Inclusion of Women and Minorities in NINDS Clinical Trials

StrokeNet Webinar

October 11, 2016

Outline

- NIH and NINDS policy
  - *Claudia Scala Moy, PhD*
- Approaches to design and analysis
  - *Yuko Palesch, PhD*
- Strategies for recruiting and retaining study participants
  - *Bernadette Boden-Albala, PhD*

Public Health Service Act
Sec. 492B, 42 U.S.C. sec. 289a-2

The Director of NIH shall ensure that

- Women and members of minority groups are included as subjects in each clinical research project
- Outreach programs for the recruitment of women and minorities are supported
- Exception – when inappropriate with respect to the health of subjects or the purpose of the research

NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research - 2001

- **Women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.**

- **Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources.**

Rationale

- *Phase III trials* – important to understand whether the intervention has a different impact in men and women and in various minority populations affected by the disorder
- *Observational studies and exploratory trials* – diversity essential to improve understanding of disease and to design subsequent large-scale trial

Requirements for "NIH-defined Phase III Clinical Trials"

Determine evidence from prior studies – 3 scenarios:

1. Prior studies support the existence of significant* differences of clinical or public health importance in intervention effect

- *Must design the trial to answer the primary question in each group where differences may be expected.*
- *Trial must enroll adequate numbers of subjects in each target group*

Requirements for "NIH-defined Phase III Clinical Trials"

2. Prior studies support no significant differences in intervention effect
   - *Sex/gender and race/ethnicity not required as selection criteria*
   - *Inclusion and analysis of gender/minority groups encouraged*

Requirements for "NIH-defined Phase III Clinical Trials"

3. Prior studies neither support nor negate significant differences in intervention effect
   - *Trial must include sufficient and appropriate enrollment of gender/minority subgroup participants to permit "valid analysis" of intervention effect*
   - *High statistical power not required*

Question

Is it sufficient to include women and minorities according to their proportion in the population?

Answer

Generally no.

Even if women (for example) are less likely to have a particular diagnosis, if there is prior evidence supporting the existence of differential treatment effect, *sufficient numbers of women must be included to answer the primary question in both men and women*.

Key definitions

- Prior studies
  - *Data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, observational (natural history, epidemiologic) studies*
- Significant difference
  - *A difference of clinical or public health importance*
  - *Distinct from "statistically" significant difference*
- Valid analysis
  - *Unbiased allocation to intervention or control groups*
  - *Unbiased evaluation of outcomes*
  - *Use of unbiased statistical analysis and proper methods of inference to compare treatment effects*
- Minority group
  - *A readily identifiable subset of the US population distinguished by racial, ethnic, and/or cultural heritage*

What about non-US participants?

- Information on sex/gender, race, and ethnicity must be reported for non-US participants
- US race/ethnicity categories may not apply; investigators should design culturally appropriate data collection instruments that allow participants to self-identify in a culturally appropriate way
- For reporting, investigators must “translate” the sex/gender, racial, and ethnic information to conform to the OMB-defined categories
- Data are reported separately for US and non-US participants

Preparing the grant application

- Discuss the prior evidence as it relates to expected treatment differences in gender and minority subgroups
- Describe the composition of the proposed study population and provide a rationale for selection of subjects in terms of sex/gender and race/ethnicity
- Provide rationale for decision to exclude subgroups
- Describe statistical analysis plan to address gender/minority subgroup differences
- Include realistic plans for outreach/recruitment/retention of women and minorities
- Ensure that the study budget includes adequate funds to support outreach efforts

Scientific Review

- Inclusion of women and inclusion of minorities will be evaluated separately and scored as “acceptable”, “unacceptable”, or if no information is presented, “absent”
- Absence of information constitutes grounds for returning the application without review
- A determination of “unacceptable” is reflected in the priority score

Review considerations

- Is the evidence supporting or negating differential treatment effect adequate?
- Is the rationale for including or excluding gender/minority subgroups appropriate?
- Is the design of the trial adequate to measure differences?
- Are the plans for recruitment/outreach adequate?
- Is the plan for “valid analysis” appropriate?

