MULTI-REGIONAL CLINICAL TRIALS

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

The Roles and Responsibilities of the IRB in Addressing Diversity in Clinical Research

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MRCT Center of BWH & Harvard

November 10, 2020
PRIM&R presentation

Disclaimer

The views and findings expressed in this presentation and the documents are those of the authors and do not imply endorsement or reflect the views or policies of the U.S. Food and Drug Administration or the affiliated organization or entity of any member who contributed to this work. Individuals have served in their individual capacity.

The seminar focuses on the role of the IRB in considering diversity, inclusion, and equity in clinical trial participation. It is not intended as a general diversity training.

The MRCT Center is supported by voluntary contributions and by grants.
www.MRCTCenter.org

Agenda

- Sarah A. White, MPH
  - Welcome
  - MRCT Center introduction
  - Introduction to Achieving Diversity, Inclusion, Equity In Clinical Research Project
- David H. Strauss, MD
  - Role of the IRB as presented in the Guidance and Toolkit
  - Ethical responsibilities
- Barbara E. Bierer, MD
  - Practical Approaches to Considerations of Inclusiveness
  - Tools and Resources

Sarah A. White, MPH
Executive Director, MRCT Center

The Multi-Regional Clinical Trials Center (MRCT Center)

Our Vision

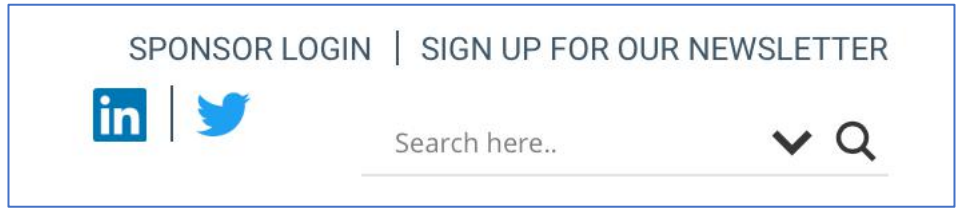
Improve the integrity, safety, and rigor of global clinical trials.

Our Mission

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

The MRCT Center's work

Addressing emerging issues of MRCTs



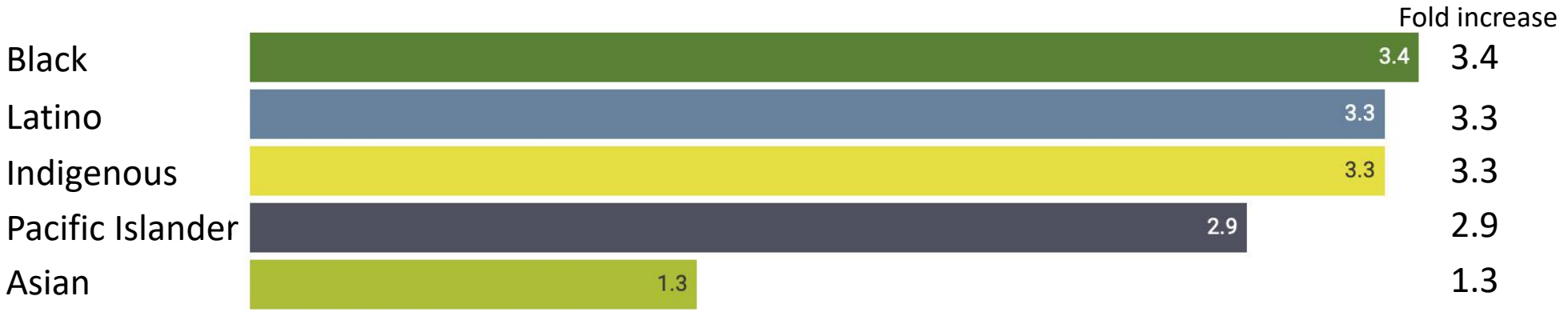
https://mrctcenter.org

Recognizing the need to focus on and with the participant

- Post trial access to medicines
- Return of Results, Aggregate and Individual
- Health Literacy
- Diversity, Inclusion, Equity

Health disparities by race and ethnicity in the COVID-19 pandemic

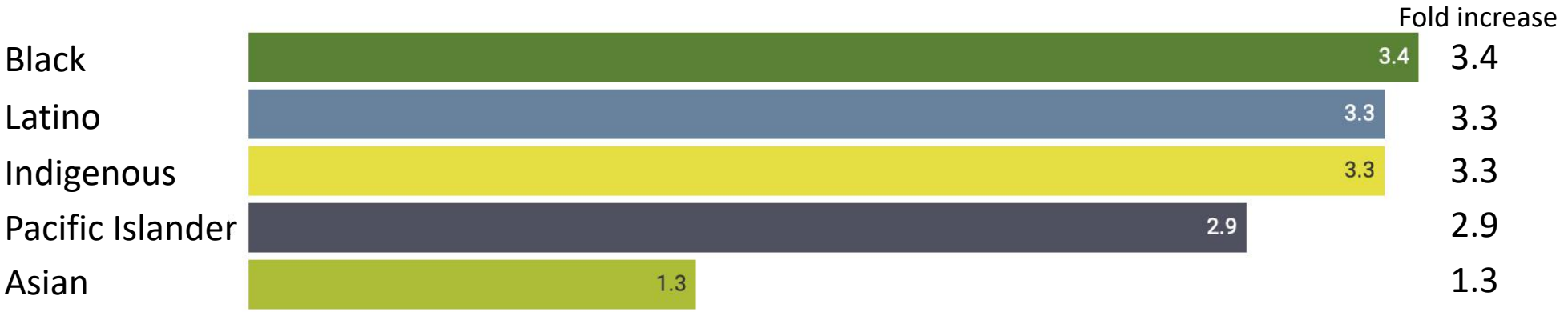
Adjusted for age, race and ethnicity widens the gap in mortality compared to Whites



https://www.apmresearchlab.org/covid/deaths-by-race

Health disparities by race and ethnicity in the COVID-19 pandemic

Adjusted for age, race and ethnicity widens the gap in mortality compared to Whites



https://www.apmresearchlab.org/covid/deaths-by-race

But are underrepresented in research

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 27, 2020

Racial Disproportionality in Covid Clinical Trials

Daniel B. Chastain, Pharm.D., Sharmon P. Osae, Pharm.D., Andrés F. Henao-Martínez, M.D., Carlos Franco-Paredes, M.D., M.P.H., Joeanna S. Chastain, Pharm.D., and Henry N. Young, Ph.D.

