Bootcamp for New Investigators in Clinical Research
Session 2. Thurs, DEC 15, 12-2 pm (virtual)

Optimizing Roles on the Study Team (10-slide max; 15 minutes each speaker)

12:00-12:15 How the strengths of CRA and the investigator tie into the audit: **Radwa Aly**

12:15-12:30 Who is part of the safety team? **Caitlin Joffe**

12:30-12:45 Optimizing stakeholder input: **Randi Streisand**

The Clinical Trial Contract (10-slide max; 15 minutes each speaker)

12:50-1:05 Budgeting and contracts: **Melanie Bossi**

1:05-1:20 Standard of care testing vs research costs: **Stephanie Bair**

1:20-1:35 Service biostatistics: **Qing Zeng**

1:40-2:00 Breakouts: **Institutional Solutions to Challenges**

Who pays for what? Who defines standard of care?
Who do you contact if there is disagreement; who helps resolve?

- **GW: Hiromi Sanders, Melanie Bossi**
- **CNH: Bobbe Thomas, Stephanie Bair**

Office of Clinical Research

How the Strengths of the CRA and the Investigator Tie Into the Audit

Radwa Aly

GW SMHS, Office of Clinical Research

15Dec2022

They're different but the same…

Monitoring visit (Act of overseeing the progress of a clinical trial):**

- Usually every 4-6 weeks or 6-8weeks, depending on phase of study
- Frequency planned as part of the protocol data management plan
- Helps maintain data integrity – check to ensure data is correct and clean
- Can be internal for Investigator initiated or CRO for external sponsors

Inspection (An official review of documents, facilities, records and other resources related to a clinical trial):**

- Verifies accuracy of data being submitted
- Planned in advance
- Usually occurs in select sites when FDA application has been submitted

Audit (Systematic and independent examination of trial-related activities and documents): Can be performed by sponsor or federal agency**

- Not – for- cause
- For-cause

Regardless of the nature of the visit: the CRA/CRC and PI should always be ready

** ICH E6

Roles and Responsibilities

Research assistant/coordinator

- Day-to-day maintenance
- Document collection
- Record-keeping and filing
- Data entry/clean up

Principal investigator:

- Be available
- Know your patients
- Know about your issues ahead of time – PI oversight is key
  - AE's
  - Deviations
  - Screen failures
  - Processes
  - Who is on your team

Organization: SOPs, processes and workflows

It is a partnership! Ultimately YOU (the PI) is responsible

Preparation Begins When the Study Begins

- Monitoring visits are planned but inspections and audits are not
- Inspections and audits can happen at any time with little to no notice
  - -Inspections (you can be given as little as 2 weeks or as much as 2 months)
  - -Audits can happen the next day if is for cause

When does prep start? Site initiation

- Keeping files up to date
- Ensuring all licenses are and GCP certificates are valid
- Data is entered in a timely manner
- Training logs are maintained
- Regulatory documents are filed
- AEs and SAEs are maintained
- Keep your PI engaged

During the Study

- Have routine monitoring visits - they will save you (even for investigator-initiated – ask the OCR to conduct for you)
- Keep up with findings from the monitoring visits
- Check your documents often
- Coordinator should be entering the data regularly and you should be reviewing the data just as regularly
- Do not expect one or the other will handle it – it is a partnership.
- Have regular meetings for study updates

What Can You Expect

Monitoring visits: Less formal - usually with the coordinator. PI has to speak with the monitor in person or by phone

- Monitors are on your side – they want you to be prepared
- Take monitoring visits seriously

Audit/inspection: Both PI and coordinator must be available for whole visit. Formal and depending on findings, can be reportable to OHRP or FDA

- Pre visit meeting/Post visit close out meeting
- Usually little to no engagement with site staff

Common Findings

Informed consent

Regulatory maintenance

Data use/access/sharing

Key Takeaways

- This is a partnership. Even though the coordinator does a lot – the PI must always be engaged every step of a study

  -CRA and PI's should be a united front

  -Make sure you are aligned with your university policies and SOPs

- Prep begins at the start of the study

- Always be audit ready – and I mean always: It's not just what you do, it's a state of operation

Resources

GW OCR: https://clinicalresearch.gwu.edu/researchers/regulatory-compliance-services

ACRP Inspection readiness course: https://acrpnet.org/courses/inspection-readiness-best-practices-managing-clinical-trial-inspections/

Article: https://www.linkedin.com/pulse/how-can-you-create-culture-clinical-trial-inspection-readiness/

THANK YOU!!!

Children's National

New Investigator Bootcamp

December 15, 2022

The Safety Team

Caitlin Joffe, MBA CCRP
Director, Research Quality Assurance

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Study Team

- Safety starts with you (and your team)
- Communication is key
    - Team meetings *with sign in sheets or record Zooms*
    - Study team trainings – continual training! Research isn't static!
    - If it’s not documented, it didn’t happen!
    - ALCOAC (attributable, legible, contemporaneous, original, accurate, complete)
    - Good documentation practices (what study, what visit, all required data points captured, etc.)

•Make the corrections BEFORE the reviewer ever schedules a visit (remote or on-site) – strike-through, initial and date!

Industrial Sponsor

- Medical Monitor: ensure the safety and integrity of the trial subjects throughout the trial; acts as the point of reference for study sites and determines how to evaluate safety events within a clinical trial
- Standard Monitoring (Sponsor representative or CRO designee)
    - Site Evaluation or Pre-Study Visit = PSV
    - Site Initiation Visit = SIV
    - Interim Monitoring Visit = IMV
    - Close Out Site Visit = COV

Internal Monitoring

- Source documents, CRFs, reg binders (paper or e-reg).
- Results of reviews are entered into a tracker
- By tracking reviews/findings we can:
    - Re-educate research staff
    - Identify new training opportunities
    - Ensure compliance with institutional and study requirements
    - Ensure timely reporting and correction of research data
    - Ensure timely and accurate reporting of deviations/ errors and catch errors before more serious FDA etc. reviews
    - Note trends in errors

Data Safety Monitoring Board

- Is a DSMB required?
  - Generally, DSMBs are needed for clinical trials of diseases with high mortality or morbidity, for clinical trials involving high risks, and for large, multicenter clinical trials.

- What does a DSMB do?
  - Periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and
  - Make recommendations concerning the continuation, modification, or termination of the trial.

FDA

- Ongoing review of FDA-regulated & IND/IDE studies
- Inspections
  - Official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and
  - that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities, or
  - at other establishments deemed appropriate by the regulatory authority(ies).