NINDS Mission

The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

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Women and Minorities in StrokeNet Trials: Plans for Analysis and Reporting

Yuko Y. Palesch, PhD
NDMC

MUSC Health
Medical University of South Carolina
Changing What's Possible

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NIH Policy and Guidelines – "Valid Analysis"

Valid Analysis - an unbiased assessment. ... A valid analysis does not need to have a high statistical power for detecting a stated eff valid analysis of the question of interest are:

But may be uninformative or misleading.
NOTE: low power = high false negative
(under superiority hypothesis)

- allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process such as *[well-designed and well-executed]* randomization,
- unbiased evaluation of the outcome(s) of study participants *[such as blinding]*, and
- use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

Most well-planned trials should be more or less good to go on these point.

Additional Comments on "Valid Analysis"

- Randomization
  - Generally, we don't recommend stratifying or adjusting randomization by sex/race/ethnic groups unless any of these factors are known strong prognostic variables, because:
    - Adds levels of complexity in the implementation of randomization, in particular, in drug accounting and distribution.
    - These factors, if used in randomization, should be included in the analysis which: (1) uses up degrees of freedom; (2) problematic if the numbers in categories of these factors are small.
  - For large studies, these factors should even out among the treatment groups.
  - For small studies, may want to consider adjusting only if the factor is deemed highly prognostic.
- Unbiased statistical analyses to compare the interventions
  - With appropriate statistical help, the analytic method should not be a problem.
  - But statistical comparison of the treatment effects within sex/race/ethnicity groups should be purely descriptive, unless the study is properly (i.e., statistically) powered/sized for detecting the "clinically" significant difference within each group.

NIH Policy and Guidelines - Scenario 1

If "Prior Studies Support the Existence of Significant Differences":

- The Research Plan (for grant applications) or Proposal (for contr… of plans to conduct analyses to detect significant differences** in i…

Recall, this is the *clinically* important differences.

- Probably a rare scenario.
- Easier scenario to design your study, assuming that "clinically" significant difference in the treatment effect among the sex/race/ethnicity groups has been quantified and accepted by the clinical community.
- Do separate parallel studies for each of the sex/ race/ ethnicity groups, as appropriate.
- Would likely require large N and feasibility will be an issue.

NIH Policy and Guidelines - Scenario 2

If "Prior Studies Support No Significant Differences":

- Sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

- Relatively easy scenario to design your study (i.e., ignore sex/race/ethnicity factors).
- However, this scenario would be very difficult to prove:
  - especially if the "no significant difference" is incorrectly equated to failure to reject the null hypothesis in the previous studies; and/or
  - if "clinically" significant difference has not been quantified by consensus, and hence, becomes subject to interpretation of various clinicians (and reviewers).
- Would require strong justification/evidence/rationale in the grant proposal to proceed with this scenario.

NIH Policy and Guidelines - Scenario 3

If "Prior Studies Neither Support nor Negate Significant Differences":

- sufficient and appropriate entry of sex/gender and racial/ethnic participants so that valid analysis of the intervention effects can be performed..
- However, the trial will not be required to provide high statistical powe
- The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct valid analysis (see DEFINITIONS – Valid Analysis) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable

Very vague

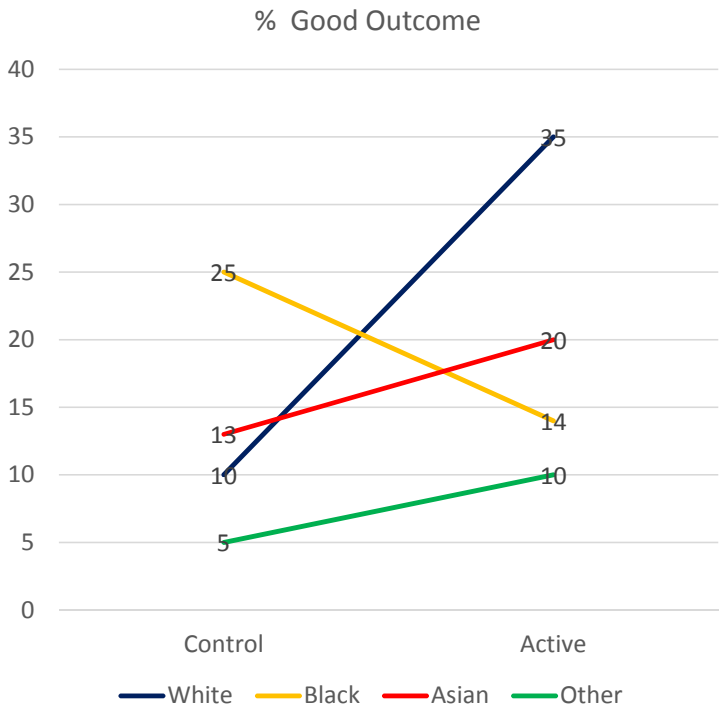
Difficulty in interpretation of analyses