News & Analysis

Medical News & Perspectives

Researchers Strive to Recruit Hard-Hit Minorities Into COVID-19 Vaccine Trials

Mary Chris Jaklevic, MSJ

https://jamanetwork.com/journals/jama/fullarticle/2769611

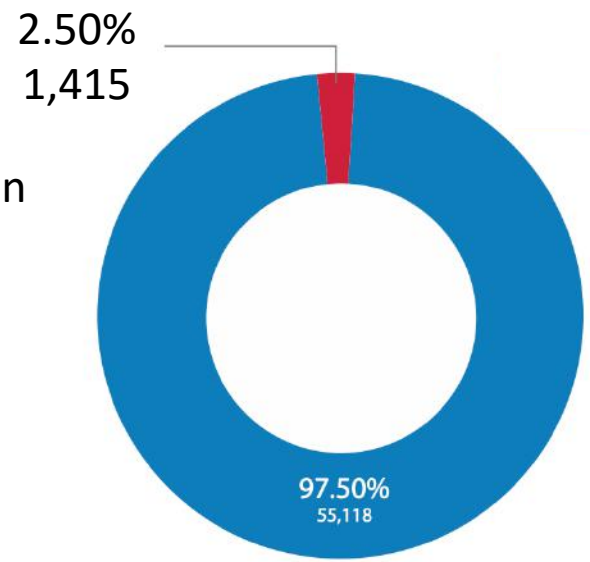
Drug Trial Snapshots: Summaries

Participation of Black or African American individuals in clinical trials for oncology, cardiology, and psychiatry

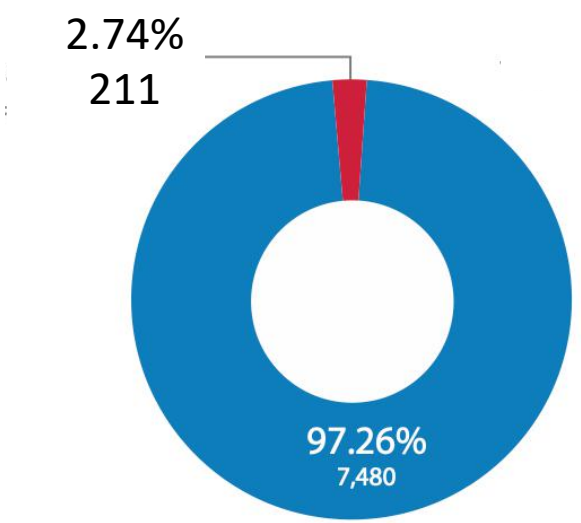
Black/African

Other race

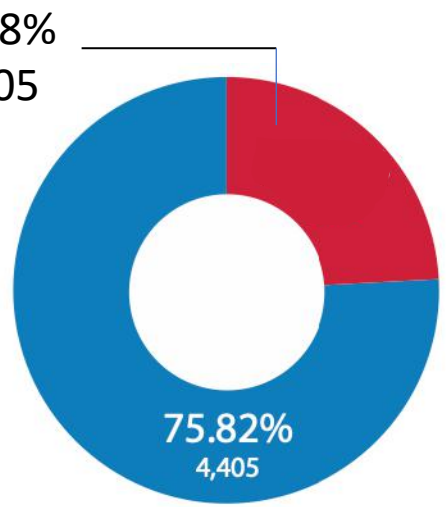
2015-2016



Cardiovascular Disease
N = 92,329

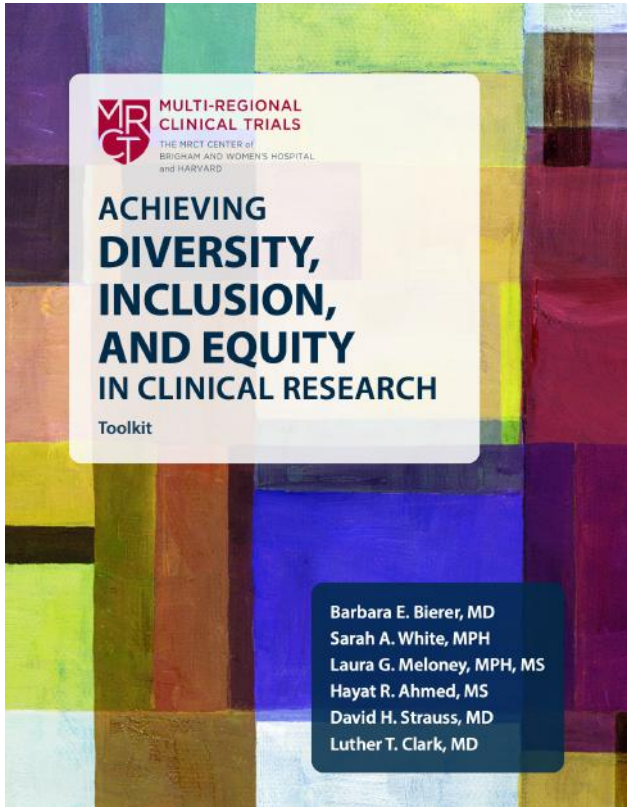


Oncology
N = 7,691



Psychiatry
N = 5,810

https://www.fda.gov/media/106725/download



Achieving Diversity, Inclusion, Equity In Clinical Research

Guidance and Toolkit

mrctcenter.org/diversity-in-clinical-trials

Released 6 August 2020

Leadership

- RADM Richardae Araojo, PharmD, MS, U.S. FDA
- Barbara E. Bierer, MD, MRCT Center
- Luther T. Clark, MD, Merck & Co., Inc.
- Milena Lolic, MD, U.S. FDA
- David H. Strauss, MD, Columbia University
- Sarah White, MPH, MRCT Center

MRCT Center staff:

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- Hayat Ahmed, MS
- Laura Meloney, MS, MPH
- Joshua Smith-Sreen, MPH

And the invaluable contributions of >50 workgroup members, representing:

- Patients, Patient Advocates
- Academia
- Pharmaceutical companies
- CROs
- Non-profit organizations
- Trade associations
- Government agencies
- Research institutes

Each serving in their individual capacity.