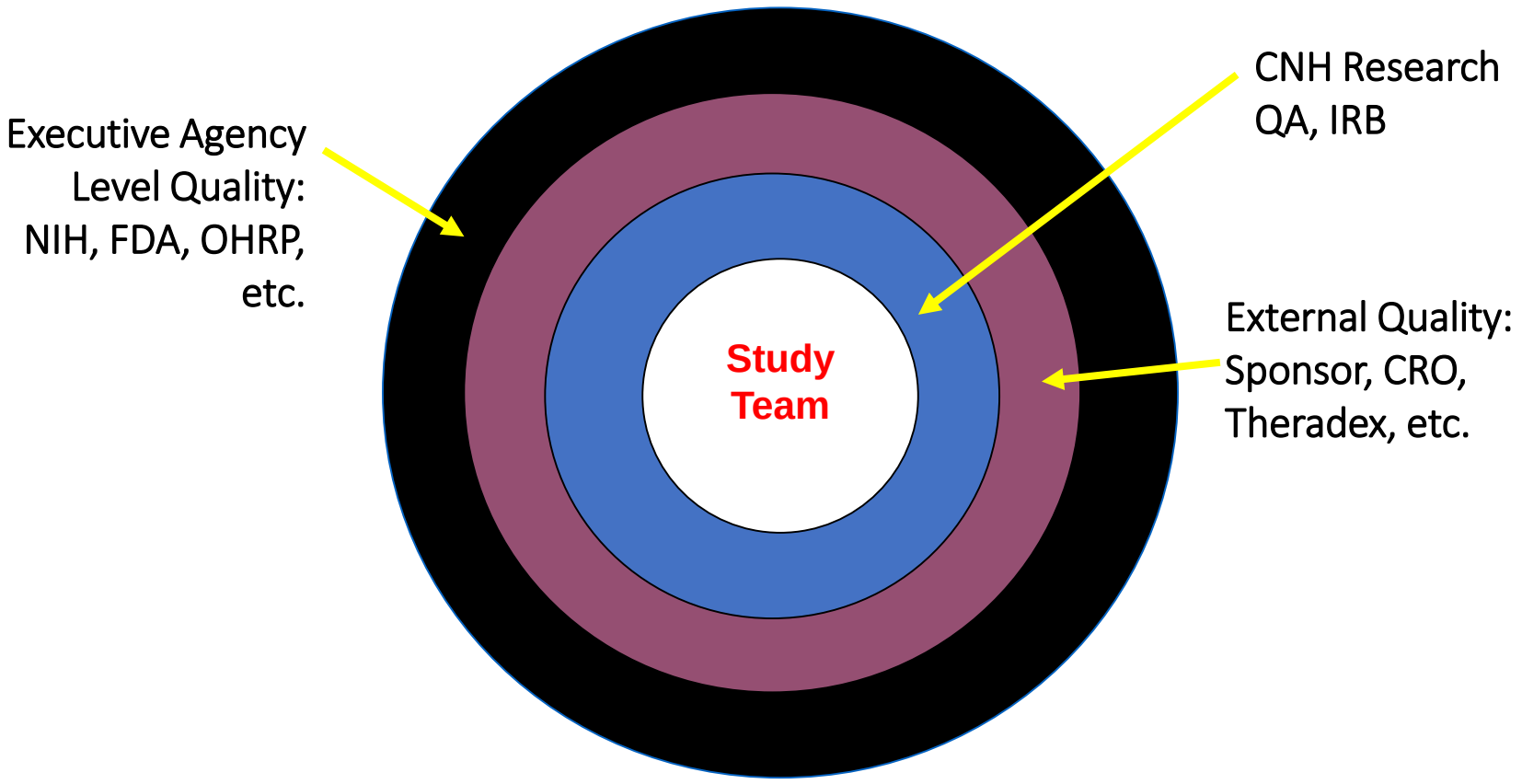
Compliance Activities

Method	Conducted By	Purpose	Outcome
Audits	Sponsor or CRO	QA measure to verify data integrity and clinical trial processes.	Potential SOP changes, recommendations for the monitoring process
Inspections	Regulatory Agency or Authority	Verify data integrity, assure compliance with regulations, confirm protection of research subjects	Affects the agency's decision to accept data supporting a marketing application. May have implications for the investigator if misconduct (e.g., fraud, falsification or fabrication) is found.
Monitoring	Sponsor or Internal QA	Critical ongoing component of conducting a clinical trial.	Assesses and assures compliance with the study protocol on an ongoing basis.

Things to consider..

- Who will do it (e.g., the research manager)?
- What will be reviewed (e.g., 100%)?
- When will it be performed (e.g., periodically, at the end)?
- How will study data be checked (e.g., QC)?
- How will corrections be made, documented, and reported?
- How will findings be communicated, and to whom?

A Diagram of Quality



Quality Matters

- Quality Assurance is everyone's responsibility (PI, Co-Is, Study Coordinators, Regulatory Coordinators, Nurses, Data Managers, etc.)

Questions?

Caitlin Joffe, Director of Research Quality Assurance
cjoffe@childrensnational.org

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Optimizing Stakeholder Input

Randi Streisand, PhD
Division of Psychology & Behavioral Health, Center for Translational Research

Overview

Objective: Describe ways to involve stakeholders in research

1. Engaging Stakeholders:

   -at Study Design
   -Prior to Study Implementation
   -After the study (in preparation for future trials)

2. Example of TOTs with Stakeholders
3. Involving the Clinical team

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Who are your Stakeholders?

Young Children with Type 1 Diabetes- supporting diabetes management and adjustment

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Stakeholders at Study Design

How do we learn where/when a new treatment/intervention is needed?

Stakeholders Prior to Implementation

Feedback on processes, content, materials

One-on-one interviews, focus groups

THRIVE!

ROUTE T1D

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Stakeholders After the Study

- Satisfaction Questionnaire from participants
- Qualitative interviews from participants and maybe clinical team

THE Young Child PROJECT

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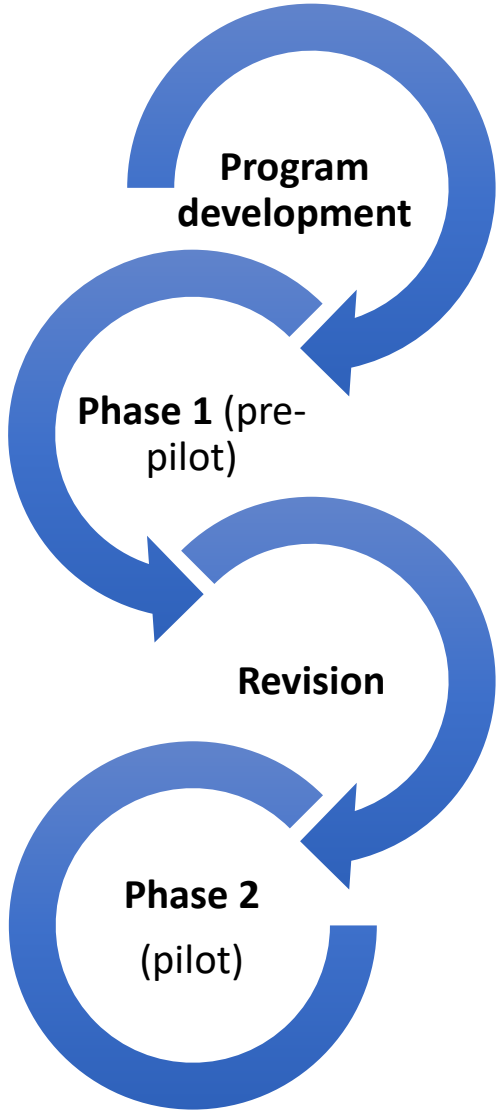
Development of TOTs: An iterative process NIH DP3 DK103998



- Previous study findings
- Feedback/approval from key stakeholders and experts
- Parent **qualitative interviews** to ensure content relevance
- Parent advisors to review and refine intervention materials

- Preliminary test (n=10)

- **Qualitative interviews** with participants
- Preliminary quantitative findings
- Discussion of findings with key stakeholders and experts

- Test refined intervention in larger RCT (n=60)

Method: Pre-Pilot Parent Interviews

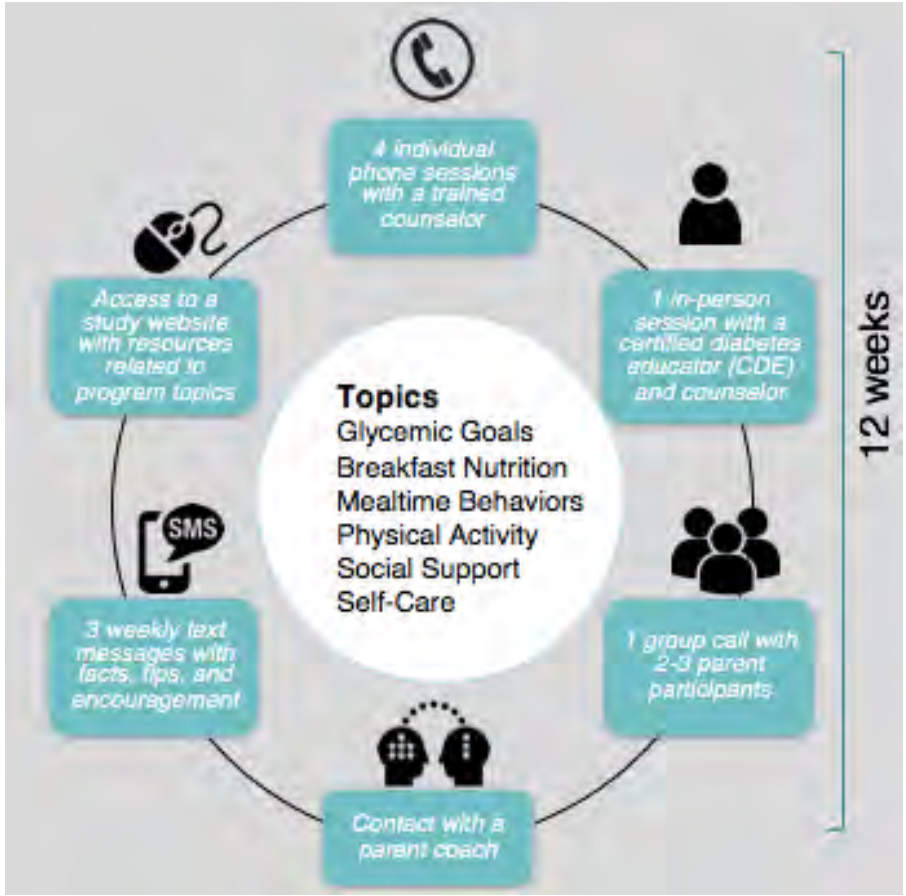
- 5 brief telephone interviews (~30 min)
- Recruited via clinic lists (matched study eligibility criteria), letters, phone calls
- Conducted by PI, CO-I, or RA about 3 months after study start
- $25 gift card compensation
- Recorded – field notes and transcriptions reviewed as a team

Open ended prompts:

- Adjustment to diagnosis
- Challenges of parenting a young child with diabetes
- Physical activity, eating, insulin administration
- Interest/usefulness of program components under consideration (website, text messages, parent coaches)

Overview of the initial TOTs Program

Intervention



Assessment

TOTs

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Method: Parent Participant Interviews after the Pre-Pilot

- Semi-structured telephone interviews (~30 min) with all parent participants after completing all data collection procedures
- Open-ended questions around feasibility and acceptability and areas for content change or expansion
- Qualitative analyses involved ongoing team discussion and reflection on participant responses to develop codes and themes

Findings: Parent Interviews after Pre-Pilot

Phone intervention:
"I wouldn't change any of [the program]. It was actually right on... like my parent coach. We had a great rapport."
"[the skills taught] were so doable. There were a lot of tools taught, and some of them I might come back to later."
"It was almost a theme a week… understand that parents who work cannot absorb that information in a week. In order to absorb it and begin to implement the techniques outlined in that chapter, they need about two weeks."

