INCLUDING DIVERSE POPULATIONS IN CLINICAL TRIALS: TECHNICAL VERSUS TRANSFORMATIONAL APPROACHES

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THE IMPORTANCE OF CLINICAL TRIALS IN MEDICINE

- New drug development
- Develop novel interventions for disease prevention & control
- New uses/doses/indications for established drugs
When the population enrolled in a clinical trial is too homogeneous....

- The results become difficult to generalize
- There can be unanticipated problems after interventions or new drugs are deployed in the public/brought to market
Example 1: Age diversity and Hormone replacement therapy (HRT)

- The age range of the original study population was relatively young;

- Estimates of cardiovascular disease risk and menopausal hormonal therapy were based on this group;

- Post-market studies were indicated because of increasing rates of cardiovascular disease and select cancers in women on hormones.

Example 2: Gender diversity and Ambien

- Original study population was male dominated;

- Preliminary review of studies by FDA note: "The results suggest a gender-related difference. However, the lack of specific details such as study design and individual data make it difficult to draw a definite conclusion--";

- Elevated Ambien levels in women have been associated with MVA due to falling asleep while driving;

Example 3: Racial diversity and Bi-Dil

- Bi-dil is a combination drug for congestive heart failure tested in a VA study (V-HeFT);
- Secondary data analysis showed increased efficacy in self-identified African American patients;
- FDA approves the drug after data from a phase II efficacy trial (A-HeFT) shows benefit.
- The drug was never studied in a phase III trial.

Ghali & Cohn, Am J Cardiovasc Drugs 2007; 7(5)
WILL BI-DIL WORK BETTER FOR.....?
RACIAL/ETHNIC DIVERSITY IS LOW IN CANCER CLINICAL TRIALS NATIONALLY

Enrollment by Race and Ethnicity
National Cancer Institute, Publicly Funded Cancer Clinical Trials (Phase I-III Treatment Studies)
January 1, 2003 – June 30, 2005

- White, 88.6%
- Non-Hispanic/Latino, 94.4%
- Black/African American, 8.0%
- Asian/Pacific Islander, 2.8%
- Native American/Alaska Native, 0.5%
- Hispanic/Latino, 5.6%
- Multiple, 0.1%

INCLUSION IS A PROBLEM IN NON-CANCER CLINICAL TRIALS

Sex/Gender disparities in randomized controlled trials of statins: the impact of awareness efforts.
Farahani P.

Minorities Remain Underrepresented in HIV/AIDS Research Despite Access to Clinical Trials

Jose R. Castillo-Mancilla,¹ Susan E. Cohn,² Supriya Krishnan,³ Michelle Cespedes,⁴ Michelle Floris-Moore,⁵ Gail Schulte,⁶ Gregory Pavlov,⁷ Donna Mildvan,⁸ Kimberly Y. Smith,⁹ and the ACTG Underrepresented Populations Survey Group
DETERMINANTS OF LOW DIVERSITY IN CLINICAL TRIALS
Lesley Stahl: If you want to understand me, they study you?

Larry Cahill: And here's why they do that. Because there's this assumption that you are me with pesky hormones... The idea is that the fundamental things are similar between you and me. So that ironically the best way to study you is to study me.

Lesley Stahl: ‘Cause you don't have pesky hormones.

Larry Cahill: Right. We're studying all the fundamental things in you without this sort of nuisance stuff. That's literally an assumption on which all of biological medicine, especially neuroscience, which I know best, has been built.

DETERMINANTS OF LOW DIVERSITY: HISTORICAL HARMS
The Tuskegee Study of Untreated Syphilis

The 30th Year of Observation

DONALD H. ROCKWELL, MD; ANNE ROOF YOBS, MD;
AND M. BRITTAINE MOORE, JR., MD, ATLANTA

20 Years of Followup Experience
In a Long-Range Medical Study

By EUNICE RIVERS, R.N., STANLEY H. SCHUMAN, M.D., LLOYD SIMPSON
and SIDNEY OLANSKY, M.D.

ONE OF THE longest continued medical surveys ever conducted is the study of untreated syphilis in the male Negro. This study

At Tuskegee, each of the 600 patients initially was given a complete physical examination, including chest X-rays and electrocardiograms.

U.S. PUBLIC HEALTH SERVICE

25

This certificate is awarded to

In grateful recognition of 25 years of active participation in the Tuskegee medical research study.

