Clinical Trial
Diversification
Better Practices

TOPIC 1(A): DIVERSITY AWARENESS
MATERIALS FOR SPONSORS

These materials were first completed on 10-April, 2015
These materials were last updated on 8-May, 2015
Version 1.1

Disclaimer: The contents of this file are not tailored to any particular factual situation and are provided “as is” without warranty of any kind, express or implied, including but not limited to fitness for a particular purpose. Neither TransCelerate, any of its Members, nor any of their employees accept any responsibility for any loss of any kind including loss of revenue, business, anticipated savings or profits, loss of goodwill or data, or for any indirect consequential loss whatsoever to any person using the Change Management Tools or acting or refraining from action as a result of the information contained in the Change Management Tools. TransCelerate and its Members reserve the right to use the Change Management Tools for their own purposes without restriction. Nothing in this presentation should be construed as legal advice, nor does anything in this presentation imply or warrant that use of this approach complies with applicable laws or regulations. Users implement the approach outlined in this presentation at their own risk, and bear the sole responsibility for ensuring their compliance with applicable laws and regulations in their respective jurisdictions.
This slide deck and the materials contained within it were compiled by the TransCelerate Clinical Trial Diversification team.

**What Was The Clinical Trial Diversification Workstream?**

This workstream aimed to improve the ability of sponsor organizations to achieve trial populations that are representative of the target indication by increasing the racial and ethnic diversity of patients participating in clinical trials.

**What Was The Vision?**

Increased awareness of the need for representative clinical trials and adoption of practices aimed to improve the recruitment and retention of racially and ethnically diverse populations.

**WHAT WAS THE APPROACH?**

- Identify practices and tools that sponsors could adopt and/or modify to improve minority recruitment and retention
- Develop guidance for each of the identified practices including the purpose of the practice and implementation strategies
- Disseminate and raise awareness of the identified practices, tools and guidelines to enhance the Sponsor’s ability to achieve representative clinical trial diversity
- Primary focus on the U.S.
Clinical trial populations are often not reflective of the target population who will use the medicine:

- Drug safety and efficacy can vary across demographic sub-groups
- Minorities have historically been under represented in clinical trial populations
- Addressing the lack of diversity in clinical trial populations is an on-going challenge for sponsors

The status quo is being challenged:

- The racial/ethnic sub-group population is growing and will soon no longer be a minority
- Marketing approvals are expected to become more stringent as regulatory authorities request more representative trial populations
- Patients, physicians and payers are increasingly demanding evidence of sub-group health outcomes
- The drive towards personalized medicine will likely require sponsors to be more expansive in their recruitment practices

KEY QUESTION:
How can sponsors improve racial/ethnic diversity in clinical trial populations to better reflect the targeted population?

Recommendation:
The Clinical Trial Diversification initiative recommend sponsors pro-actively raise awareness and encourage use of practices which reduce the barriers to ethnic minority participation in clinical trials. This presentation provides an overview of the business case and references key practices which can be readily adopted by sponsor study teams.
Objectives and Target Audience

THE OBJECTIVES OF THE FOLLOWING CONTENT IS TO:

Provide sponsor organizations with information and tools to help raise awareness of the need to achieve clinical trial populations which are representative of the target indication.

Content provided in this presentation is intended for sponsor resources responsible for supporting trial execution and / or overseeing aspects of Clinical Operations relating to patients. In particular, those in the following roles:

- Analysis & Reporting
- Reimbursement Oversight
- Clinical Operations
  (Protocol Managers & Site Managers)
- Site Monitors
- Medical
- Site Selection & Recruitment
- Regulatory Affairs
- Study Management
Minorities are Under-Represented in Industry Sponsored Trials

Proportion of Study Volunteers by Race and Ethnicity in Clinical Research Studies[1]

- Total US Population
- NIH Funded Clinical Research
- Industry-Funded Clinical Research

<table>
<thead>
<tr>
<th></th>
<th>All Minorities</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total US Population</td>
<td>36.3%</td>
<td>16.7%</td>
</tr>
<tr>
<td>NIH Funded Clinical Research</td>
<td>36.1%</td>
<td>63.7%</td>
</tr>
<tr>
<td>Industry-Funded Clinical Research</td>
<td>16.7%</td>
<td>63.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83.3%</td>
</tr>
</tbody>
</table>

Industry trials are not subject to the same controls regarding sub-group recruitment as NIH trials.