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Gerren Wilson*, Genentech/ A Member of the Roche Group
Crispin Woolston, Sanofi
Honghui Zhou*, Johnson&Johnson

Guidance Document

- Multi-stakeholder contributions and consensus
- Practical and actionable recommendations
- Accountability section considers how each stakeholder can change the paradigm
- Toolkit provides adaptable resources not easily found elsewhere

mrctcenter.org/diversity-in-clinical-trials

David H. Strauss, MD
Senior Advisor, MRCT Center
Special Lecturer, Columbia University

Diversity and Inclusion in Clinical Research: a role for the IRB

- Beyond COVID-19, is there a problem to solve?
- Is a role for the IRB justified?
- What practical steps can be taken?

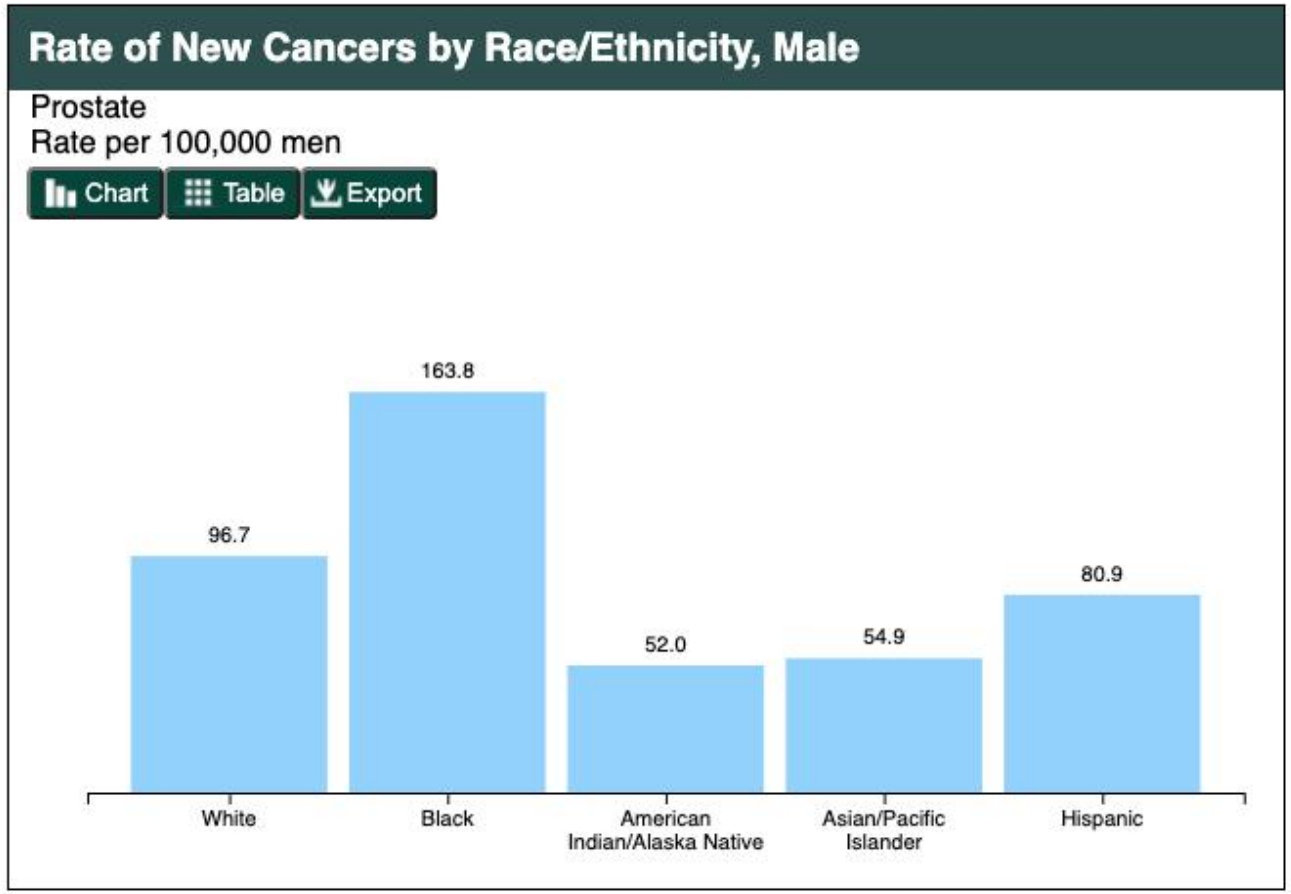
Drug Trial Snapshots (2019): US Food and Drug Administration

In 2015, of 45 novel drugs approved, and with over 105,000 enrolled participants, only 40% of patients were women, and strikingly only 5% were African American.

INDICATION	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 and OLDER	UNITED STATES
Treatment of prostate cancer	0	79	3	13	3	87	9

https://www.fda.gov/media/135337/download

Prostate Cancer (CDC, 2017)



- Prostate cancer rates are highest among African-Americans
- African-Americans are twice as likely to die from prostate cancer
- Increase risk is associated with low SES, unequal access to diagnosis and treatment, and (?) other factors

https://gis.cdc.gov/Cancer/USCS/DataViz.html

Drug Trial Snapshots (2019): US Food and Drug Administration

INDICATION	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 and OLDER	UNITED STATES
Treatment of prostate cancer	0	79	3	13	3	87	9
Treatment of advanced breast cancer	100	66	1	22	14	44	9
Treatment of schizophrenia	24	21	75	1	9	0	100

https://www.fda.gov/media/135337/download

The importance of ***inclusion***

- Analyses of group differences in safety and efficacy among diverse populations can promote identification of both underlying biological factors and socially relevant factors that affect health, the "social determinants of health" (Beneficence)
- Seeks fairness in the distribution of the benefits of research (Justice)
- Builds public trust

Belmont Report

Justice:

- "Who ought to receive the benefits of research and bear its burdens? "
- "…moral requirements that there be fair procedures and outcomes in the selection of research subjects."
- "An injustice occurs when some benefit to which a person is entitled is denied without good reason…"

§46.111 Criteria for IRB approval of research.