- Most common scenario and most difficult to address.
- Need to: (1) quantify the clinically important treatment-by-sex/race/ethnicity interaction effect; and then, (2) ensure adequate sample size to detect cient statistical power.
- Analyze to ascertain statistical (and clinical per above) significance of the interaction effect between sex/race/ethnicity and treatment.
- Will require larger N's for adequately powered study, unless the sex/race/ethnicity treatment effect differences of clinical significance is large.
- But type I error need not be limited to 0.05 for testing interaction.

Very difficult tasks!

Tx-by-Sex/Race/Ethnicity Interaction Effect

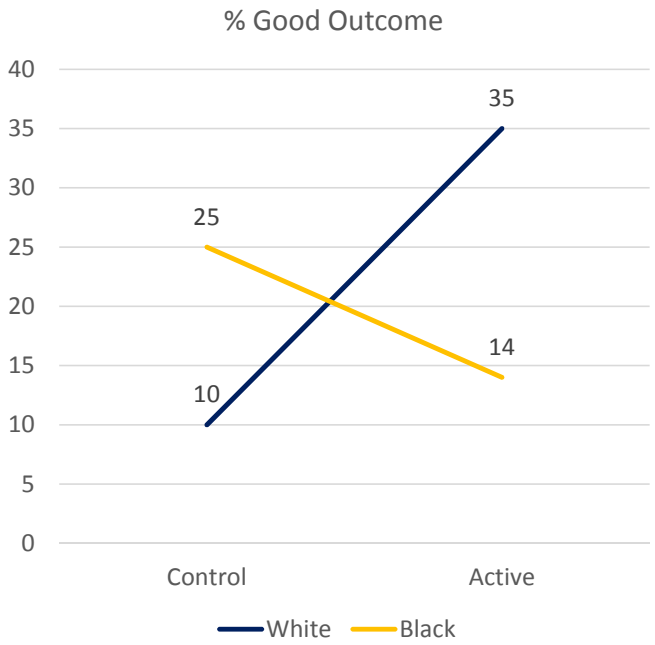
Hypothetical example outcome by race groups from a prior study(ies):



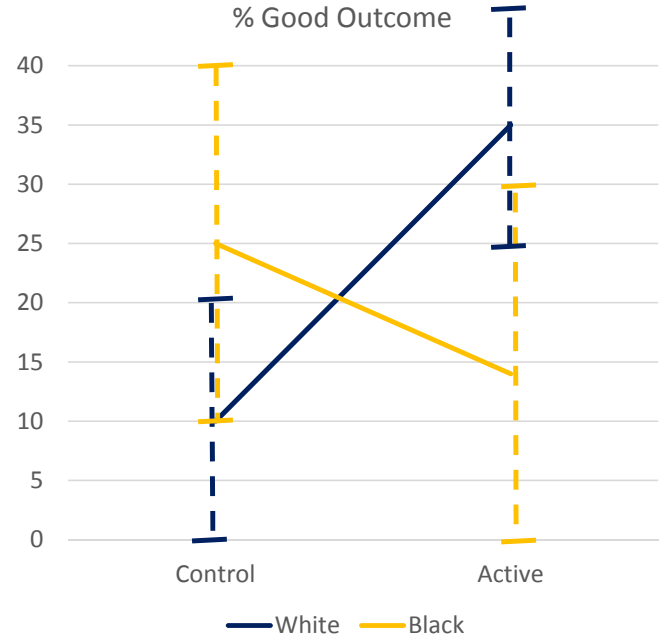
- All races, except Blacks, had higher % of good outcome in the Active (Treated) Group than the Control Group.
- Do the treatment effect differ between race groups?

Tx-by-Sex/Race/Ethnicity Interaction Effect

Qualitative Interaction:



Tx effect is clearly different between Whites and Blacks



Or is it…?