CGM: *"You want to feel like you can trust the numbers, but then sometimes they are wrong or sometimes you wish you didn't know. It's like with everything else with diabetes, you just can't EVER let your guard down."*

Website: *"I've only been to … the hospital downtown, in the waiting room. Just looking at that population you serve, it's mostly Hispanic and African Americans. And I'm looking at the menu items [on the study website], and I'm thinking, none of this is going to be a hit. I'm thinking, this is White food."*

How To's for Stakeholder Input

- Include qualitative interview in the study consent form and protocol
  - "A subset of participants may be asked…"
- Make sure the interviewer is a study team member who has not worked closely with the family but knows the study well
- Practice recording of interviews before you actually record
- Pre-schedule a 30 minute appointment and reimburse for time (gift card)
- When possible, include collaborator with expertise in qualitative methodology

Involving the Clinical Team

- Clinical Team Collaborators
- Study Kick Off Meeting
- Regular Research Updates (at least Yearly)

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Conclusions

- Obtain qualitative feedback from diverse stakeholders for development, implementation, and evaluation

- Engage, inform, and update the clinical team

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Thank You!

Bootcamp on Clinical Research for New Investigators: Session 2

Clinical Research Contracting and Budgeting

Presented by:
Melanie J. Bossi, MPA
Sr. Director, Business Operations
GW Office of Clinical Research

Types of Legal Transactions that Support Clinical Research

- **Confidentiality Agreements** (CDA or NDA)
- **Clinical Trial Agreements** (CTA)
  - Sponsor-initiated or Investigator-initiated
- **"Master" Agreements** and **Work Orders**
- **Amendments** (Supplements, extensions, and modifications to an existing agreement)
- **Notice of Grant Award from a Federal Awarding Agency**
- **Grant Agreement from a Foundation, Association, or other Non-Profit Sponsor**
- **Subaward/Subrecipient Agreements issued under a Federal Grant or Contract held by another Prime Grantee organization**
- **Memorandums of Understanding**
- **Data Use Agreements**
- **Material Transfer Agreements**

Clinical Trial Agreement

- **Clinical Trial Agreement**: A legally binding and fully executed Clinical Trial Agreement (CTA) is required before a Principal Investigator may conduct a clinical trial when the study drug or device, financial support, and/or proprietary information is provided by a for-profit sponsor.

- Through a negotiation process, the CTA upholds institutional policies and regulations while also allowing the investigator to provide data and/or results, contribute to publications and improve clinical care options for patients. The CTA allocates risk, responsibility, funds, and obligations while also protecting the interests of the Institution, and where applicable, and the sponsor.

- CTA includes an agreed upon budget for the sponsor to provide funding to cover the costs to conduct the clinical trial.

Key Clinical Trial Contracting Provisions

- Indemnification & Subject Injury
- Intellectual Property (IP)
- Data Ownership
- Confidentiality
- Publication rights - The ability to publish is essential to a university's/research institution's mission
- Termination
- GDPR Compliance/international components with complex data issues
- Record Retention
- Right to audit and/or inspect
- Fair Market Value
- Use of Name
- Representations and Warranties
- Limiting the pharmaceutical company's ability to assign
- Export Controls

If there is a research injury, serious complication, or even death as a result of administration of the investigational agent, implant of an investigational device, or performance of tests and procedures required by the Protocol, the contract must include the Sponsor's indemnification obligation, and separate terms for subject injury that confirm the Sponsor's obligation to pay for the cost of medical care and treatment required for a research injury.

Clinical Trial Budget

Federal vs. Non-Federal Clinical Trials

- Federal Trial
  - Develop a proposed study budget in order to respond to the Federal request for proposal (RFP).
  - Salary cap can apply based on sponsor.
  - Apply Federally negotiated F&A rate
  - Apply Medicare Rate for patient care costs
- Non-Federal Trial
  - Most corporate sponsors will provide a proposed budget at the very start of the negotiations.
  - Budget Negotiated in accordance with Industry Research Charge Master and Fee Schedule

In Preparing to Develop Budget

- Obtain final version of Protocol:
  - Read the Protocol to understand the visits and complexity of the trial
  - Determine if there will be other affected departments/areas
  - Look at all of the components of the Protocol:
    - Schedule of events
    - Schema
    - Visit detail
    - Informed consent template
    - Case Report Forms
- Obtain clarifications from sponsor (i.e., use of central lab, supplied equipment, additional reporting, training, etc)
- Assess needs and key components required for the implementation of the Protocol
- The Investigator plays a key role in accurate budget and Medicare Coverage Analysis. It is essential to recognize the importance of an Investigator's guidance on study implementation workflow, and how this impacts the budget development and negotiation process.

Laboratory

- Central lab vs local lab
- Who's drawing the blood
- Who will process the samples

Radiology

- Copies of Films
- Who will read the Films
- Specialized scans or MRIs?

Cardiology

- Echos
- Reading fees

Pulmonary

- PFTs

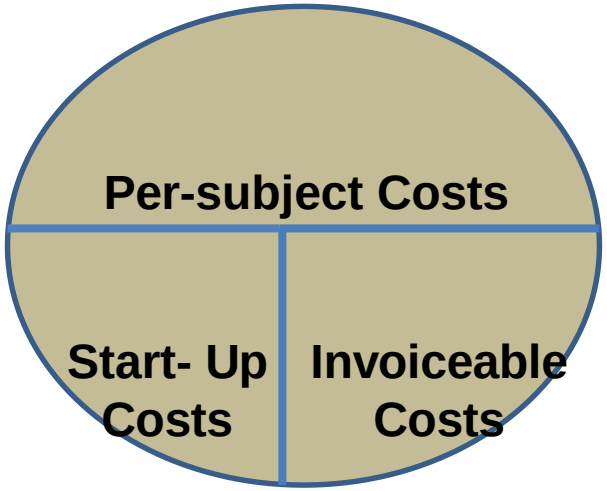
Pharmacy

- Preparation
- Drug Dispensing
- Annual Maintenance
- Drug return or destruction at conclusion of trial

Pathology

- Reading Fees
- Additional Slides or Blocks

Key Areas of a Clinical Trial Budget



- Start up and Site level costs
  - Non-subject charges
  - Mandatory Fees
- Per-subject costs
  - Budget for visit activities completed per subject
    - ➢ Includes: Patient care tests, procedures
    - ➢ Personnel Costs: Physician, Coordinator, Nursing, Lab
    - ➢ Participant Costs: Stipends, travel, parking
- Invoiceable/variable costs
  - Events that may or may not occur during the study
    - ➢ Screen fails, pregnancy test

Coverage Analysis for Clinical Research

Stephanie Bair

What is a Coverage Analysis?

- An independent review of study procedures to determine what procedures/assessments can be billed to insurance/participants and what needs to be paid by the sponsor based on Medicare rules.

Sample of simple coverage analysis

	visit 1	visit 2	visit 3
PI time	Research	Research	Research
coordinator time	Research	Research	Research
nurse time	Research	Research	Research
physical exam	Standard of Care	Research	Standard of Care
lab test	Research	Research	Research

Why is a Coverage Analysis Required?

- Required under the Federal Clinical Trials Policy

  →Also known as National Coverage Determination

- Helps to comply with the False Claims Act

  → no double dipping

- To ensure the trial meets the federal definition of a Qualifying Trial

  → insurance may be billed for standard of care items

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Why is Coverage Analysis Important?

- Facilitating Billing Compliance, especially with the Federal False Claims Act
- Ensure all parties, including the patient, are aware of potential costs that they may incur
- Promote fair and transparent contract negotiations

How is a Coverage Analysis Completed?

- It utilizes study documents, which include but may not be limited to the protocol, informed consent form (ICF), budget, and contract.
- An independent party makes determinations using published practice guidelines and/or National (NCD) and Local (LCD) Medicare Coverage Determinations

How is a Coverage Analysis Completed (continued)?

- It is often reviewed by the principal investigator and study team for accuracy
- Once it is confirmed accurate, it is:
  - Used in the Informed Consent Form to let participants know who will pay for what
  - Is used when creating and negotiating budgets with sponsors
  - Used to assist in the billing once patient visits have occurred.