African Americans represent 12% of the U.S. population but only 5% of clinical trial participants[2]

Hispanics make up 16% of the population but only 1% of clinical trial participants[2]


Clinical trial populations should be diverse and representative of their respective target indication in the general population

CURRENT GUIDANCE

Good Review Practice[1]: Clinical Review of Investigational New Drug Applications:

7.2.5 Racial Groups:
"The database submitted in a marketing application should reflect usage in a diverse racial population, one reflective of the likely patient mix post marketing…"

At time of writing, there are no mandates in terms of what constitutes a diverse / representative population.

FDASIA action plan has been published which identifies future focus areas for the FDA for the collection, analysis, reporting and dissemination of sub-group data.[2]

"Enrollment should reflect the patients most likely to use a medical product. Sponsors should design clinical trials using available information from the relevant medical literature, clinical knowledge base, and health statistics for the disease."[2]

Sponsors are coming under increasing pressure to ensure clinical trial populations reflect the disease state.

Changing pressures to ensure representative diversity in clinical trial populations:

**REGULATORY / POLITICAL**
Regulators are increasingly focused on ensuring trial populations are representative of the indicated population.

**SCIENTIFIC**
The standard practice of generalizing scientific conclusions is challenged by the demand for personalized medicine.

**COMMERCIAL**
In the US, traditional minority populations are growing rapidly and expected to become the majority.

**SOCIAL RESPONSIBILITY**
Broad recognition of the need to develop drugs with all patients in mind.
Sponsors are being encouraged to pay closer attention to their sub-group enrollment targets, efforts and outcomes:

Increased regulatory focus and external pressure on trial population diversity

FDA has published the FDASIA action plan on subgroup inclusion [Link]

Two key FDA efforts may impact how sponsors prioritize their sub-group enrollment efforts:

FDASIA action plan
Drug Trial Snapshots

THERE IS AN OPPORTUNITY TO SHAPE THE ENVIRONMENT BY PROACTIVELY ADDRESSING THESE ISSUES
The Food and Drug Administration Safety and Innovation Act (FDASIA) was:

Signed into law on July 9, 2012, expands the FDA’s authorities and strengthens the agency's ability to safeguard and advance public health.

FDASIA Section 907: Inclusion of Demographic Subgroups in Clinical Trials is intended to:

“Address the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race and ethnicity is included in applications...”

3 PRIORITIES INCLUDING 27 ACTIVITIES WERE IDENTIFIED BY THE FDA:

<table>
<thead>
<tr>
<th>Priority 1: Quality</th>
<th>Priority 2: Participation</th>
<th>Priority 3: Transparency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve completeness and quality of subgroup data collection, reporting and analysis</td>
<td>Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation</td>
<td>Make demographic subgroup data more available and transparent</td>
</tr>
</tbody>
</table>

Potential Impact for sponsors

The FDA are currently formulating how recommendations will be implemented and timelines for completion.

No changes to sponsor practices (specifically mandatory enrollment targets) have yet been made obligatory by the FDA, though the adequacy of existing guidance are currently under review.

