MULTI-REGIONAL CLINICAL TRIALS

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

ACHIEVING DIVERSITY, INCLUSION, AND EQUITY IN CLINICAL RESEARCH

Toolkit

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Toolkit

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About the *Toolkit* Supplement

The *Toolkit* is a supplementary resource for the *Achieving Diversity, Inclusion, and Equity in Clinical Research* Guidance Document. The tools, checklists, and case studies in the *Toolkit* are practical and actionable resources that are based on the recommendations from the Guidance Document and are not designed to be prescriptive nor determinative. Further, we were selective in which tools we chose to include: if good resources were already available elsewhere, we did not attempt to duplicate or include here. The resources within are intended to be adapted and modified to accommodate the clinical trial, site, protocol, and context. We appreciate that every trial has an intended participant population that may have different needs and require different approaches. We hope that the *Toolkit* will be of benefit for sponsors, contract research organizations (CROs), sites, investigators, study teams, and participants.

The *Toolkit* is a living document that will benefit from iterative and continuous improvements to its existing resources, as well as the development of new resources. We hope that users will share feedback, specific applications for use, and examples of successes and challenges in using the tool. We welcome suggestions, additions, and proposed changes. Please share feedback with the MRCT Center at mrct@bwh.harvard.edu.

Introduction to Logic Models

What is a logic model?

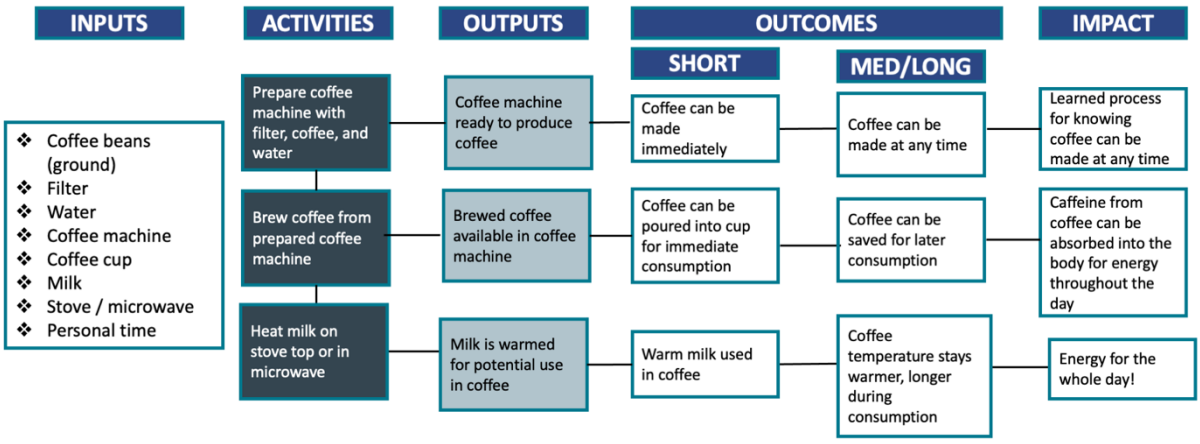
A logic model is a visualization of a program and presents the relationships between inputs (resources), activities, outputs, outcomes and impact of the program. Essentially, logic models visualize the inputs of a program and their desired effects. Logic models often have predefined categories to link resources and inputs into activities, and outputs into effects, outcomes and impacts. Logic model construction an integral component in the "Describe the Program" step in the U.S. Centers for Disease Control and Prevention's {CDC) Program Evaluation Framework (see Figure 1).[1]

Figure 1: The CDC's Program Evaluation Framework. Logic models would fall into the framework's "Describe the Program component" step.

Available at:
https://www.cdc.gov/eval/steps/step2/index.htm

A simple, everyday example of how to apply a logic model is depicted in Figure 2 below:

Figure 2: A simple example of a logic model - making coffee



[1] Logic Models. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/eval/logicmodels/index.htm. [Accessed on 30 June 2020].