At what stage should a Coverage Analysis be performed?

- As soon as the protocol can be reviewed and ideally before budget development.

- Whenever an amendment to the protocol is done.

What Studies should have a Coverage Analysis Completed?

- Any study that qualifies under Medicare rules.
- All Studies that have patient cost.
- Organizations that receive federal funding.

General rule of thumb: If you're not sure whether it's required, send it for review.

Using the CA for billing purposes

- Once the contract is signed, the billing office uses the coverage analysis as the basis for analyzing payors and amounts for each procedure at each patient visit.
- Often, a template such as a billing grid will be set up and is the preferred method for the billing office to receive patient visit information.

Using the CA for billing purposes

- On a regular basis, the investigator and/or study team should communicate with their research billing office regarding patient visits.
- The billing office will verify all charges against the billing grid and ensure that the procedures are invoiced to the appropriate entity for payment.
- The payment amount depends upon the contract with the payor. Often, the insurance and the study sponsor may agree to a different rate even for the same procedure.

Questions??

Thank You!

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WASHINGTON, DC

Analytical Services and Data Resources

Qing Zeng-Treitler

Biomedical Informatics Center, George Washington University

- Data Sources (each with pros and cons)
  - Cerner
  - All of Us
  - VA
  - NISQUIP, SEER, NHIS, NHANES, your own datasets
- Consultation
  - https://docs.google.com/forms/d/e/1FAIpQLScX9eBXojuAoAZd0bIU2d1qPlFpPtBKCQA-OBfzhlGOnzkJQg/viewform

- Initial consultation
- Approval for data access
- Confirmation of study plan
- Data curation and analysis
  - Dataset preparation, statistical analyses, machine learning (AI)
- Results reporting

- Cerner Real-World Data offers researchers access to national, aggregated, de-identified, encrypted and secured clinical data sets.
    - Geographic Range of the data
        - EHR-based data from 100+ U.S. health systems national widely
    - Time Range of the data
        - RWD goes back from the 90s or early 2000s.
        - RWD releases a new set of database quarterly
            - Latest Database Version: 2021Q4
                - Data entry up to 2021 Sep