Awarded 1958

Surgeon General
Henrietta Lacks’ cells were taken and reproduced as the first immortalized cell line used for mass production research
- First to be cloned in the lab
- Most commonly used cell line in medical research
- Used for mass testing of the polio vaccine (Salk)
- Have been used in cancer research, HIV research, and gene mapping
- Over 11,000 patents based on work with HeLa cells

Skloot, Rebecca. The Immortal Life of Henrietta Lacks (February 2010).
DETERMINANTS OF LOW DIVERSITY: LOCATION OF CARE

Patient Race/Ethnicity in 3 Cancer Care Settings

Safety-Net Hospital (SNH)

Academic Medical Center (AMC)

Community Private Practice (CPP)

Regional data courtesy of Dr. Daniel Dohan, UCSF Institute for Health Policy Studies
PROVIDER BASED BARRIERS TO INCLUSION VARY

Provider factors include:

- The interdisciplinary care team, the lack of continuity of care, and competing provider priorities of clinical care, teaching, and research. (Joseph & Dohan; Contemp Clin Trials 2009 Nov; 30(6))

- Lack of available protocols/lack of provider awareness; Provider attitudinal barriers related to patient adherence; Provider communication (can act as both barrier and facilitator) (Howerton & Gibbons; Cancer 2007 Feb 1;109(3))
Visits with AA patients were shorter overall

- There were fewer mentions of and less discussion of clinical trials

There was less time spent discussing the purposes and risks of trials

HOW WE FRAME THE PROBLEM DETERMINES THE POTENTIAL SOLUTIONS
WHAT WE KNOW:
- Clinical Trials are a critically important aspect of advancing medical care
- Diversity in clinical trials is important because it enhances the validity and generalizability of the results
  - Potentially avoids unintended consequences down the line
- Diversity in clinical trials is limited due to accessibility of trials; historical patterns of research and relationships between scientific industrial complex and vulnerable populations; provider effects
FRAMING THE PROBLEM: TECHNICAL VERSUS TRANSFORMATIONAL CHALLENGES

**TECHNICAL APPROACH**
- Problem definition is clear
- Solutions provided by leader or experts based on old approaches
- Easy problem: Leaders/experts apply force until change is achieved

**TRANSFORMATIONAL (ADAPTIVE) APPROACH**
- Problem definition is clear
- Solution requires new learning and new skills
- Complex problem: Both leaders and followers are responsible for the solution

Ron A. Heifetz, MD Harvard Kennedy School of Government. *Leadership Without Easy Answers*
THE TECHNICAL APPROACH

The \textbf{CHECKLIST Manifesto}
HOW TO GET THINGS RIGHT

ATUL GAWANDE
Best-selling author of Complications and Better
THE TECHNICAL APPROACH: CULTURAL COMPETENCE

Definitions

- The ability to interact effectively with people of different cultures and socioeconomic backgrounds
- The level of knowledge-based skills required to provide effective clinical care to patients from a particular ethnic or racial group
### Published Barriers to Clinical Trials Participation by Race/Ethnicity

<table>
<thead>
<tr>
<th>Hispanic/Latino Populations</th>
<th>African American Populations</th>
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<tbody>
<tr>
<td>- Fear</td>
<td>- Fear</td>
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<tr>
<td>- History of past abuses/discrimination</td>
<td>- Mistrust of the research and medical system</td>
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<tr>
<td>- Family/work responsibilities</td>
<td>- Hopelessness</td>
</tr>
<tr>
<td>- Poor provider-patient communication</td>
<td>- Family/work responsibilities</td>
</tr>
<tr>
<td>- Limited English proficiency</td>
<td>- Perceived harms of participation</td>
</tr>
<tr>
<td>- Use of folk remedies</td>
<td></td>
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Compiled by Sanya Springfield, Director Center for Reducing Cancer Health Disparities, NIH; 2010
<table>
<thead>
<tr>
<th>Asian American/Pacific Islander Populations</th>
<th>American Indian/Alaskan Native Populations</th>
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<tbody>
<tr>
<td>Different Values</td>
<td>Historical Trauma</td>
</tr>
<tr>
<td>- Who makes decisions?</td>
<td>- Past discrimination</td>
</tr>
<tr>
<td>- Group welfare</td>
<td>- Lack of trust</td>
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<tr>
<td>- Family centrality</td>
<td>- Tribal “taboo” to lose body parts</td>
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<tr>
<td>Degree of acculturation</td>
<td>- Limited English proficiency</td>
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<tr>
<td>- Limited English proficiency</td>
<td>- Other co-morbidities</td>
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<tr>
<td>Mistrust of research</td>
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</tbody>
</table>

Sanya Springfield, Director CRCHD, NIH; 2010
LIMITATIONS OF THE TECHNICAL APPROACH: CULTURAL COMPETENCE

- Static state of achievement; assumes provider mastery of a patient’s culture/lifestyle
- Maintains the power imbalance between providers and patients
- “One-size fits all” approach
- Provides no analytic recourse when interactions do not go as planned
- Fails to recognize broader forms of diversity
- May fail to earn trust
“The medical profession should not focus on making minorities be more trusting; we should focus on ensuring that we are becoming (more) trustworthy.”

THE TRANSFORMATIONAL (ADAPTIVE) APPROACH
Definition

A lifelong process of self-reflection and self-critique. The starting point for such an approach is not an examination of the client’s belief system, but rather having health care providers give careful consideration to their assumptions and beliefs that they bring to, and the goals of, their encounter with the client.

Tervalon & Murray-Garcia, J Health Care Poor and Underserved, 1998
**BENEFITS OF THE CULTURAL HUMILITY APPROACH**

- Breaks down the power imbalance between providers and patients by transforming the provider into a co-learner.

- Allows for consideration of cultural influences (beyond those of race/ethnicity) on the decision to discuss and/or participate in clinical trials.