Need to compare the CIs on Tx effects (e.g., RR=3.5 vs 0.56); signif. depends on the N's

Tx-by-Sex/Race/Ethnicity Interaction Effect

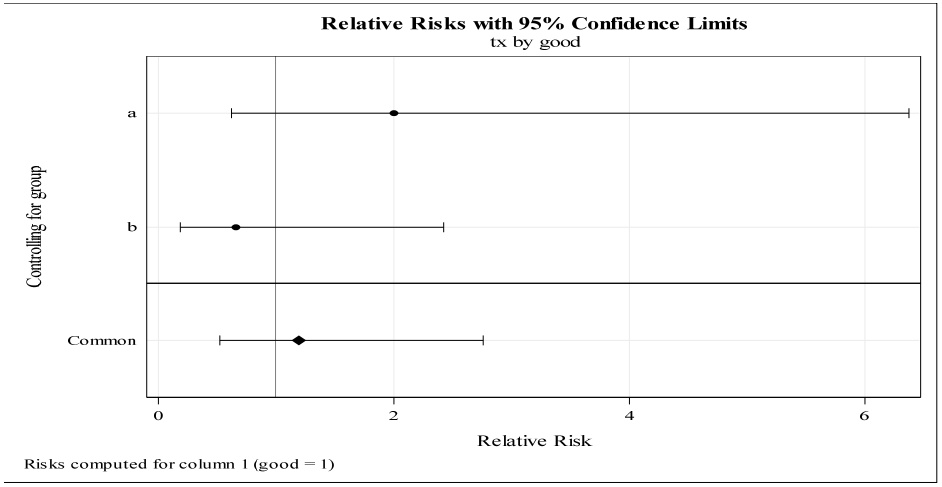
Tx effects of 40% vs -20% with N=20.

Table 1 of tx by good

Frequency Row Pct	1	2	Total
1	4 80.00	1 20.00	5
2	2 40.00	3 60.00	5
Total	6	4	10

Table 2 of tx by good

Frequency Row Pct	1	2	Total
1	2 40.00	3 60.00	5
2	3 60.00	2 40.00	5
Total	5	5	10



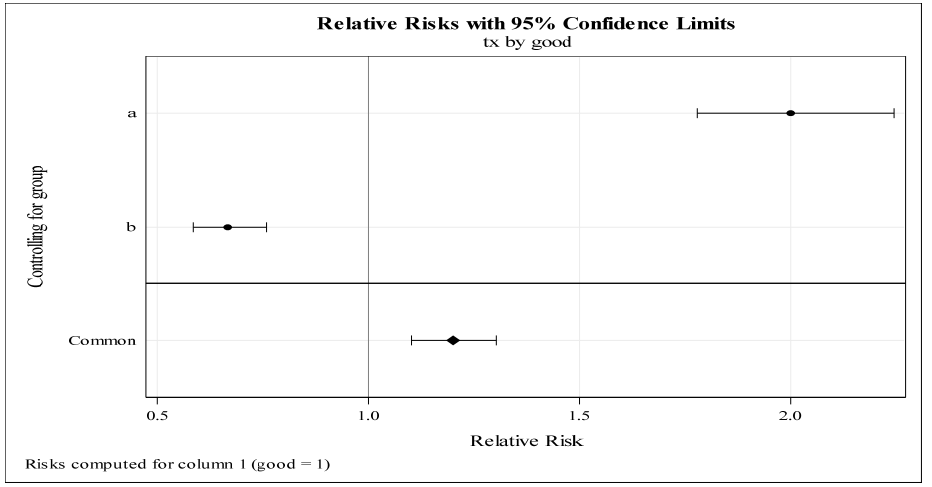
Tx effects of 40% vs -20% with N=2000.

Table 1 of tx by good

Frequency Row Pct	1	2	Total
1	400 80.00	100 20.00	500
2	200 40.00	300 60.00	500
Total	600	400	1000