Data contributor extraction

EHR Data Source

Data cleansing

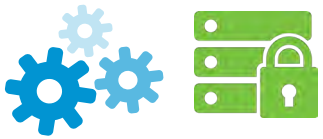
Concept normalization

Data standardization

Person matching

Reference records

De-identification



De-identification per HIPAA standards and applying safe harbor methodology

Data mart creation

Real-World Data access

Data Analysis

Encounter

Demographic

Questionnaire

Condition | Problem List | Allergy

Lab | Clinical Event | Measurement

Medication | Medication Administration

Immunization

Order List

Procedure

96M
patients

1.4B encounters

767M outpatient encounters	44M inpatient encounters	106M emergency encounters

2.1B diagnoses

2.7B medications

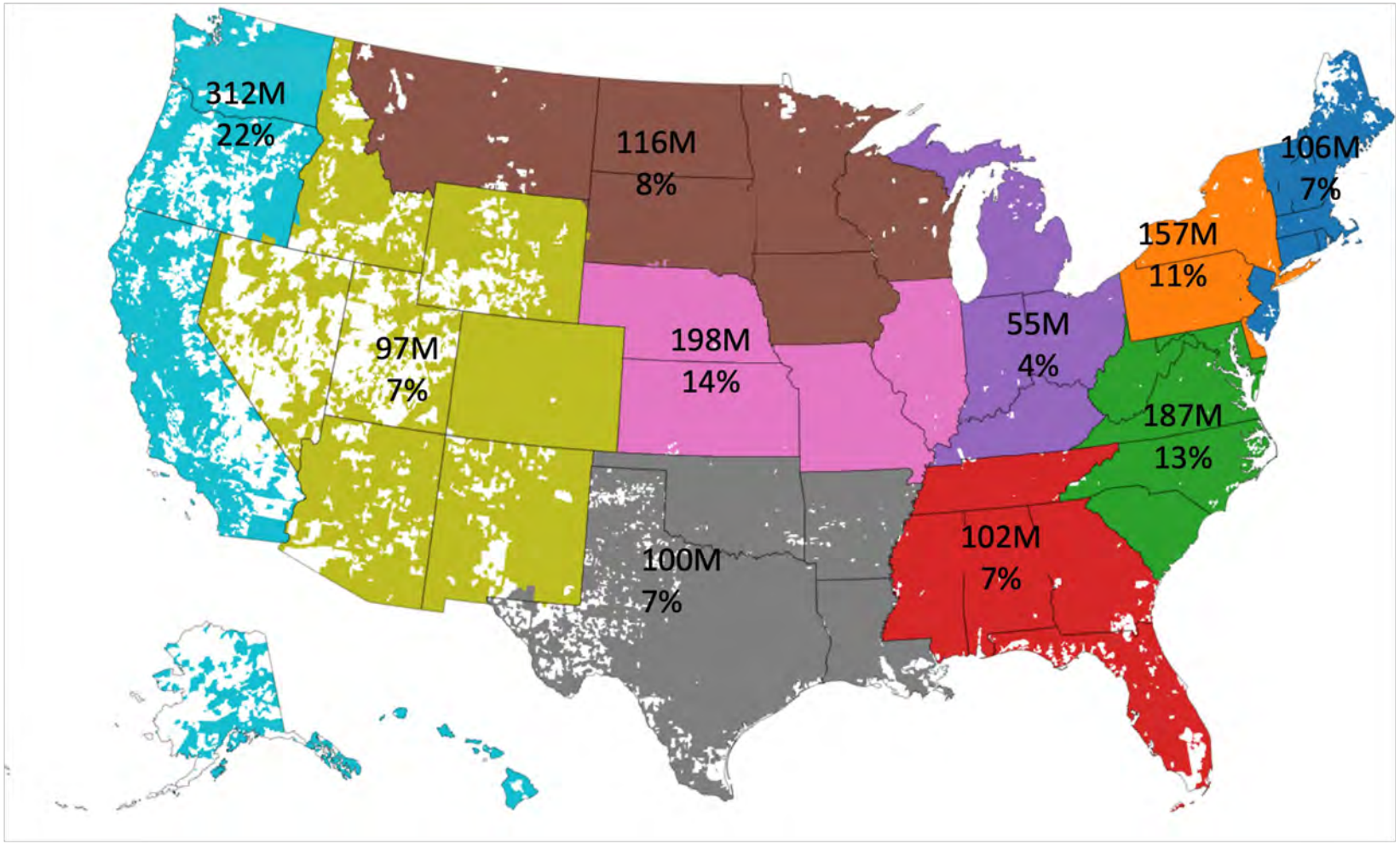
446M procedures

10.8B Lab results

104M immunizations

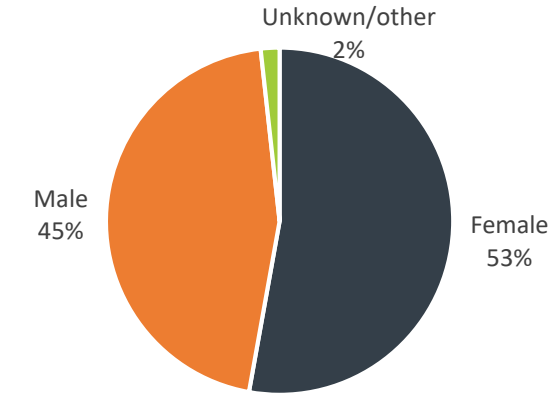
264M Questionnaire

* Database Version 2021q4

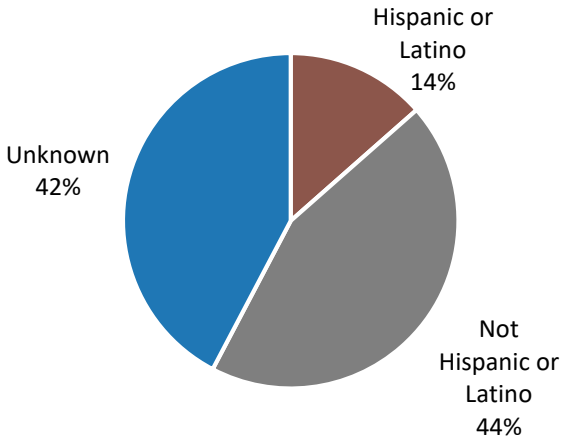


* Database Version 2021q4

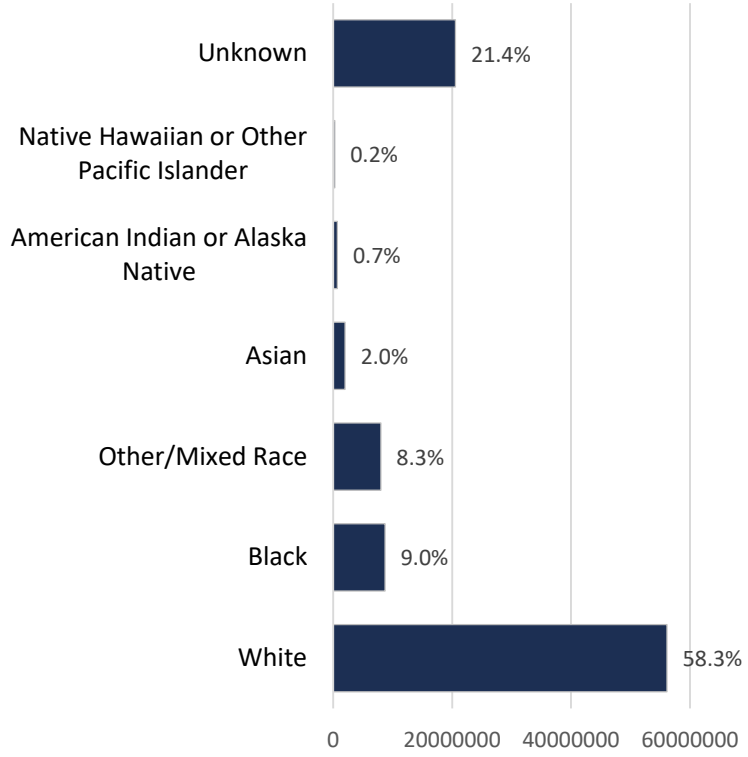
Gender Distribution



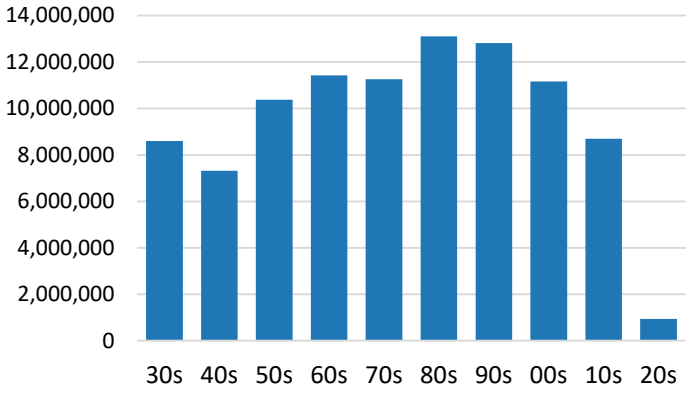
Ethnicity Distribution



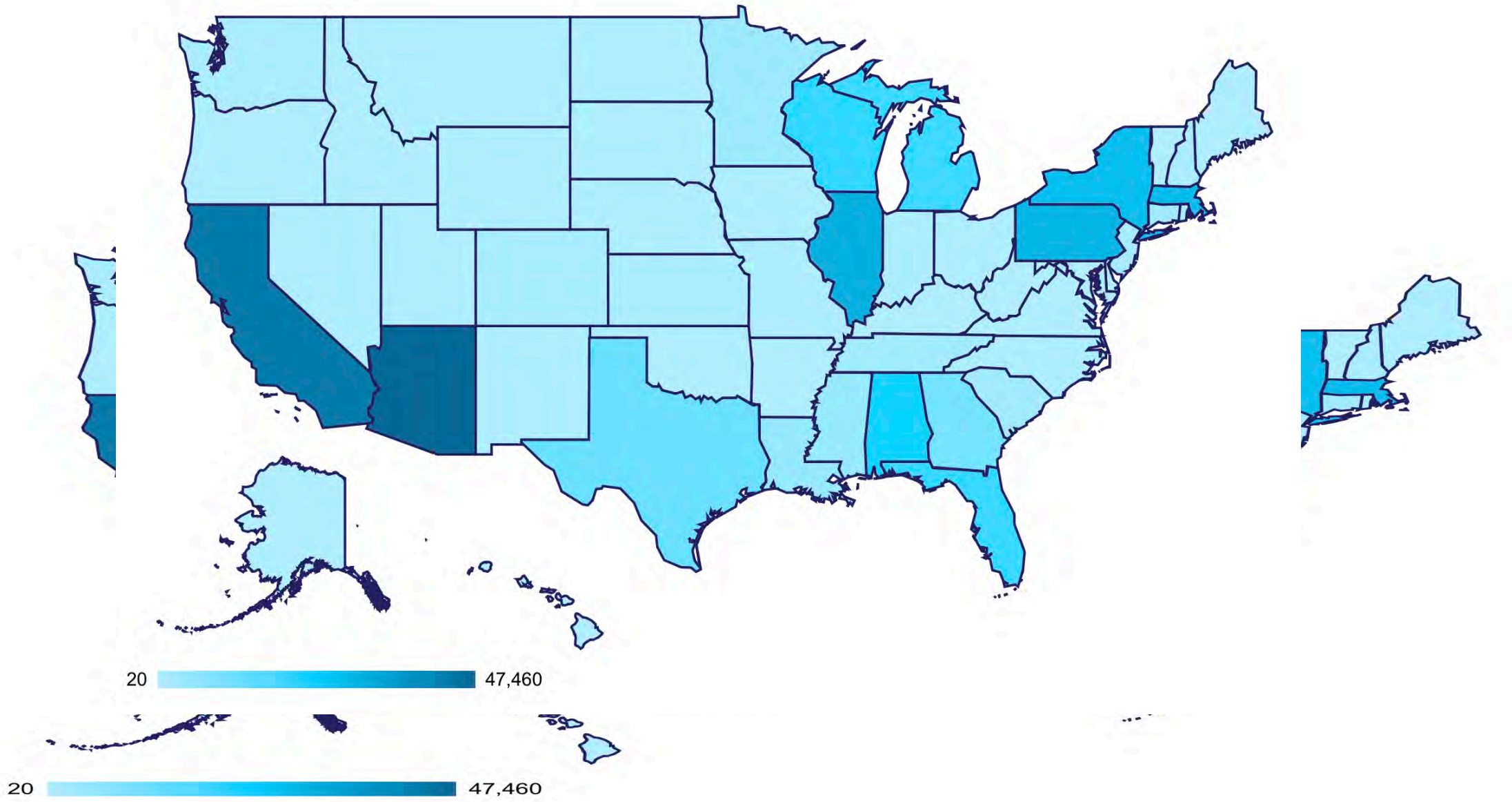
Race Distribution



Distribution by Birth Decades



- *All of Us* Research Program is inviting one million people across the U.S. to help build one of the most diverse health databases in history.