During 2015, the FDA will continue to develop proposals by working with stakeholder organizations.
Beginning in 2015, the FDA intends to post a Snapshot for every approved NME and original biologic[1]

The Drug Trials Snapshot project is currently being piloted and is intended to:

Provide information about the sex, age, race and ethnicity of clinical participants

Solicit feedback on the content, format and overall usability of the format

Snapshots will provide information to the public about who participated in the clinical trials for drugs, including:

- Gender, age, race and ethnicity of clinical participants
- How the studies were designed
- Results of the efficacy and safety studies
- Differences in efficacy and side effects among subgroups

Generalizing drug safety and efficacy assessments is standard practice but carries risk:

Drug effectiveness and safety data can vary across patient subgroups (see examples).
Too narrow populations limit our understanding of disease and treatment effectiveness.

Pressure to produce scientifically robust data on demographic subgroups

Increasing focus on personalized medicine.
Greater demand for characterization of ethnic sensitivity to medicines.

Whites are more likely than those of Asian and African heritage to have abnormally low levels of enzyme CYP2D6\(^1\)

Blacks respond poorly to several classes of antihypertensive agents\(^2\)

Racial differences have been noted in skin structure and physiology\(^1\)

Blacks have demonstrated lower responses to interferon-alpha used in the treatment of hepatitis C\(^1\)

---


At present:

There is often limited availability of data to draw conclusions on sub-group outcomes.

Lack of representation can result in a need for additional sub-group studies.

During a 2014 survey, many TransCelerate Member Companies reported experiencing penalties or additional post-approval requirements due to lack of representation in a trial or limited power to determine significant associations among patients in specific subgroup.

1. By 2020, “minorities” are projected to account for over 40% of the nation’s population\(^1\)
2. By 2050, Hispanics will make up to 29% of the U.S. population\(^1\)

**Sponsors are coming under increasing pressure to achieve representative diversity from a number of sources:**

Increasing regulatory scrutiny on appropriate representation of demographic subgroups in clinical trials.

Expanding population of minority consumers.

More consumer and payer driven demand for evidence of patient outcomes in sub-groups.

---

There is an increasing awareness of a broader role companies can play in the welfare of society and the environment:

Patients want reassurance that patients like them have been adequately represented in the clinical trial populations.

Patients are often seeking access to new treatment options, but aren't aware of or invited to participate in clinical trials.

Demographic shifts make it increasingly untenable to have minorities under-represented in clinical trials.
Barriers to Minority Patient Participation in Clinical Trials

A broad range of clinical trial patient participation barriers undermine the ability of sponsors to achieve representative diversity.

Clinical Trial Participation Barriers originate from multiple sources

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Site</th>
<th>Patient</th>
<th>Societal / environmental compounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited understanding of what the patient wants or needs to participate</td>
<td>Lack of minority investigators and research staff</td>
<td>Practical obstacles to participation</td>
<td>Qualified subjects are not always offered the opportunity to participate</td>
</tr>
<tr>
<td>Low willingness to work with research naïve sites/investigators</td>
<td>Site start up costs are expensive</td>
<td>Lack of trust in pharma and medical research</td>
<td>Research naive sites are over looked despite having clinical trial potential</td>
</tr>
<tr>
<td></td>
<td>Lack of referral to trials</td>
<td>Low health literacy/language barriers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of community engagement</td>
<td>Lack of awareness of trials</td>
<td></td>
</tr>
</tbody>
</table>
Six focus areas have been identified in which sponsors can take steps to improving minority recruitment

1. **Awareness**
   - Educating and increasing awareness on the need for diverse trials that are representative of target population

2. **Patient Engagement**
   - Providing guidance on the use of patient engagement techniques to strengthen protocol design and clinical trial feasibility.

3. **Cultural Competency**
   - Highlighting the value of understanding cultural differences and the ability to communicate effectively with broad populations. Also, summarizing available training.

4. **Reimbursement**
   - Providing insights from Institutional Review Boards on reimbursement for patient clinical trial participation.

5. **Informed Consent Short Form Guidance**
   - Providing guidance on the use of the informed consent short form, including when it should be used and how it should be used.