According to the CDC, logic models have a number of uses, listed below:

- Communicate the purpose of the program and expected results.
- Describe the actions expected to lead to the desired results.
- Become a reference point for everyone involved in the program.
- Improve program staff expertise in planning, implementation, and evaluation.
- Involve stakeholders, enhancing the likelihood of resource commitment.
- Incorporate findings from other research and demonstration projects.
- Identify potential obstacles to program operation so that staff can address them early on.

How can logic models inform performance indicators?

Performance indicators are measurable information used to determine if a program is being implemented as expected and achieving its desired effects.[2] Logic models describe the inputs, activities, outputs, outcomes and impacts of a program in discrete language. In this way the models provide a useful tool for constructing indicators tied directly to that language.

Indicators can be developed for any component of a logic model. For example, an indicator could be constructed to measure whether an activity's output has been achieved, or whether its long-term outcome has been achieved. In either case, indicators can be based directly on the logic model to measure whether program activities are being conducted as planned, and whether the program's desired effects are being achieved.

What is the purpose of logic models in the Diversity Toolkit?

The purpose of the constructed logic models is to describe activities proposed throughout the Guidance Document in discrete frameworks. These logic models should help to conceptualize activities to promote diverse inclusion within a particular clinical research domain (i.e., workforce development, site selection, etc.). Furthermore, along with the proposed indicators, the logic models should help in considering measurement of diverse inclusion activities. Essentially, **these logic models aim to help operationalize the numerous recommendations made in the *Achieving Diversity, Inclusion, and Equity in Clinical Research* Guidance Document, so that diversity-related initiatives can be seamlessly embedded into an existing clinical research program.**

Key elements to consider prior to use of these logic models:

- **Non-exhaustive** – each logic model contains a non-exhaustive list of activities pertaining to the specific domain of diverse inclusion in clinical research (i.e., workforce development, patient engagement, study design, etc.).

[2] Indicators. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/eval/indicators/index.htm. [Accessed on 30 June 2020].

- **Audience** – the audience for each logic model has been defined and presented. The activities displayed in these sample logic models pertain to that particular stakeholder, though this should not limit use more broadly.
- **Scope** – all logic models emphasize activities that strive to increase the diversity of clinical trial populations. However, the scope of activities varies across each logic model provided. Some apply the lens of diversity to activities that are routine, with well-established processes (see "Logic model for Study Design"). Others include activities that are somewhat novel, recommended in the Guidance Document, and therefore their processes must be considered more carefully (see "Logic model for Workforce Development").
- **Adaptability** – as each logic model contains a non-exhaustive list with a defined audience and scope, each can be adapted to the unique needs and programs of the particular stakeholder at hand. The blank logic model is provided for this purpose.
- **Measurement definitions required** – in translating logic model components to performance indicators used for measurement, an important step is to define key terms within the logic model and/or indicators. For example, a logic model output might be that "comprehensive diversity & inclusion trainings are available at the organization," and the associated output indicator to measure the reach of the initiative is the "number of employees that received a comprehensive D&I training." In order to operationalize this measurement, a "comprehensive D&I training" must be defined. Defining concepts is an integral part of using logic models and indicators, and further allows for the adaptation of these models to a particular organization's needs.
- **Intersectionality** – note that in the aim to have a clearly defined scope, these logic models may overlook some of the intersectionality between very interrelated domains of the clinical research enterprise, within a particular organization or between organizations. Logic models may be linked, as the outcomes of one logic model might provide the inputs of another (i.e., study design materials are required as inputs during study conduct and recruitment). Again, given the adaptability of these models, these tools can be used to better capture interrelationships present at particular organizations.

As always, we welcome any and all feedback on this set of tools at mrct@bwh.harvard.edu.