  - Includes environmental, biological, and lifestyle data
  - Starting in May 2017
    - 100+ funded partner organization
    - 400+ sites
    - ~450k enrolled
      - ~320k completed baseline survey, ~270k EHR records, 336k biosamples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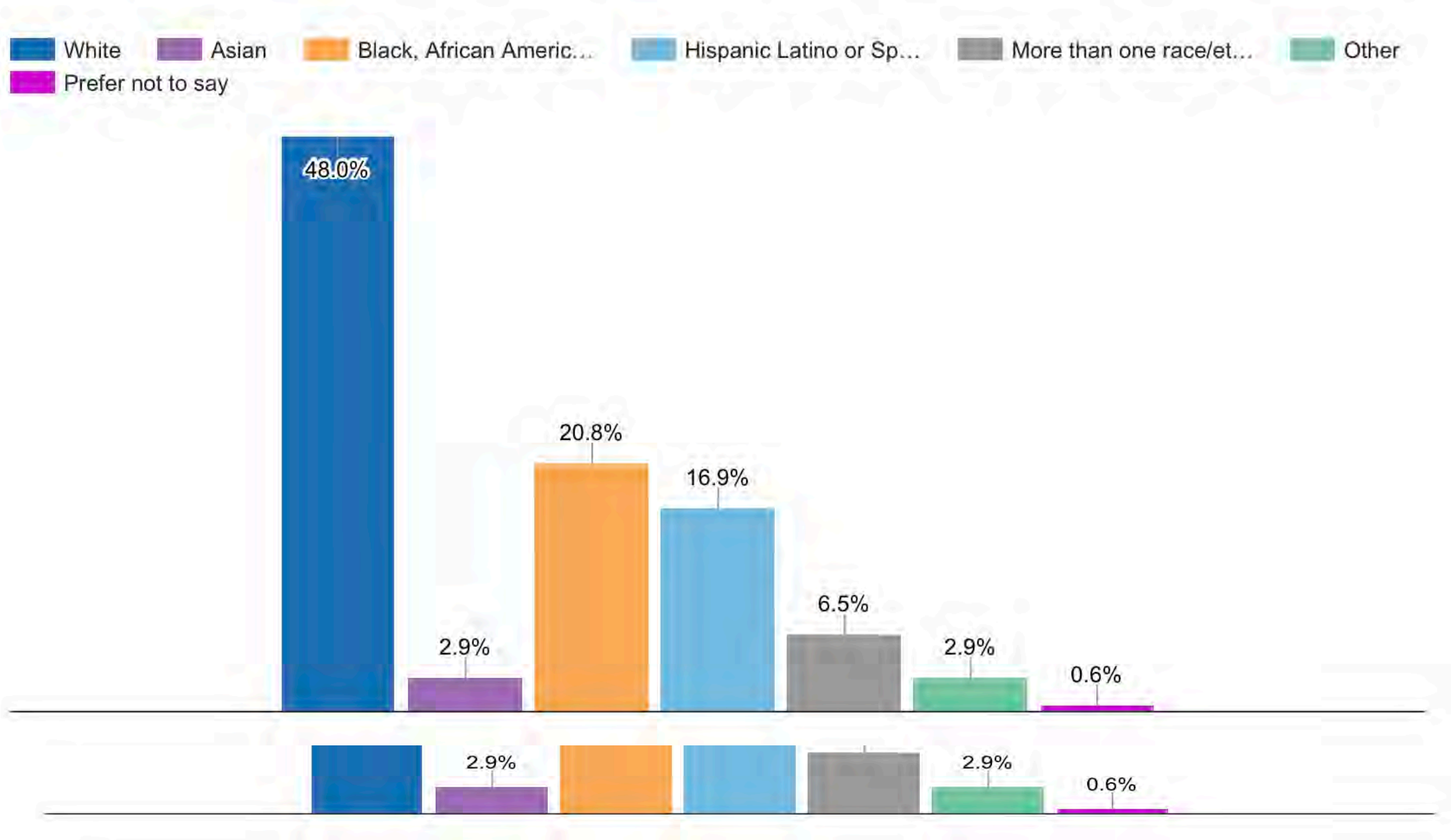
White
Asian
Black, African Americ…
Hispanic Latino or Sp…
More than one race/et…
Other
Prefer not to say
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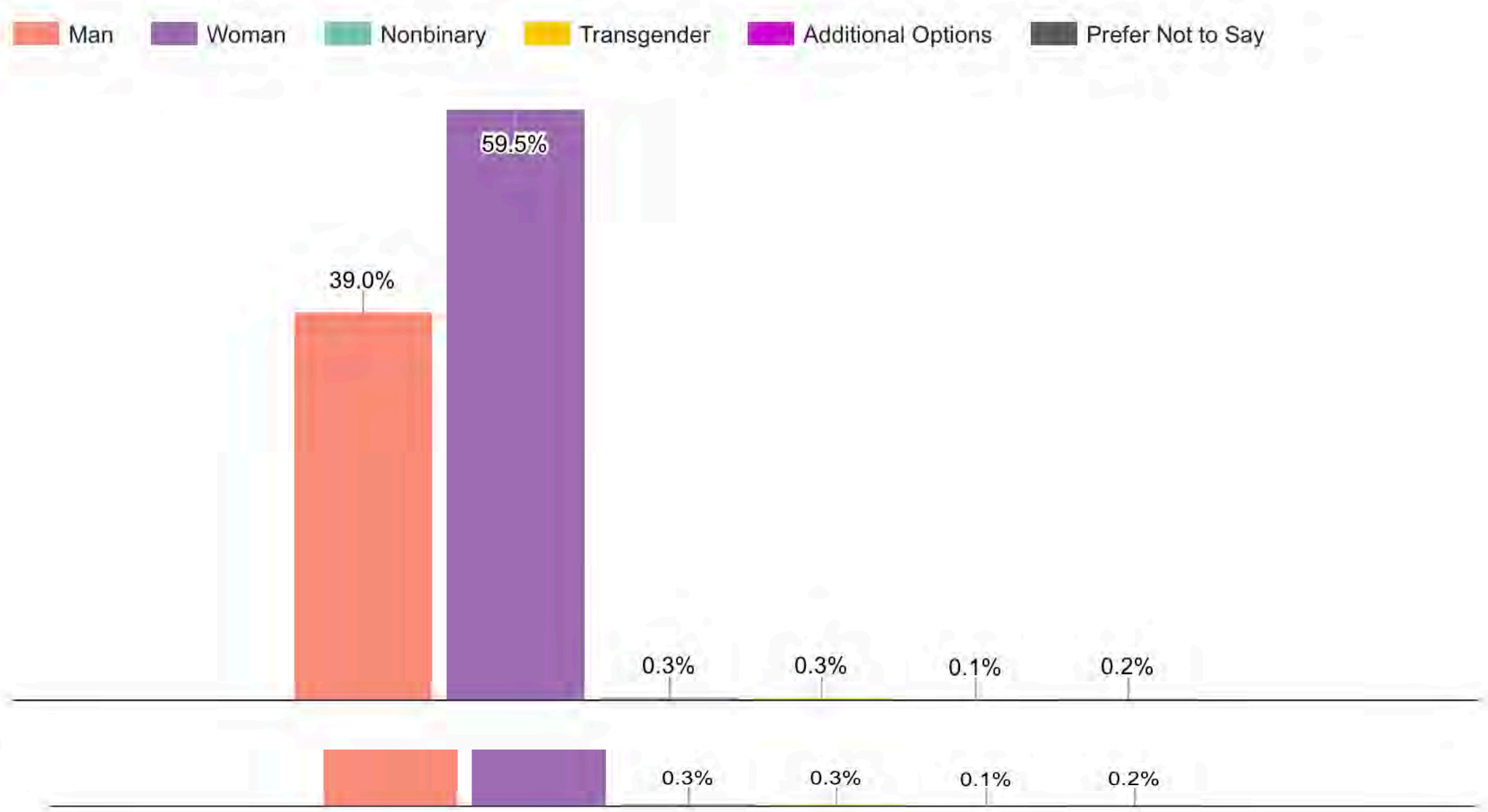
Man
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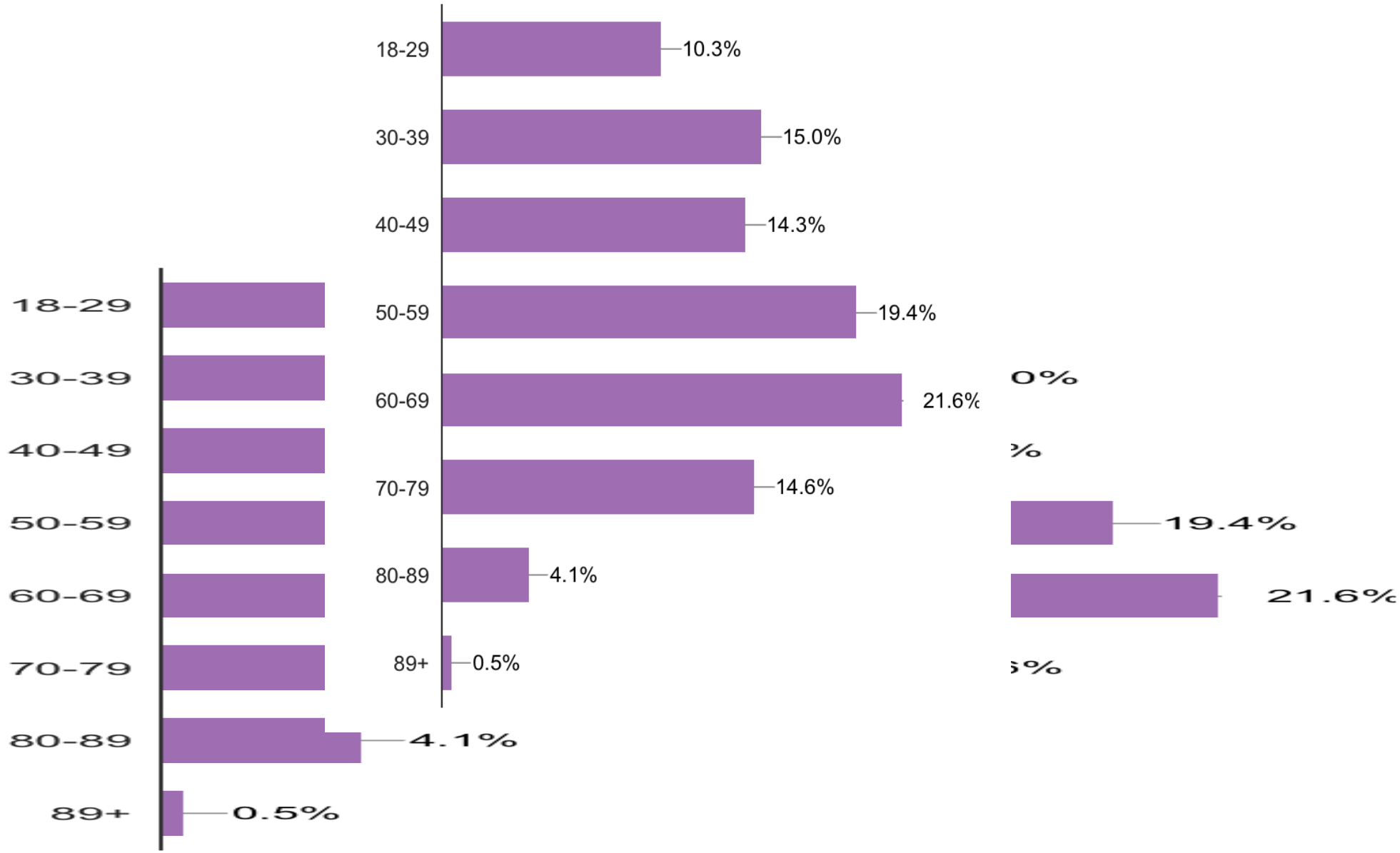
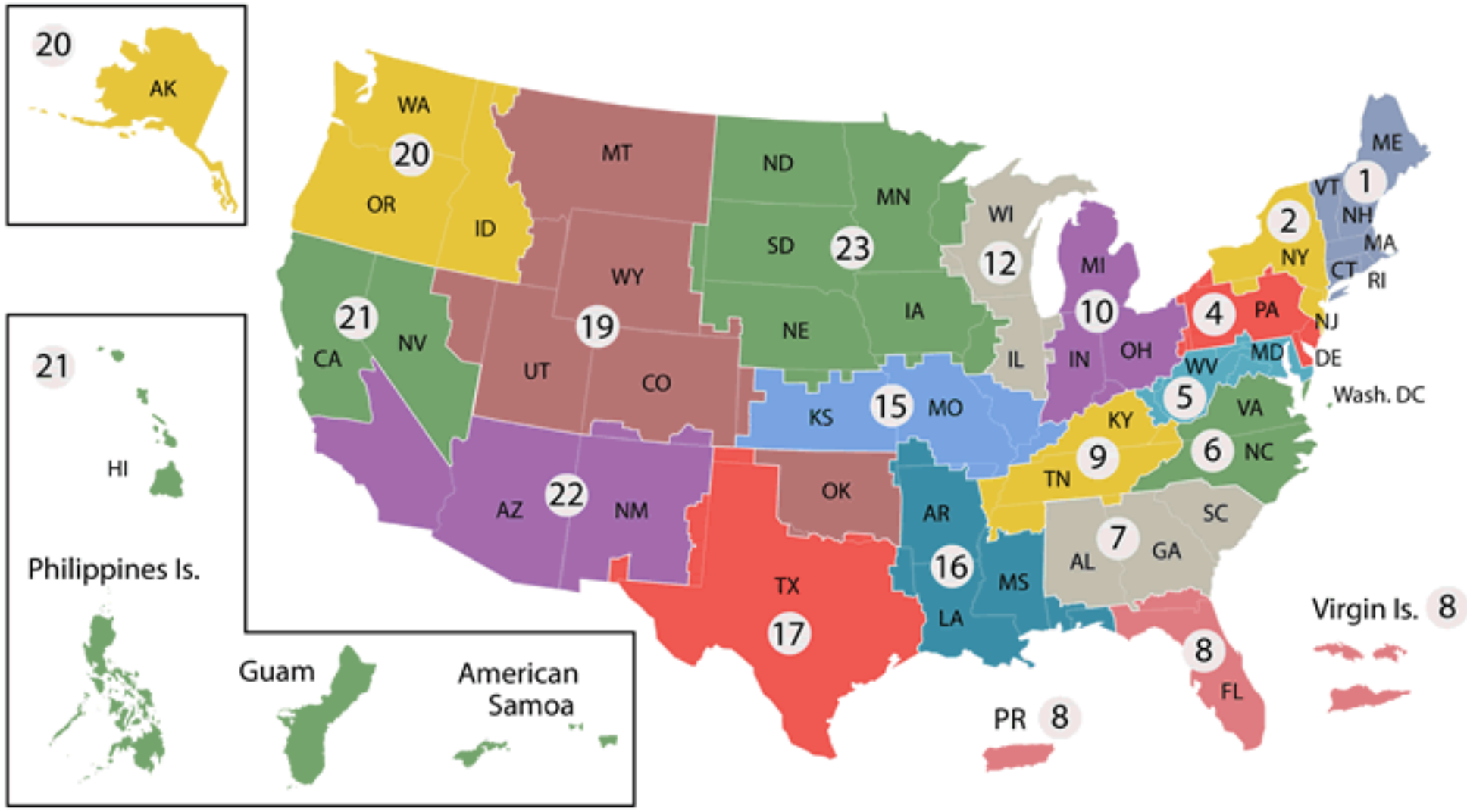