(3) Selection of subjects is equitable.

Beneficence

- In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the **maximization of benefits**…
- In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result…

Belmont Report

- Respect for Persons
  - Obligations to treat individuals as autonomous agents
  - Obligations to protect those with diminished autonomy

Application of the Belmont principles

- Ethics and protection from research risk
- Ethics and access to the direct benefits of novel/investigational therapies
- Ethics, Inclusion, and access to the benefits of scientific knowledge

Oversight and ethical responsibility

- Attention to diversity and inclusion may be an under-recognized and under-appreciated role for many IRBs, but
- It is embedded in the language of Belmont and the Common Rule
- It is essential to the ethical conduct of clinical research

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Professor of Medicine (Pediatrics), Harvard Medical School
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The role of the IRB

- Ensuring ethical research
- Creating expectations, promoting dialogue
- Establishing accountability
- Fostering competence, education, and the development of infrastructure

- Institutional support for the role and responsibility of the IRB
- Responsibilities of HRPP in addition to IRB

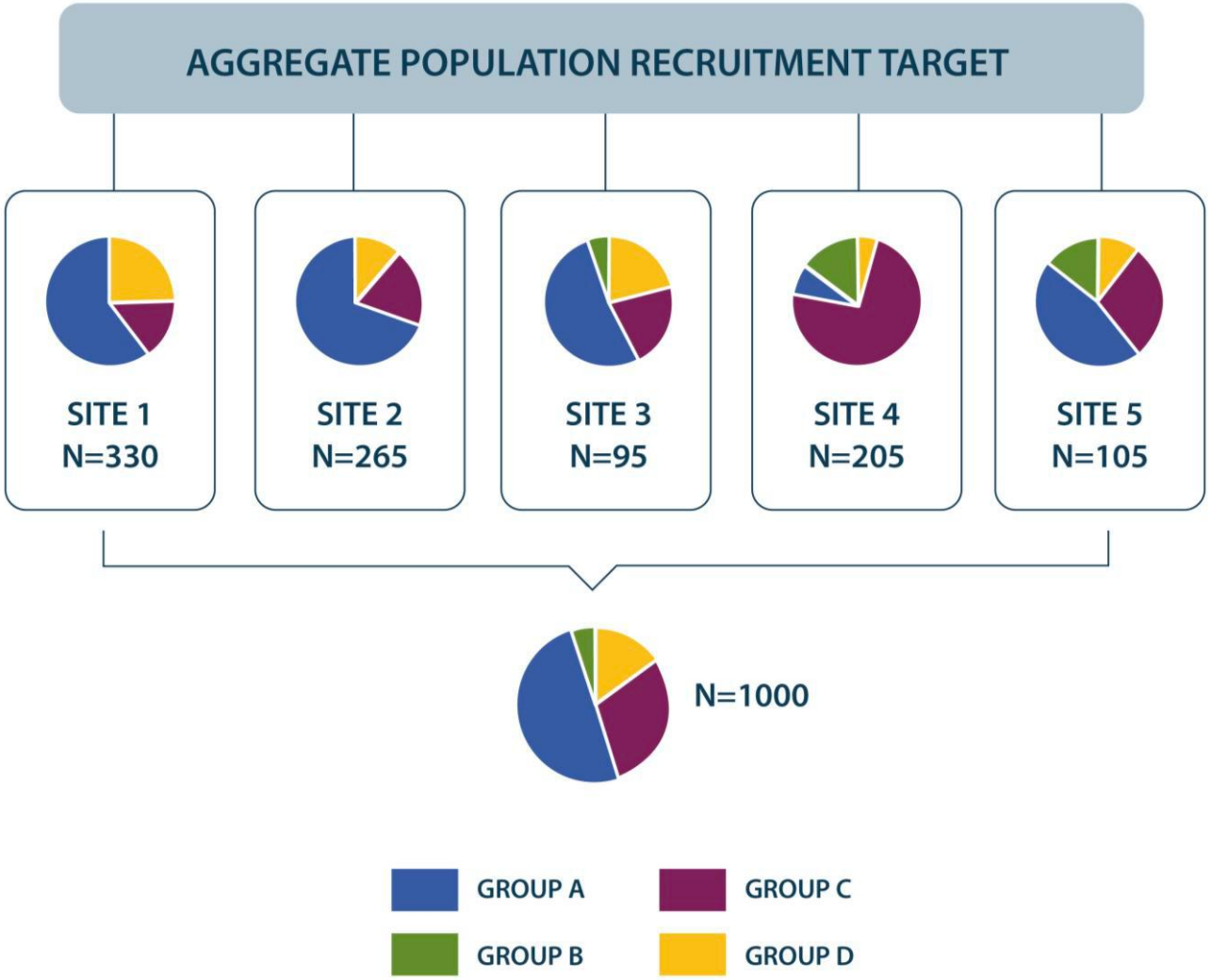
Ask the question.

IRB: Demographics and Overall plan

- Optimal recruitment target: Epidemiology of the disease and/or those for whom the product is intended
- Reasonable reasons for deviation, e.g.,
  - Phase 1 healthy volunteers
  - Exploratory study
  - A given population is the object of specific study
  - Geophysical mapping
- Exceptions should be justified and documented

- If one starts from the assumption of the recruitment target, the study protocol should contain:
  - Information about the demographics of the disease and/or those for whom the product is intended
  - Prior research relevant to the current study

IRB: Overall plan



Focusing on the role of the IRB in advancing diversity

- Initial Review:
  - Study Aims and Subject Selection
    - Do the demographics of the proposed sample reflect that of the population affected by the condition or for whom the intervention is intended?
      - When it does not, is the deviation adequately justified?
      - Is planned under- or over- representation by age, race, ethnicity, or gender in the sample scientifically justified?
      - Is there a statistical plan for examining heterogeneity in outcome or across subgroups?