Blank Logic Model – for download

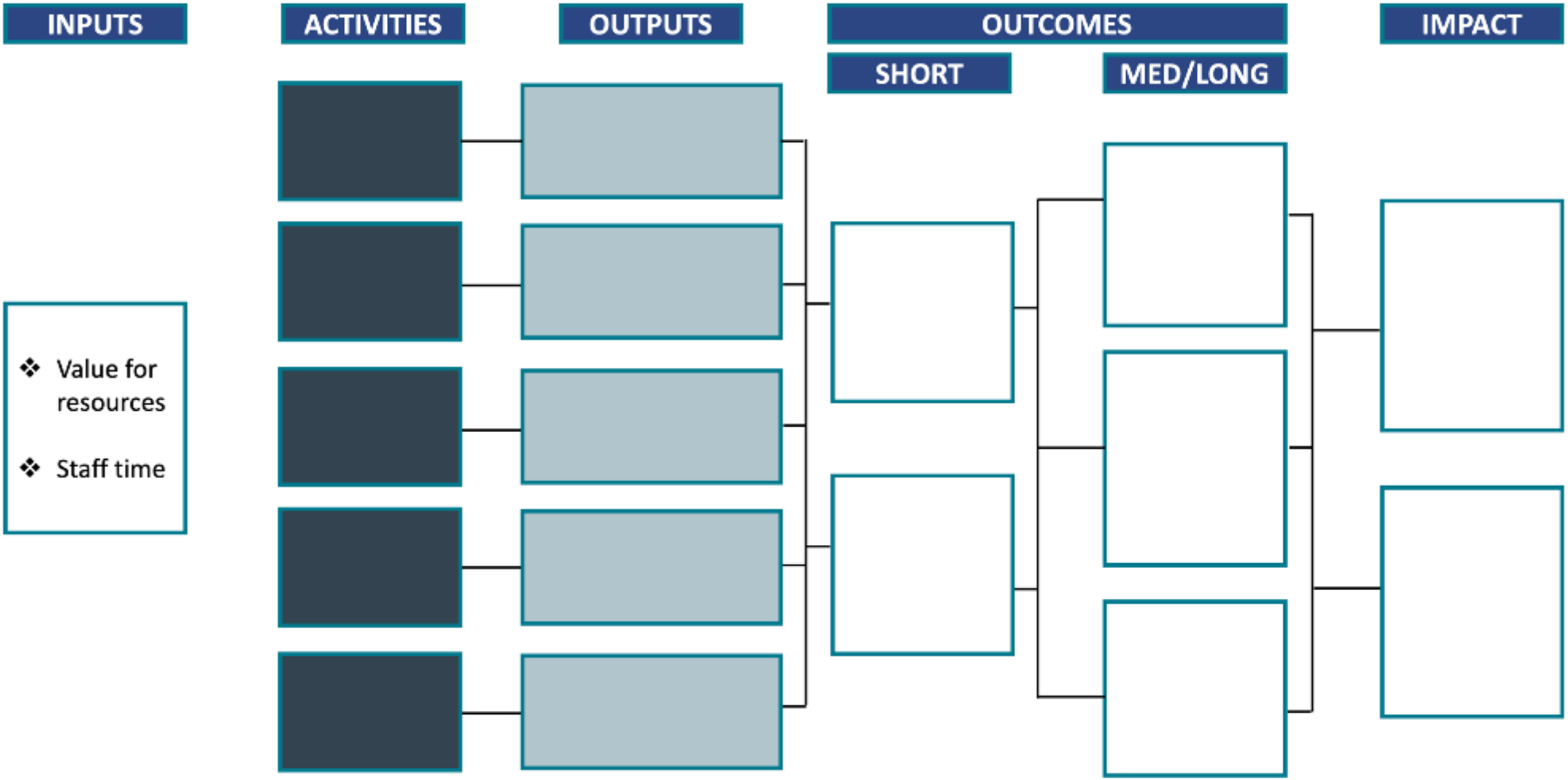
Audience: All stakeholders

Purpose: To provide a template for stakeholders to develop logic models tailored to their unique needs and programs

Considerations for use:

- See *Introduction to logic models* for detailed instruction on the use of logic models in general and in the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.
- The set of logic models provided within the document (with defined scope and audience) can be used as a reference in developing organizationally-tailored logic models using this template.