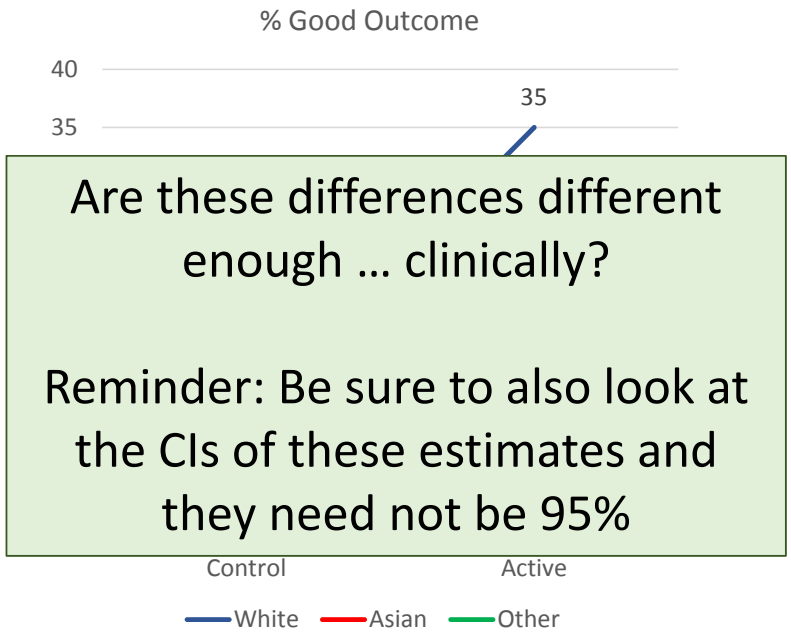
Table 2 of tx by good

Frequency Row Pct	1	2	Total
1	200 40.00	300 60.00	500
2	300 60.00	200 40.00	500
Total	500	500	1000



Tx-by-Sex/Race/Ethnicity Interaction Effect

Quantitative Interaction:



Are these differences different enough … clinically?

Reminder: Be sure to also look at the CIs of these estimates and they need not be 95%

Treatment effect within each race

	Absolute Difference	Relative Difference
White	35% - 10% = 25%	35% / 10% = 3.5
Asian	20% - 13% = 7%	20% / 13% = 1.5
Other	10% - 5% = 5%	10% / 5% = 2.0

Differences in the treatment effect among races

	Absolute Difference
White vs Asian	18%
White vs Other	20%
Asian vs Other	2%

Comments

- “Valid analysis” requirements can be met by careful planning and execution of the trial. Most trials should be capable of meeting these requirements.
- However, without “high” (or even “adequate”) statistical power, hypothesis testing is likely to be uninformative at best, and worse, misleading.
- Defining/quantifying “(clinically) significant differences” in the treatment effect among sex/race/ethnicity subgroups is a big challenge.
- Without adequate statistical power, Scenario 3 will require clinical input in determining what is “sufficient and appropriate” number of subjects, and how to ensure and monitor compliance with this requirement.
- Carefully consider other factors that may influence differential outcomes among sex/race/ethnicity, e.g., characteristics of clinical centers that affect outcome (like DCT, DNT, etc for acute stroke); health care access parameters (like insurance coverage, especially for rehab), etc.
- Requires a strong collaboration between the clinicians and statisticians to address the issue of women and minorities in clinical trials.

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Questions?

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Practical Approaches to Improving Recruitment with Emphasis on Minority Recruitment

Bernadette Boden-Albala, MPH, DrPH

October 11, 2016

Two Approaches

1. Trial Design

2. Trial Implementation

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1. Trial Design

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Site selection guidance

- **Percent of admitted patients' race-ethnicity and gender**
  - Information to make reasonable projections

- **Each site's feasibility to enroll**
  - Use ICD-9 codes
  - Get with the Guidelines metrics
  - Real time experience

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Key Questions

- What is the underlying minority population that could be in the study? (ex: how many people of X group pass through the doors of Y site)
- How many of out that populations would fit eligibility criteria
- What percentage of those people do investigators actually have access to?

StrokeNet Advisory committee: Trial Recruitment and Retention for Under-represented Minorities and Ethnicities

Bernadette Boden-Albala, MPH, DrPH (Co-Chair)
Dawn Kleindorfer, MD (Co-Chair)
Clare Binley, RN
Devin L. Brown, M.D., M.S
Dorothy Edwards, PhD
Jose Romano, MD
Olajide Williams, MD
Patricia Tanzi, RN, BSN, CCRC
Alicia Bennett, D.O.
Maggie Baker
Salina Waddy, MD

Minority Recruitment and Retention Plans

A. Trial mechanics

1. Trial's eligibility criteria
   - Do the criteria systematically exclude a specific group of people?
2. Patient population demographics
   - Vulnerable populations, age, sex, race, ethnicity
3. Type of recruitment sites
4. Each site's resources
   - CTSA, community outreach etc.
5. Enrollment
   - Setting, enrollment hours, language translation services
6. Retention
   - Compensation, length of follow-up

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Minority Recruitment and Retention Plans

B. Researcher Narrative

1. Reflect recruitment and retention experience
   - Best practices
   - Barriers

2. Based on past experience, what would you do differently?

StrokeNet Recruitment and Retention Plan

1) Describe the disease/condition of interest and summarize the evidence regarding potential differential treatment effect of your proposed intervention in underrepresented populations and women.