18-29
10.3%
30-39
15.0%
40-49
14.3%
50-59
19.4%
60-69
21.6%
70-79
14.6%
80-89
4.1%
89+
0.5%

- VA CDW is a national level database housing clinical, administrative and financial Veterans Health Administration (VHA).
  - Starting from before 1999
    - 1,293 health care facilities, including 171 VA Medical Centers and 1,112 outpatient sites of care of varying complexity (VHA outpatient clinics) to over 9 million Veterans currently enrolled
    - 25 million total veterans (~20 million with clinical data)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AK
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Virgin Is. 8
21
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Philippines Is.
Guam
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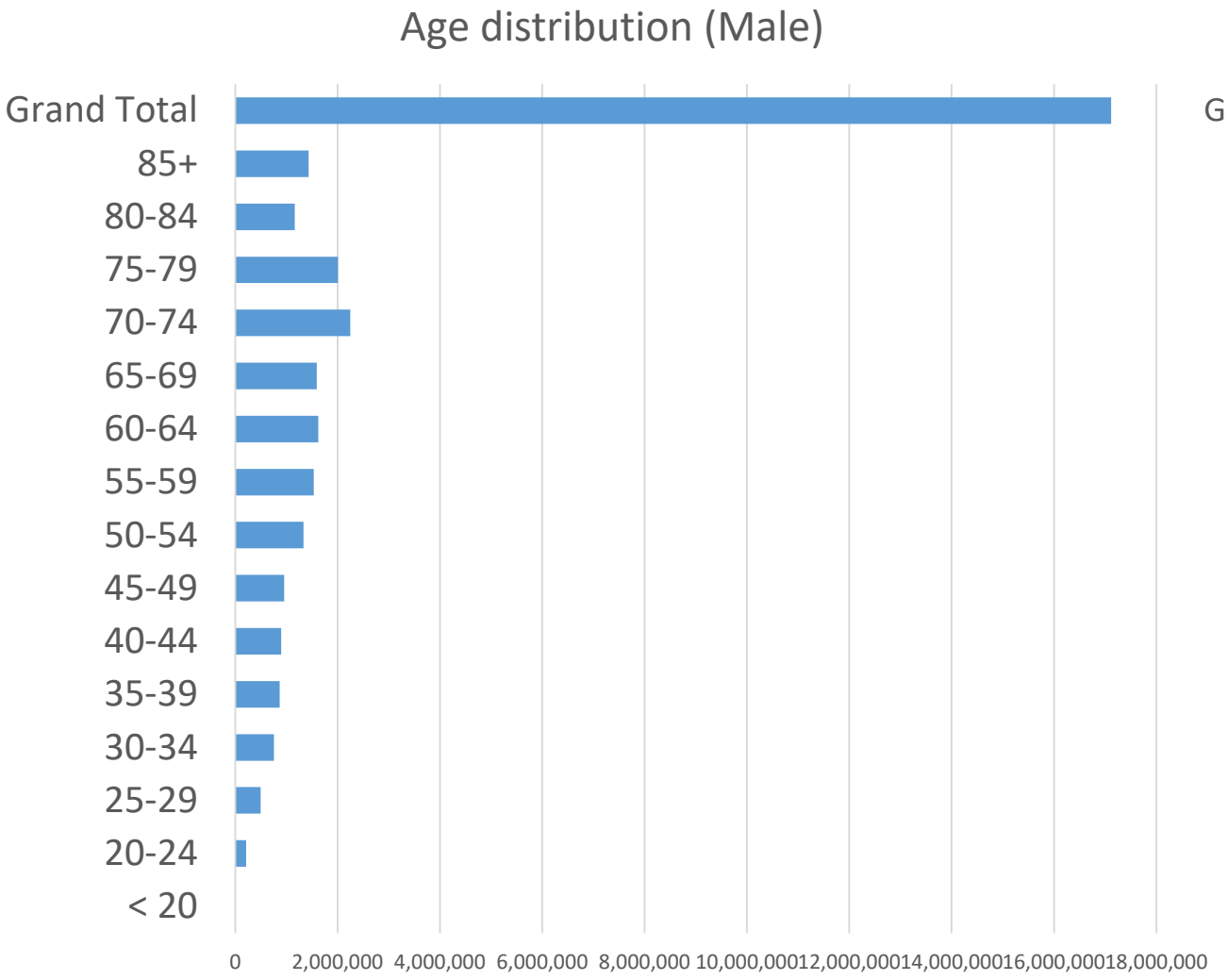
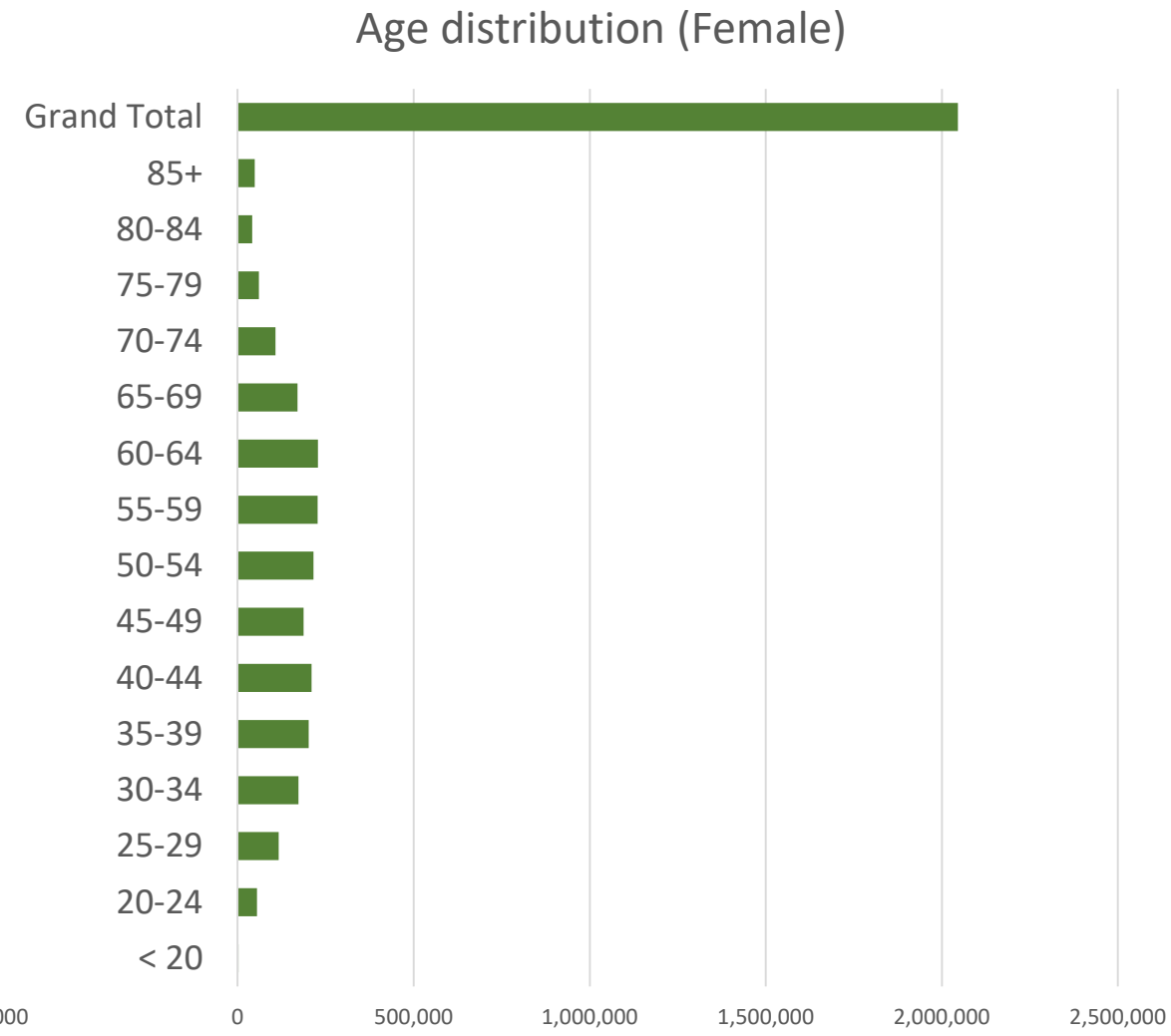
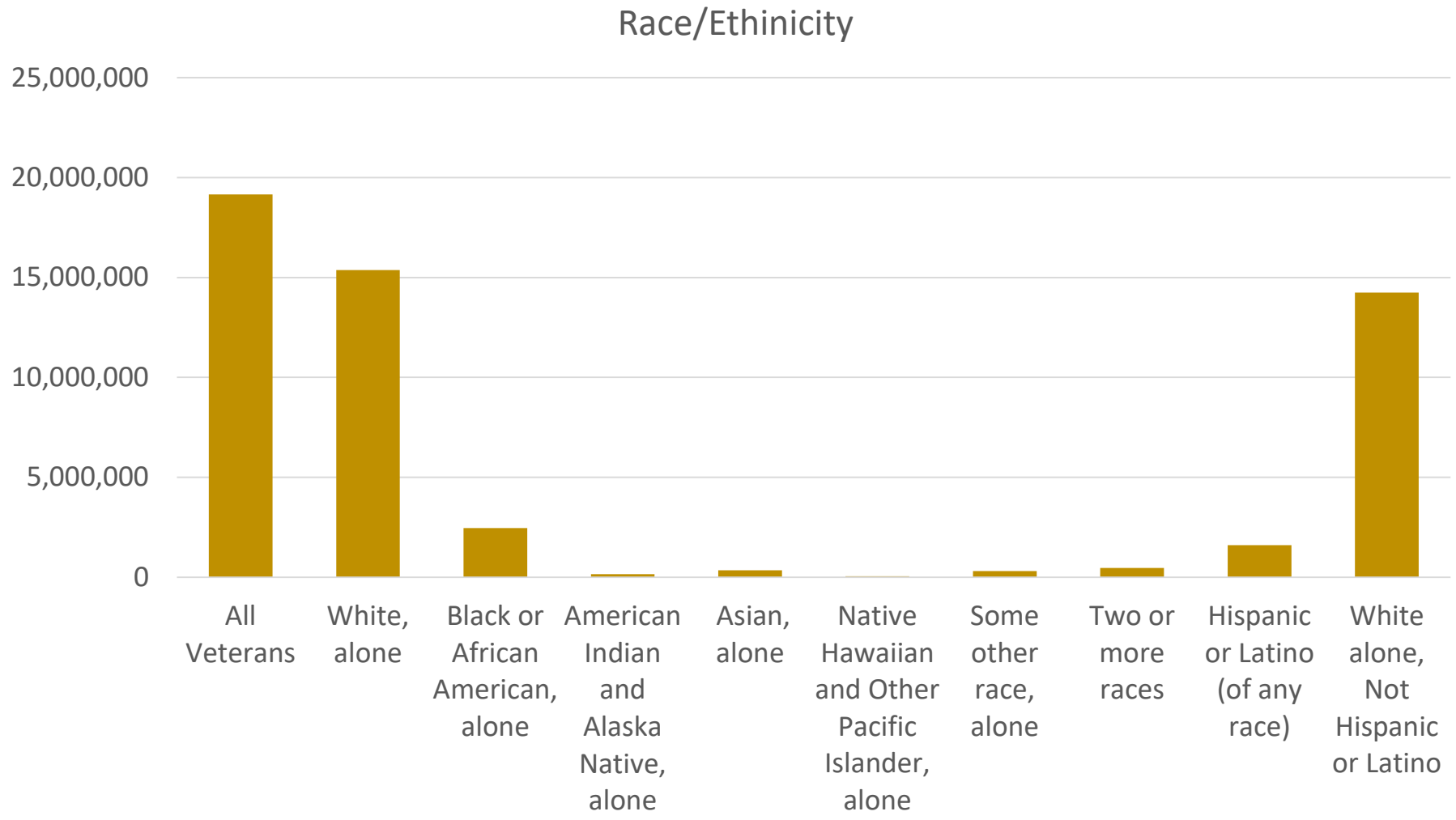
Samoa


Age distribution (Male)
Grand Total
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
< 20
0
2,000,000
4,000,000
6,000,000
8,000,000
10,000,000
12,000,000
14,000,000
16,000,000
18,000,000


Age distribution (Female)
Grand Total
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
< 20
0
500,000
1,000,000
1,500,000
2,000,000
2,500,000


Race/Ethinicity
25,000,000
20,000,000
15,000,000
10,000,000
5,000,000
0
All Veterans
White, alone
Black or African American, alone
American Indian and Alaska Native, alone
Asian, alone
Native Hawaiian and Other Pacific Islander, alone
Some other race, alone
Two or more races
Hispanic or Latino (of any race)
White alone, Not Hispanic or Latino

- A few reminders
  - Allow for ample time (there are other requests in the queue, new dataset)
  - Most tasks take longer than expected (e.g., need extra cleaning, subgroup analyses, etc.)
  - Need careful study design before hand (e.g., sample size, missing data, potential confounders, consistency in variable definition)
  - Need to know the dataset well
  - Have realistic expectation about statistical and machine learning models