- Can generate mutual respect, compassion and **TRUST**(worthiness)
GUIDANCE FROM THE LITERATURE: GUESS WHICH POPULATION?

- using multi-recruitment strategies;
- defining the demographic and social profiles of the population to be included;
- using focus groups to identify any potential barriers;
- consulting representative community members to provide assistance in the study;
- ensuring eligibility criteria are set as wide as possible;
- developing educational and recruitment approaches to attract ethnic minority health professionals;
- ensuring health professionals are adequately trained in culturally and ethnically orientated service provision;
- determining the most effective mass media to use in study promotion and recruitment;
- and targeting inner-city, single-handed practices likely to have high ethnic minority populations.

Hussain-Gambles & Leese; Health Tech Assess 2004; Oct 8(42)
INSTITUTIONAL EFFORTS TO INCREASE DIVERSITY AND INCLUSION IN CANCER CLINICAL TRIALS
POTENTIAL TRIAL PARTICIPANTS COME FROM NEAR AND FAR...

Hawk, ET; Habermann EB; Ford JG. Cancer 2014 March; 120 (supp S7).
INSTITUTION LEVEL FACTORS TO INCREASE INCLUSION

- Building relationships outside the institution
  - With community members, advocates and key gate keepers
  - With referring providers

Welcome Community Partners
INSTITUTION LEVEL FACTORS TO INCREASE INCLUSION

- Enhancing the physical environment
  - Increasing signage to raise patient awareness
  - Readily available (language appropriate) information on trials
  - Allocation of space for comfortable setting for discussion
    - Avoid disrupting flow of clinic time
INSTITUTION LEVEL FACTORS TO INCREASE INCLUSION

Did you know?
Asian Americans are the only racial group in the United States who experience cancer as the leading cause of death. Yet, very few join clinical trials. As a result, there is very little knowledge about treatments for Asian Americans. You are the key to finding new treatments that can save lives and help with early cancer detection and prevention. You can help to improve care for Asian Americans. To make progress in the fight against cancer, we need cancer patients, cancer survivors, and healthy people from all backgrounds to participate in clinical trials.

Courtesy of Asian American Network for Cancer Awareness Research and Training, Available at www.cancer.gov/APICEM
INSTITUTION LEVEL FACTORS TO INCREASE ACCRUAL

- Enhancing the organizational culture about clinical trials
  - Is the staff trained on the collection of race/ethnicity and language data from patients?
  - Does everyone on the care team know that a clinical trial is an option for the patient?
  - Is the staff knowledgeable about resources available for trials information?
  - Are there open invitations for patients to discuss trials?
    - Buttons
Successful recruitment requires suitable trials, clinicians who are willing to enroll patients, and effective hand-off of potential participants from clinicians to research coordinators.

(Figure courtesy of Dr. Daniel Dohan, UCSF-IHPS)
“But Institutions cannot build trust; it is individuals within the institution that build trust (worthiness)"

Durant & Wenzel. Cancer 2014; April 1
PROVIDER BASED APPROACHES TO INCREASING DIVERSITY
Race has been the basis for severe and egregious discrimination in the US

- This has occurred in lock step with the development of clinical trials and the health care system
- Consider that the standard patient has long been 70Kg (white) man

Religion and other individual characteristics have also been used to withhold privilege or to discriminate in the past

These facts cannot be changed, but we also cannot ignore them.
Define your own personal culture/identity: ethnicity, age, experience, education, socio-economic status, gender, sexual orientation, religion...

Identify a time when you were granted privilege on the basis of your appearance, the way you talk, who you were with...

Describe a time when you became aware of being different from other people. How did it feel?
OPERATIONALIZING SELF REFLECTION IN THE CLINICAL SETTING

- Call attention to your awareness of the potential fears up front
  - Acknowledge the past history of clinical trials in this country and allow the participant to ask questions or express concerns

- Discuss the possibility that the trial may include a placebo arm, and potential side effects
  - Reassure patients that they will not be treated differently whether they decide to participate or not

- Be clear about time commitments and expectations of the trial
  - While you may be knowledgeable about the trial—you probably have no idea how participation would impact on the participants life circumstances—and try not to guess
But also be clear about the goals of the study, the purpose and importance to the individual as well as to the society at large
  - If there is no benefit to the participant—ADMIT THIS

Don’t demand a commitment right away; but don’t lose touch
  - If possible, provide some time for the participant to think things over
  - Set up a subsequent appointment specifically to discuss trial participation

Be yourself
  - Most people in the vulnerable clinical setting, want to feel human; want to be treated like a human being. This is a guaranteed commonality between you and the patient
**Cultural Competence—Technical Approach**
- Understand barriers faced by patients
- Know that these concepts should not be STRICTLY applied
- Be cautious because one-size does not fit all

**Cultural Humility—Transformational Approach**
- Understand your own cultural perspective (and that of your institution)
- Be aware of how your perspective may influence your interaction with patients

**Bring it all together**
- Remember: there are many different types of diversity
- Listen actively
- Ask questions when unsure
- Be open and willing to learn from the patients
QUESTIONS?
Contact:
Kim.rhoads@stanford.edu

Thank you!