Blank Logic Model – for download



Comprehensive Logic Model: Parts C, D, E of Guidance Document

Audience: Sponsors/CROs

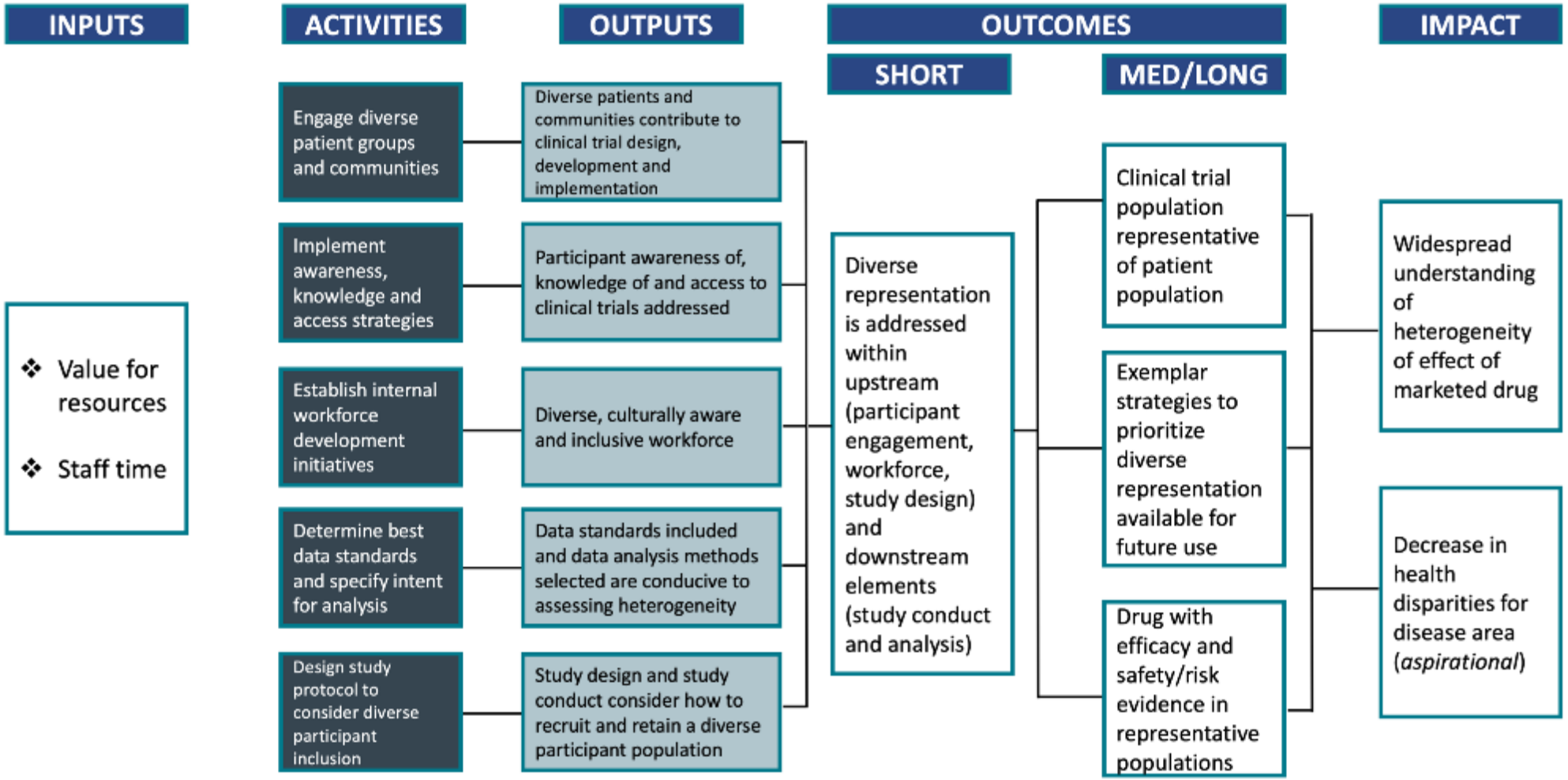
Purpose: To provide a high-level operational overview of the activities being proposed in Parts C (Broadening Engagement), D (Data Standards and Analysis), and E (Study Design, Conduct, and Implementation) of the Guidance Document, linking these activities to their intended effects (outputs, outcomes and impact).