Focusing on Role of the IRB in advancing diversity

- Criteria for Inclusion and Exclusion
  - Will inclusion and exclusion criteria inadvertently or unnecessarily result in under- or over-representation of understudied subgroups?
  - Have alternative approaches to minimizing risk that do not rely on exclusion been considered?
- Recruitment
  - Have recruitment procedures considered specific approaches to engage underserved populations?
  - Are materials available in languages understandable/primary to the participants?
  - Are participant materials translated? If not, why not?
  - Do all participant-facing materials conform to health literacy principles?

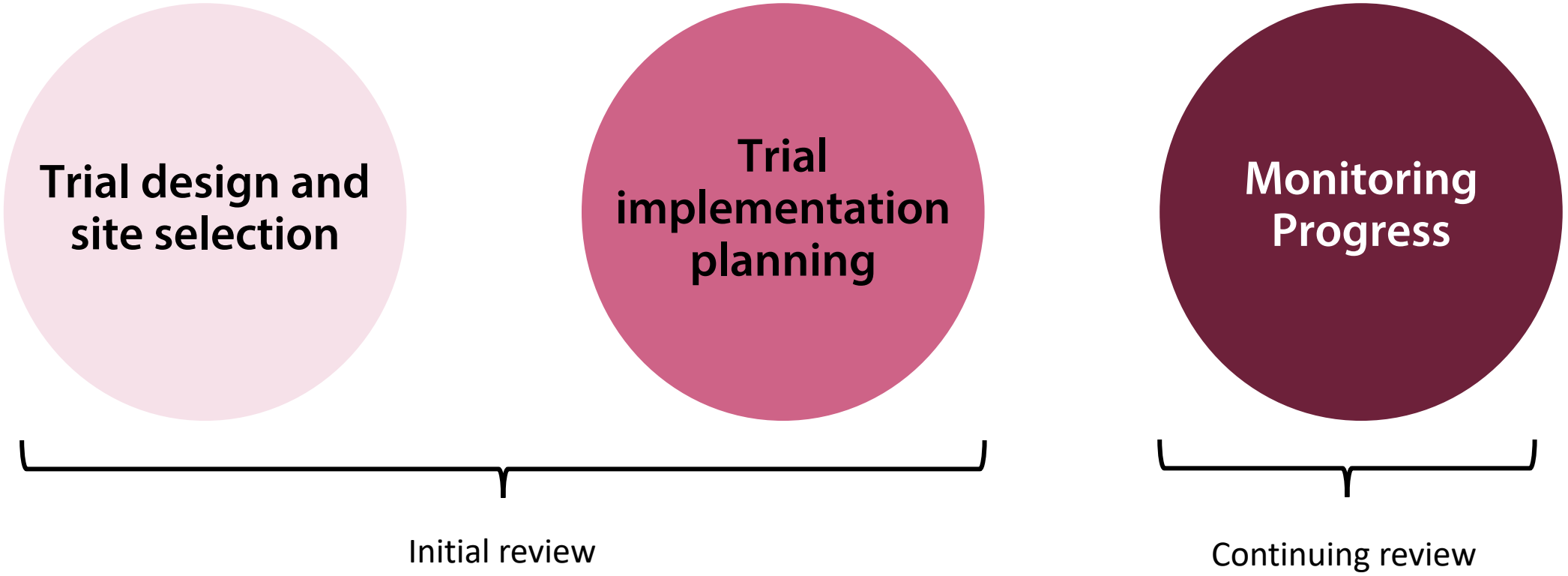
Focusing on Role of the IRB in advancing diversity

- Study Conduct
  - Are study procedures flexibly organized to accommodate the needs of under-represented groups?
  - Are all in-person visits essential? Can any be done locally or virtually if appropriate?
  - Is reimbursement for expenses of participation provided?
- Payment
  - Is payment sufficient to cover costs of participation?
- Return of results
  - Are study results intended to be returned in a manner that meets the needs of populations studied?

Focusing on Role of the IRB in advancing diversity

- Continuing review:
  - Has the study fulfilled its recruitment/accrual goals?
  - Is demographic distribution on track to approximate the study goals?
  - If not, are adequate corrective actions described, sufficient, and likely to be successful?