6. **Community Engagement Toolkit**
   - Providing sites with a suggested process to better engage with and build relationship with their community including templates for initiating communication.
In order to frame the problem which is being addressed, a summary of the business need, barriers and suggested solutions to minority enrollment has been created for use by a range of stakeholders within sponsor organizations and sites.
# Patient Engagement

## Issue
- Lack of adequate trial diversity
- Patients are not consulted when trial teams are determining a trial's clinical plan
- Patients are not fully aware of clinical trials as potential treatment options

## Consequence
- Lack of full understanding of treatment safety and efficacy
- Lower recruitment and retention rates
- Outcomes that are meaningful to the patient are not captured
- Potentially fewer treatment options available to patients

## Remediation
- Patient engagement throughout the development lifecycle can help identify actionable insights to help address underlying causes of inadequate trial diversity

### Disease Prioritization
- Identify priority diseases and therapies by seeking advice from patients/patient advocates

### Patient Enrollment
- Drive recruitment through outreach to patients, community and providers

### Patient Education
- Relay trial results to the broader patient community

### Disease Insight
- Provide patient perspective on unmet medical need and burden

### Trial Design & Optimization
- Identify participation barriers, provide input on trial endpoints, risk/benefit preference

### Mid-trial Assessment
- On-going assessment of trial progress

### Post Mkt Approval
- Provide continued support for post-market surveillance initiatives

---

*Copyright ©2015 TransCelerate BioPharma Inc.*
Adapting to the social and cultural influence on patients' beliefs and behaviors can help sponsors better connect with their patients and support their needs.

- Awareness of unique, and defining characteristics of various populations
- Recognition of the importance of social and cultural influences on patients' health beliefs and behaviors
- Expression of the researcher's awareness in their actions and the incorporation into the research design, conduct and interpretation

Cultural Competency

**CORE CAPABILITIES:**

- Value Diversity
- Acquire & Institutionalize Knowledge
- Assess Competency
- Manage Differences
- Ensure Adaptability

**BEFTER PRACTICES:**

**SPONSORS**

- Design clinical plans which better meet the practical needs of patients (e.g. visit designs, etc.)
- Prepare informed consent documentation and other patient literature
- Offer sites / PIs culturally appropriate tools to better engage patients

**INVESTIGATORS**

- Improve awareness of where / how to locate patient populations
- Increase recognition within patient groups of clinical trials being applicable to them
- Improve patient engagement through culturally appropriate communication
- Increase the likelihood of enrolling patients and obtaining informed consent
- Improve patient retention
Use of reimbursement and compensation is recommended for clinical trial participation, as it may have a disproportionately beneficial impact on retention for those with lower incomes. However, sponsors sometimes lack a clear understanding of what is acceptable vs. coercive payment. Here, IRBs provide their perspectives on the matter:

**IRB Guidance Summary:**
- Some form of reimbursement or compensation is encouraged but not required
- Reimbursement and/or compensation should be applied equally to all study patients
- Compensation based on level of risk is discouraged or disallowed
- Expedited payment methods such as third party debit cards are encouraged but patients should have the ability to opt for direct payment
- In addition, specific informed consent language should be included in advance

In addition, reimbursement is different to compensation and each has their own definitions regarding acceptable practice:

<table>
<thead>
<tr>
<th>REIMBURSEMENT</th>
<th>COMPENSATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Payment for actual expenses incurred</td>
<td>• Payment for time required to participate in the study</td>
</tr>
<tr>
<td>• Usually limited to travel and meal costs for attending study visits</td>
<td>• Should be paid accordingly to pre-determined hourly or per-procedure rates</td>
</tr>
<tr>
<td>• Amounts are typically capped for specific modes of transportation and/or per visit totals with review process to make exceptions for excessive travel</td>
<td>• Consider not compensating for screening visits and adding a larger payment at the end for study completion</td>
</tr>
</tbody>
</table>
Informed Consent Short Form Guidance

Consent form wording complexity and document length can reduce clinical trial participation rates\(^1\). The Short Form accompanied by a presentation offers a more patient-friendly option for obtaining consent:

<table>
<thead>
<tr>
<th>IF...</th>
<th>THEN...</th>
</tr>
</thead>
<tbody>
<tr>
<td>A subject or their legally authorized representative:</td>
<td>The Short Form process may be considered for use(^2):</td>
</tr>
<tr>
<td>1. Is unable to read or understand English or</td>
<td>1. Information contained in the consent long form must be orally presented, with assistance from an interpreter if needed, in the same quantity and quality in person or via video recording</td>
</tr>
<tr>
<td>2. Is unable to read due to illiteracy or blindness or</td>
<td>2. Presentation must be witnessed by an impartial person not otherwise connected with the clinical investigation</td>
</tr>
<tr>
<td>3. Has low literacy and/or numeracy</td>
<td>3. Short form is signed after the presentation</td>
</tr>
<tr>
<td></td>
<td>4. Subject is provided with a translated version of the written summary (usually the long consent form) and a copy of the short form</td>
</tr>
<tr>
<td></td>
<td>5. Witness must sign both the short form and the written summary. Person obtaining consent must sign the written summary.</td>
</tr>
</tbody>
</table>

**CONSENT SHORT FORM SUMMARY**

- 2-3 pages
- Translated versions only need to be prepared once (Generic content)
- Easier for the subject to comprehend
- May enable non-English speaking patients to be enrolled in trials as quickly as English-speaking patients

<table>
<thead>
<tr>
<th>RESPONSIBLE</th>
<th>SIGN AND DATE</th>
<th>PROVIDE DOCUMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>Copy of IRB-approved English version of long form (written summary)</td>
<td>File copy of signed short form and English version long form</td>
</tr>
<tr>
<td>Subject</td>
<td>Short form</td>
<td>IRB-approved, translated short form, English version of long form, and later, translated long form.</td>
</tr>
<tr>
<td>Witness (Interpreter may serve as witness but not person obtaining consent)</td>
<td>Short form and copy of IRB-approved English version of long form (summary)</td>
<td></td>
</tr>
</tbody>
</table>


Community Engagement Toolkit

PURPOSE
To provide a simple step-by-step process for sites to improve minority patient recruitment by:

- Engaging their community
- Raising awareness about clinical trials
- Providing access to clinical trials
- Educating and supporting the community they serve

TOOLS
Contents of the toolkit include:

- Guidance for study teams to rollout the toolkit
- Templates for initiating contact with organizations
- List of organizations serving diverse populations
- List of clinical research organizations providing support materials

COMMUNITY ENGAGEMENT APPROACH:

EXPLORE
- Understand community needs and health issues
- Identify appropriate community leaders, members and organizations

CONNECT
- Contact and engage community leaders, members and organizations

ASSESS
- Identify and assess areas of common needs and collaboration opportunities

MAINTAIN
- Build a rapport
- Stay connected
- Share information
- Provide feedback
The TransCelerate Clinical Trial Diversification Team concluded its efforts in Q2 2015. However, the following team members have offered to act as points of contact for further enquiry on each of the better practice focus areas:

**Contact Information**

For general questions regarding the Clinical Trial Diversification workstream, please contact Jonathan.zung@ucb.com

### Awareness:
- Jill Abell (Janssen)
  jabell2@its.jnj.com

### Patient Engagement:
- Lori Abrams (BMS)
  lori.abrams@bms.com

### Cultural Competency:
- Dejuana Hall (Lilly)
  hall_dejuana_p@lilly.com

### Reimbursement:
- Nariman Nasser (Genentech)
  nasser.nariman@gene.com

### Informed Consent Short Form:
- Theresa Devins (Boehringer Ingelheim)
  theresa.devins@boehringer-ingelheim.com

### Community Engagement Toolkit:
- Karen Brooks (Pfizer)
  karen.brooks@pfizer.com or
- Kelly Kirsch (Lilly)
  kirsch_kelly@lilly.com

For general questions regarding the Clinical Trial Diversification workstream, please contact Jonathan.zung@ucb.com
Appendices
“American Indian or Alaska Native” refers to a person having origins in any of the original peoples of North and South America (including Central America) and who maintains tribal affiliation or community attachment. This category includes people who indicated their race(s) as “American Indian or Alaska Native” or reported their enrolled or principal tribe, such as Navajo, Blackfeet, Inupiat, Yup’ik, or Central American Indian groups or South American Indian groups.