Considerations for use:

- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.
- This particular logic model is especially high-level, presenting the strategy types within the clinical research domains covered in these sections of the *Guidance Document*. This is useful as an organizational framework but lacks the granularity of other logic models contained in the document possess.

Comprehensive Logic Model: Parts C, D, E

Audience: Sponsors/CROs



Logic Model: Participant & Community Engagement

Audience: Sponsors/CROs, sites/investigators

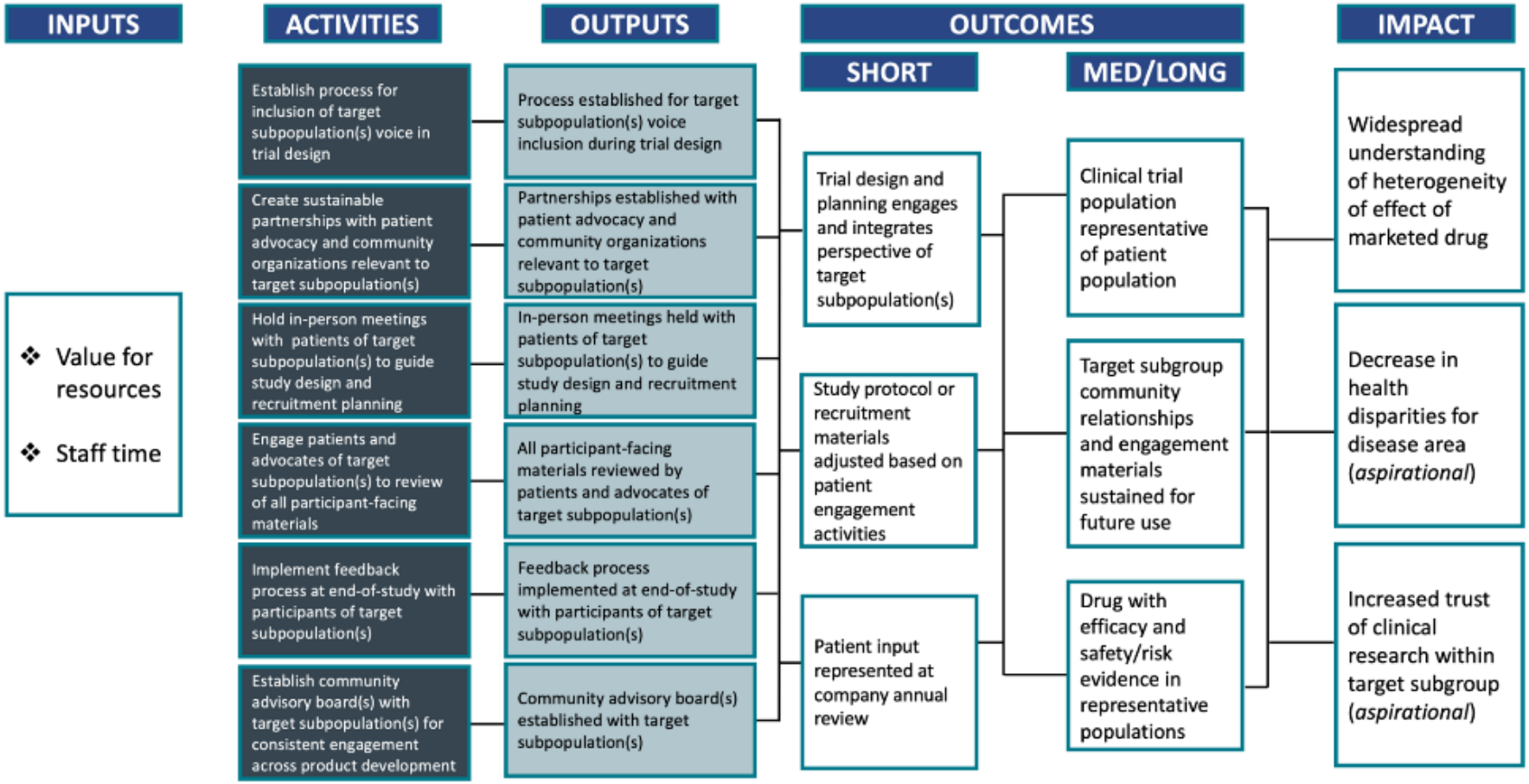
Purpose: To provide a sample of activities, linked to their intended effects (outputs, outcomes and impact), that might be included in a diversity-oriented community and patient engagement strategy during clinical research. A non-exhaustive sample of key performance indicators for such astrategy is also provided in order to demonstrate how this logic model can be used to construct performance metrics.