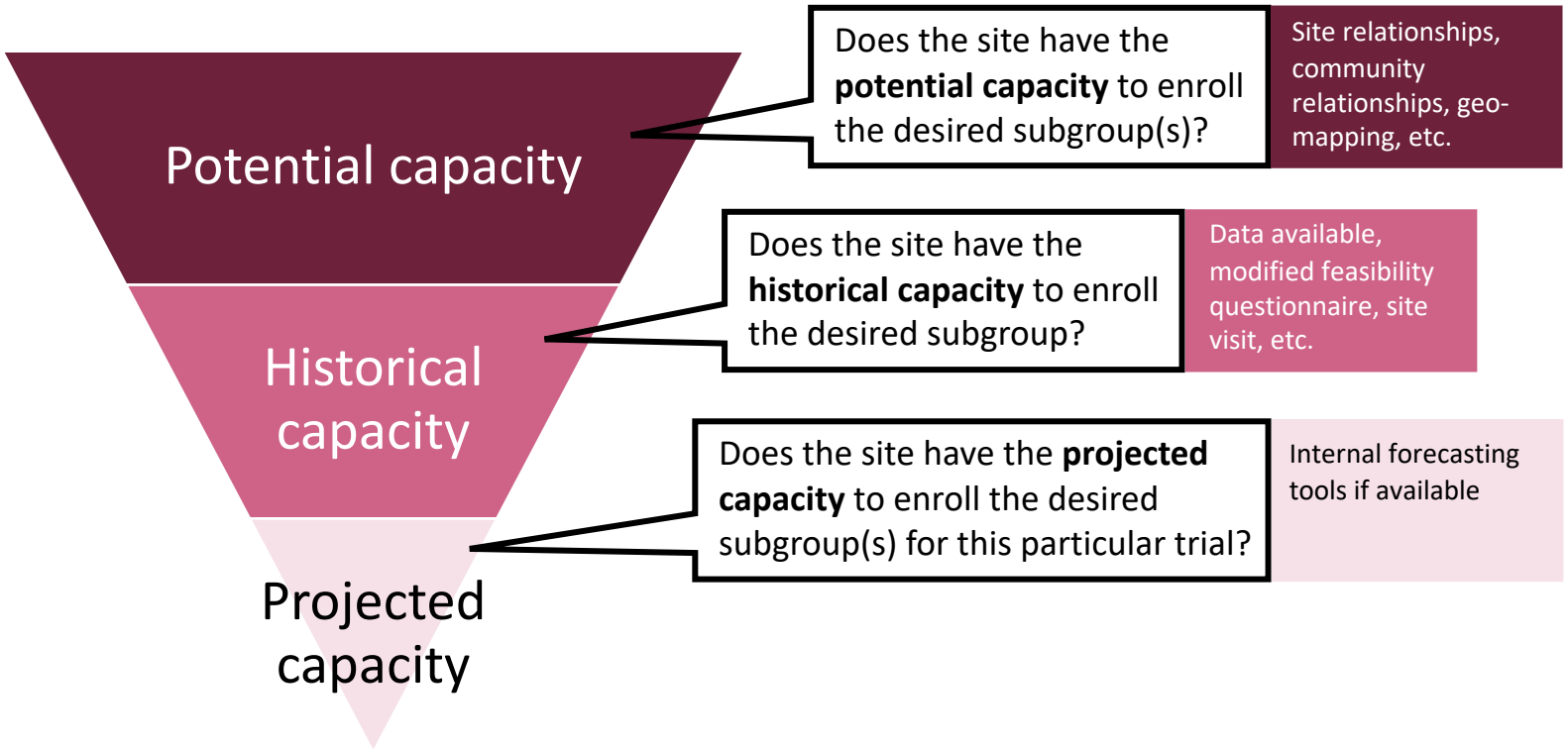
What tools can an IRB leverage to support investigators in advancing diversity for multi-center trials?



Site Selection – ensuring study sites have capacity to enroll a diverse population

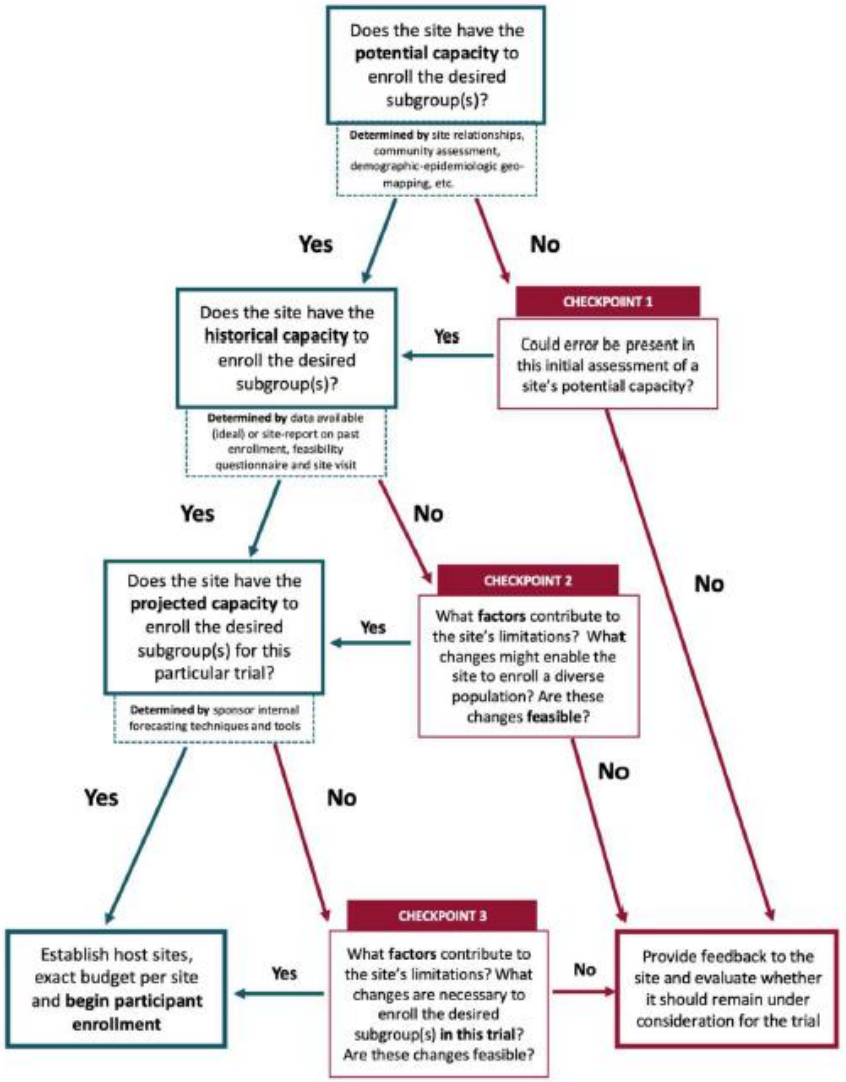
Trial design and site selection

Feasibility Assessment tool



Site Selection – ensuring study sites have capacity to enroll a diverse population

Site selection decision tree tool



Trial design and site selection

Checkpoint	Capacity Tier	Purpose
Checkpoint 1	Potential Capacity	Assessment of methods used to determine a site's lack of "potential capacity" for enrollment of desired subgroup(s). If bias/inaccuracy is detected in these methods, the site remains eligible for consideration in site selection for enrollment of that subgroup(s).
Checkpoint 2	Historical Capacity	Identification and assessment of factors that contribute to a site's lack of "historical capacity" for diverse enrollment, the changes needed in order to build that capacity in the future, and whether supportive measures might be feasible for the sponsor/CRO to provide. If changes are deemed feasible to make, the site remains eligible for consideration in site selection for diverse enrollment.
Checkpoint 3	Projected Capacity	Similar to that of "historical capacity," identification and assessment of those factors limiting a site's "projected capacity" for diverse enrollment *in the trial at hand*, according to whatever diversity goal and target population established by the sponsor. If identified changes are feasible to make, the site should be included in the study at hand.