2) List your site selection criteria, and did you utilize site selection to ensure adequate representation.

3) What is the investigator's track record for recruiting and enrolling minorities and women into previous research? Do the sites selected have a track record of diverse recruitment?

4) Describe specific strategies that you will use to enhance recruitment and retention of under-represented minorities and women into your trial.

5) (FOR PHASE III TRIAL CONCEPTS) Describe the statistical analysis plan that will specifically address the NIH requirement for a valid statistical analysis by sex and under-represented minorities.

NIMICT Toolkit for Recruitment and Retention

NIMICT

NATIONAL INITIATIVE FOR MINORITY INVOLVEMENT IN NEUROLOGICAL CLINICAL TRIALS

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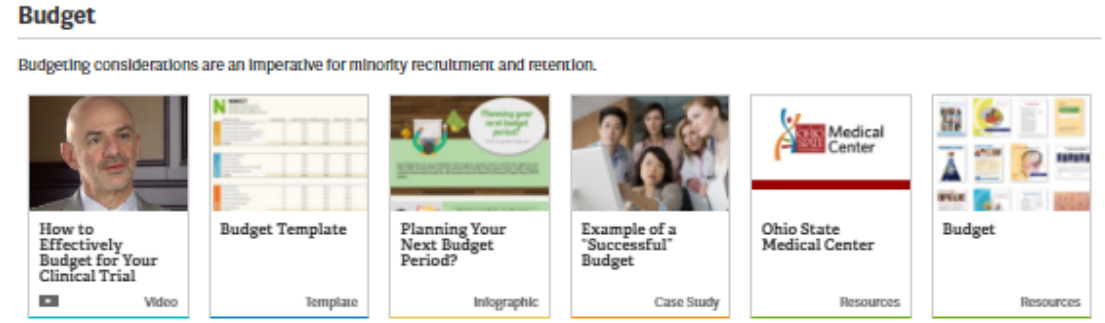
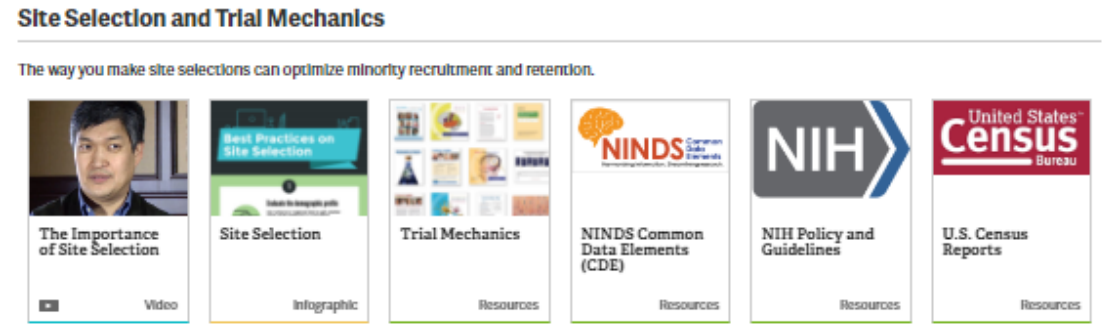
NIMICT's Tools and Resources

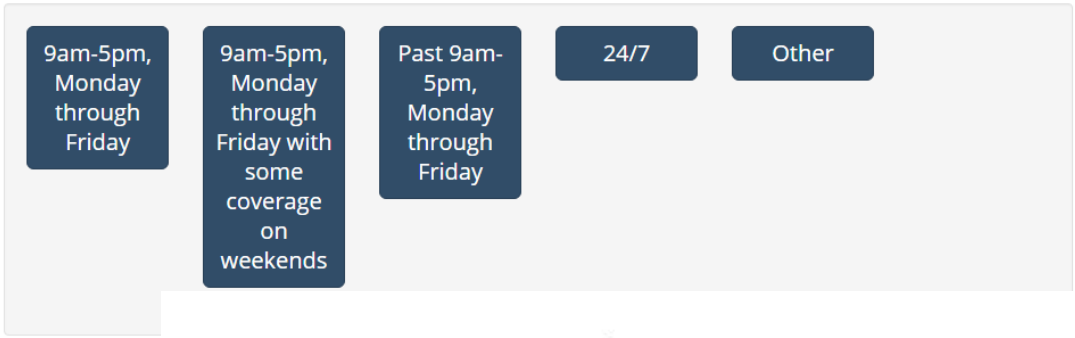
- *Researchers Discuss* video series
- Diagnostic tools
  - Key questions to help researcher think about study design, recruitment, and retention practices
- Templates
- Case studies
- Best practices
- Checklists
- Collection of pre-existing resources by topic





Diagnostic Tool: Enrollment

During what hours of each day, can you recruit patients?