“Asian” refers to a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. It includes people who indicated their race(s) as “Asian” or reported entries such as “Asian Indian,” “Chinese,” “Filipino,” “Korean,” “Japanese,” “Vietnamese,” and “Other Asian” or provided other detailed Asian responses.

“Black or African American” refers to a person having origins in any of the Black racial groups of Africa. It includes people who indicated their race(s) as “Black, African Am., or Negro” or reported entries such as African American, Kenyan, Nigerian, or Haitian.

“Hispanic or Latino” refers to a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race.

“Native Hawaiian or Other Pacific Islander” refers to a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. It includes people who indicated their race(s) as “Pacific Islander” or reported entries such as “Native Hawaiian,” “Guamanian or Chamorro,” “Samoan,” and “Other Pacific Islander” or provided other detailed Pacific Islander responses.

“Some Other Race” includes all other responses not included in the White, Black or African American, American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander race categories described above. Respondents reporting entries such as multiracial, mixed, interracial, or a Hispanic or Latino group (for example, Mexican, Puerto Rican, Cuban, or Spanish) in response to the race question are included in this category.

“White” refers to a person having origins in any of the original peoples of Europe, the Middle East, or North Africa. It includes people who indicated their race(s) as “White” or reported entries such as Irish, German, Italian, Lebanese, Arab, Moroccan, or Caucasian.
Patient Barriers

Lack of trust:
- Historical mistreatment of minorities
- Fear of being used as a guinea pig
- General negative perception of industry and gov’t

Lack of awareness:
- Not aware of CT in general
- Not aware of how CT advance medical care

Practical obstacles:
- Lack of transportation, childcare, unpaid leave, etc.

Study eligibility criteria:
- Existing medical conditions, concomitant medications

Cost / lack of insurance:
- Fear of out of pocket expenses not covered by their benefit plan

Language / linguistic differences:
- Many U.S. clinical trials require English proficiency

Low Literacy:
- Complex and technical consent forms
- Concerns about loss of control and legal rights once consent signed

Lack of understanding of benefits:
- No clear immediate benefit.
- Long-term benefits unknown
Investigator / Physician Barriers

Did you know:
• 50% of all registration trials occur in 10 states?
• 52% of all FDA drug trials occur in 1.2% of zip codes?
• Minority Serving Site is defined as a site in which >25% of subjects are from minorities

Lack of minority investigators and site staff:
• Minority patients may prefer or place greater trust in minority physicians
• Sponsors are hesitant to recruit research naïve investigators limiting change in the profile of investigators

Lack of physician awareness
• Physicians who are not affiliated with research institutions may be less aware of ongoing trials, the referral process and patient eligibility

Lack of patient referral to a trial:
• Misassumptions about patient eligibility
• Concerns over administrative / financial burdens for referral
• Inability to have readily available information on all trials to make referrals

Lack of community engagement:
• Physicians may lack cultural awareness of the population they serve

Inability to navigate the trial landscape:
• Ability of the primary physician (and patient) to help identify appropriate trials and support the patient throughout trial is hindered by trial complexity
• Time/Personnel issues
• Limited Start up funding
Additional Factors

Regulators
The FDA provides guidelines on the standardization of data collection of racial and ethnic minorities participating in clinical trials without requiring appropriate racial and ethnic inclusion. Compliance with this guidance has been optional and low.

IRBs
Knowledge of disparity criteria when reviewing and approving protocols