Site Selection – ensuring study sites have capacity to enroll a diverse population

Modified Feasibility Questionnaire

Trial design and site selection

ACTION: Modify feasibility questionnaires to include questions in **designated areas** focused on enrollment of representative populations

Implement feasibility assessment

OUTCOME: Data generated on site capacity to enroll specified populations

Data analysis & forecasting

IMPLICATION: Informed decision-making for site selection to achieve enrollment of a representative population **in aggregate throughout the trial**

☐ Population Availability

Guidance Questions for Demographic Data:

- How likely are potential study participants to be non-English speakers? *(Very Unlikely, Unlikely, Neutral, Likely, Very Likely)*
  - *If Neutral or greater, what languages (English, Spanish, Mandarin, etc.)*
- Provide the most likely demographic composition *(by sex, age, race/ethnicity and income)* of the study population based on demographic and epidemiological data describing the site's catchment area. Provide a justification for this predicted composition.

☐ Population Accessibility

Guidance Questions for Demographic Data:

- Provide evidence of the historical accessibility of specified subpopulations to the site, based on EHR search results, registries, longitudinal studies, past participation, etc.
- Provide evidence of community engagement for this site for specified demographic subpopulations, through letters of commitment from community leaders, sites, primary care physicians, etc.
- Provide evidence of prior recruitment success in recruiting and/or retaining specified demographic subpopulations.

☐ Targeted Recruitment Strategy

Guidance Questions for Demographic Data:

- Describe the recruitment team's experience recruiting and retaining particular demographic subgroups and underrepresented populations in general. If no experience, describe how your team will acquire the cultural competencies.
- Describe specific recruitment activities to ensure the enrollment of specified subpopulations and who will be responsible for execution of these activities.
- Describe the use of compensation, reimbursement of costs and other financial incentives for participants of the specified subpopulation if applicable.

☐ Barriers & Supports

Guidance Questions for Demographic Data:

- What barriers does the site anticipate for recruiting the specified subpopulation (*either inherent to the protocol, the site, or the subpopulations*) in the given timeline?
- What supports does the site have to aid the study team in targeted recruitment of the specified subpopulation?
- What supports/resources/trainings would the site need to overcome unaddressed barriers? Other than the sponsor/CRO, what are some additional avenues that the site could use to acquire anticipated supports?

Recruitment Strategies – planning for recruitment of a diverse population

Trial implementation planning

Recruitment Strategy Documents – Potential Key Performance Indicators (KPIs)

Output indicators

- ☐ Trial-level recruitment plan for diversity available at site, including all the proposed elements to consider (See Achieving Diversity, Inclusion and Equity in Clinical Trials Guidance Document, Table 12, Part E, Section 13.5)
- ☐ Site-specific recruitment plan for diversity available at site
- ☐ Monitoring mechanisms for recruitment targets by demographic established
- ☐ Suggested recruitment strategies tailored to target population(s) available at site

Outcome indicators

- ☐ Site investigator-reported understanding of diversity enrollment objectives
- ☐ Data on demographic profile of enrolled participants available to sponsor in a suitable amount of time
- ☐ In the case that demographic profile data indicate site will not meet target enrollment of target subpopulation, contingency plan implemented

Recruitment Strategies

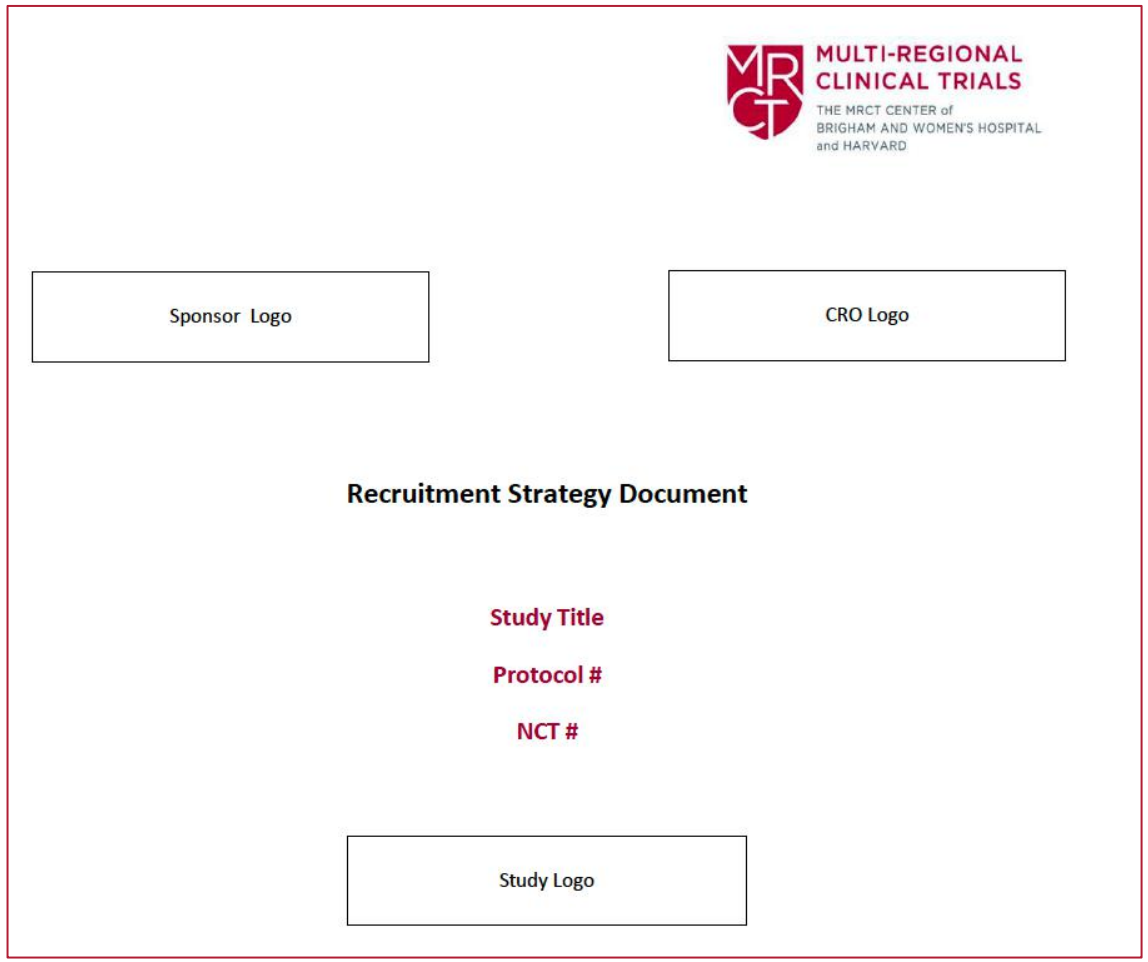
Elements to consider within a trial-level recruitment strategy document