A NIMICT Suggestion

You need to get a sense of when people arrive to your site, especially those who are eligible for the study. if 30% of eligible patients arrive outside of "business hours," we highly recommend extending your enrollment hours.

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Budget Considerations

for Recruitment and Retention

	Item
Recruitment	▷ Screening procedures ▷ Approach After hours coverage ▷ Informed Consent Translation services Bilingual staff member or translation device Print materials For patients and providers ▷ Staff meetings / in-services
Retention	▷ Follow-up procedures Flexibile visits ▷ Travel Mileage reimbursement or travel voucher ▷ Tokens of appreciation Pens, bags, mugs, holiday/birthday cards ▷ Contact line For patients and providers ▷ Recognition events for community members and participants

Paradigm Shift in Clinical Trial Proposal and Planning

- Nothing can be accomplished in isolation

- Stakeholder engagement
  - NIH
  - Reviewers
  - Principal Investigators
  - Research community

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2. Trial Implementation

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Research Staff Training

- Motivational Interviewing is collaborative, person-centered form of guiding to elicit and strengthen motivation for change.
  - Supportive counseling style used in recruitment methods.

- Cultural competency training

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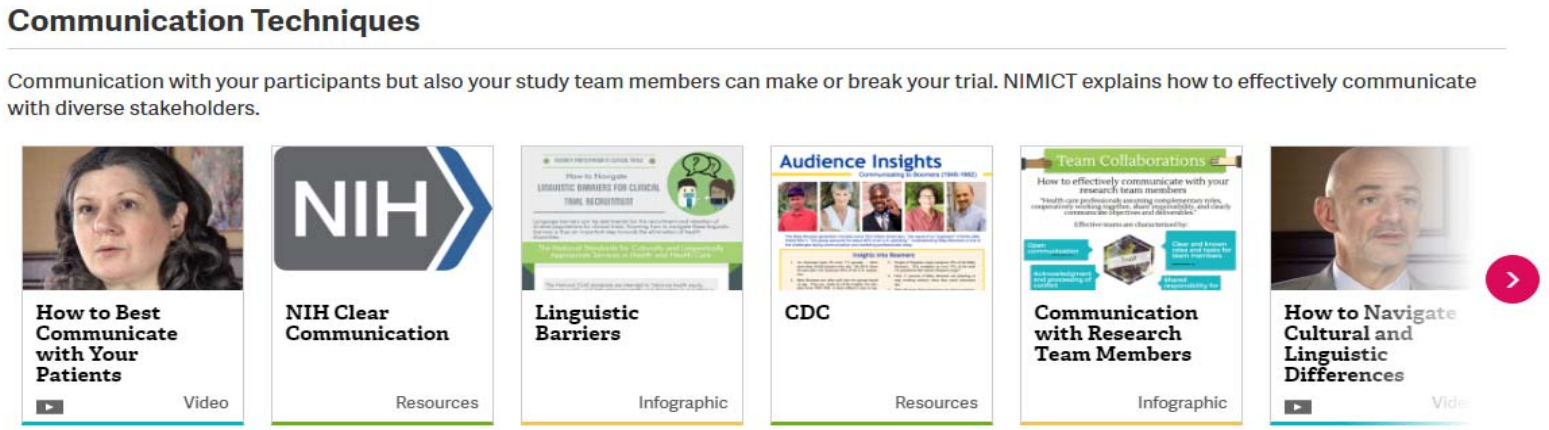
Communication Tools

- Use video series and narratives to help communicate time-sensitive concepts to patients, families and caregivers
  - Culturally sensitive and responsive video for families in acute and adverse circumstances
- NIMICT communication resources: videos, infographics, NIH and CDC guides, case studies



Community engagement

- Include a community advisory board:
  - Reviews study protocol to ensure cultural appropriateness

- Engage primary care physicians in recruitment:
  - Provide them with a toolkit with active trial information

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Questions?