Workforce Diversity

Intentionality: funding students, trainees, and others from diverse backgrounds
Supplemental awards for people who represent underserved communities
Engage in and/or fund health fairs for the recruitment of future workforce
Create (direct) or Fund (indirect) honorific awards, microgrants, training, internships

Possible roles and actions: Funders

Equitable Access to Trial Participation

- Require diversity action plans
- Create (Direct) or Fund (Indirect) community advisory board review
- Require payment to patient partners as a condition of service
- Enable participant navigators
- Require plain language review of materials, user testing by patient/pt advocates
- Recommend or require translation and interpreter services
- Require accommodations
- Require reimbursement and compensation and allow incentive payments
- Provide advice on tax and means-tested eligibility implications
- Require (fund) or provide transportation
- Digital enablement
- Return of results (individual and aggregate data) to participants and the communities that they represent

Possible roles and actions: Funders

Comprehensive and Consistent Data

Collect, aggregate, and provide data

- Epidemiology of the disease or condition, by demographic variable
- Common data elements and standards
- Fund development of standards and data sharing

As a condition of grant award:

- Recommend data standards
- Require data dictionary and data sharing

Accountability

Self-assessment of current state
Diverse representation on BoD, standing committees
Review of, and metrics to inform, grant portfolio
Bias training and cultural sensitivity training of defined populations

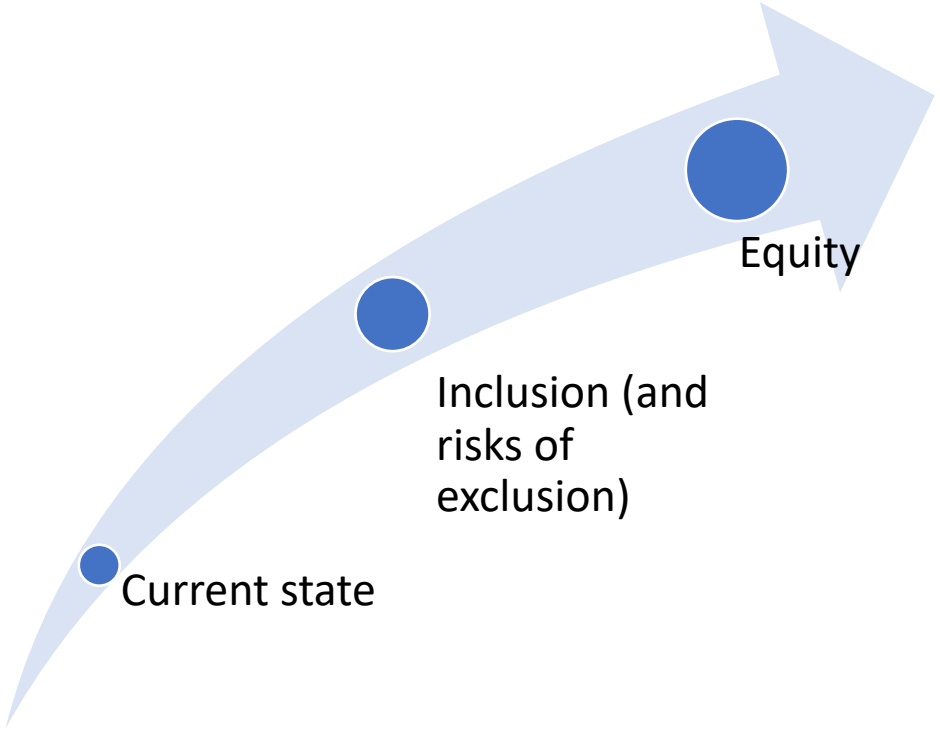
What can we do now?

- Know your own strengths and challenges, individually and together
- Ask tough questions of – and support – each other (& others)
- Provide the resources where you can (training, tools, $)
- Advocate and educate before you agitate and aggravate
- It's a journey. What you know today will differ from what you know tomorrow
- It's a marathon, not a sprint

http://davidmmasters.com/wp-content/uploads/2016/10/when-the-going-gets-tough-the-tough-get-going.jpg

https://www.nationalww2museum.org/students-teachers/student-resources/research-starters/women-wwii

We are accountable for making measurable progress



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