RECRUITMENT DOCUMENT ELEMENT	JUSTIFICATION
Trial sample size (N) calculation to achieve treatment effect as provided in protocol	Typical power calculation included in recruitment planning to provide the goal for overall study population across all sites
Overall epidemiology of disease	Available measures of disease frequency (prevalence, incidence, etc.) to characterize the burden of disease by geographic region
Epidemiology of disease by demographic	Measures of disease frequency (prevalence, incidence, etc.) by available demographics and by region, to highlight the subpopulations for whom the intervention is intended
Heterogeneity assessment across subgroups and effect on sample size	Assessment based on literature, ongoing trials, or prior evidence for differences in disease manifestation or treatment response in particular subpopulations, to justify modified methods for recruitment, sample size and analyses of the intended subpopulations.
Potential limiters and enablers for strategic recruitment	Logistical, economic, capacity-related, and sociocultural elements that might enable or limit recruitment in particular subpopulations or regions
Diversity guidelines and subpopulations for trial	Development of objectives to achieve a diverse trial population, with overall trial-level enrollments for specified subpopulations, to highlight recruitment expectations

Trial implementation planning

Recruitment Strategies – making the plans to recruit a diverse population

Recruitment Strategy Document



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Sponsor Logo

CRO Logo

Recruitment Strategy Document

Study Title

Protocol #

NCT #

Study Logo

Trial implementation planning

Recruitment Strategy Document

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Trial implementation planning

Eligibility and Enrollment Log – monitoring tools for investigators

Monitoring Progress

A. Study Information

Protocol Number:	
Protocol Title:	
Principal Investigator:	

B. Participant Information:

Participant Name/Pre-Screening ID:
Age: ☐ >=18 - <65 years ☐ >=65 - <74 years ☐ >=75 - <84 years ☐ >=85 years
Sex: ☐ Male ☐ Female ☐ Unknown or undifferentiated
Gender: ☐ Male ☐ Female ☐ Trans-Male ☐ Trans-Female ☐ Gender nonconforming or unknown
Ethnicity[1]**:** ☐ Hispanic or Latino ☐ Not Hispanic or Latino
Race[1]**:** ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ White ☐ Other

C. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation**[2]
1.	☐	☐	
2.	☐	☐	
3.	☐	☐	
4.	☐	☐	
5.	☐	☐	

Exclusion Criteria (From IRB approved protocol)			
1.	☐	☐	
2.	☐	☐	
3.	☐	☐	
4.	☐	☐	
5.	☐	☐	

D. Enrollment Tracking

Enrolled?		**If no, why? Provide supporting Documentation**[3]
Yes	**No**	
☐	☐	

E. Statement of Eligibility[4]

This individual is [☐ **eligible** / ☐ **ineligible**] for participation in the study.

Signature:	Date:
Printed Name:	

Support of the institution

- Institutional endorsement and support of the IRB
- Policies that support the positions of the IRB
- IRB membership:
  - Diverse membership
  - Community voice represented
  - Cultural competence and implicit bias training
- Challenging in a world of single site review of multi-site trials

Argument for collective approach and harmonization

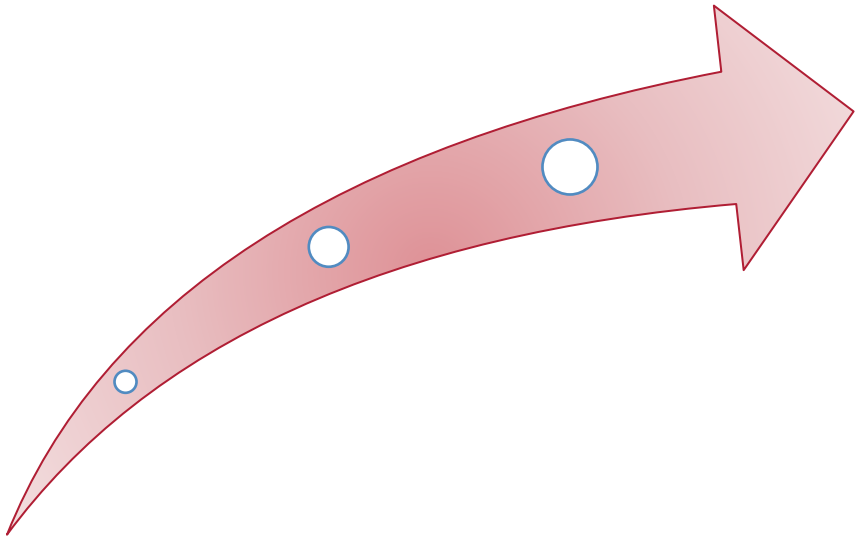
Key Performance Indicators

Monitoring Progress

The importance of:

- Metrics
- Transparency
- Accountability

Progress takes time



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Discussion and Questions

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Join us:

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