Considerations for use:

- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.

Logic Model: Participant & Community Engagement

Audience: Sponsors/CROs, sites/investigators



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Participant & Community Engagement – Potential Key Performance Indicators (KPIs)

Output indicators

- ☐ Process established for target subpopulation(s) to voice inclusion during trial design
- ☐ Number of partnerships established with patient advocacy and community organizations relevant to target subpopulation(s)
- ☐ Number of in-person meetings held with patients of target subpopulation(s) to guide study design and recruitment planning
- ☐ Proportion of participant-facing materials reviewed by patients and advocates of target subpopulation(s)
- ☐ Proportion of clinical trials with patient feedback processes at the end-of-study with patients of target subpopulation(s)
- ☐ Community advisory boards established for target subpopulation(s)

Outcome indicators

- ☐ Adjustment to study protocol and/or recruitment materials made based on target subpopulation(s) engagement activities
- ☐ Target subpopulation(s) input represented at annual review
- ☐ Proportion of subpopulation(s) relationship sustained across more than one trial

Diverse Participant Engagement Strategies

A checklist for sponsors, CROs and investigators on the four stages of clinical research

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Priority setting

- [ ] Build relationships with communities of potential participants
- [ ] Ensure essential research questions are relevant to target population
- [ ] Ensure outcomes are relevant and meaningful to target population
- [ ] Incorporate participant voice in study decision-making

Study design

- [ ] Incorporate novel study designs that support diverse enrollment
- [ ] Implement review processes for informed consent and outcome measures
- [ ] Utilize social networks to aid in study recruitment

Conduct

- [ ] Create understandable, health literate study materials in languages relevant to target population
- [ ] Nurture patient and researcher/study team relationship

Dissemination

- [ ] Create understandable, health literate dissemination materials in languages relevant to target population
- [ ] Interpret study results for patients from diverse backgrounds
- [ ] Prioritize outreach to additional audiences
- [ ] Share results widely, considering all types of media outlets

Adapted from: Greenhalgh T, Hinton L, Finlay T, Macfarlane A, Fahy N, Clyde B, Chant A. Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. Health expectations: an international journal of public participation in health care and health policy. 2019; 22(4):785-801.

Awareness Raising Initiatives to Promote Diverse Participant Engagement: a model checklist for implementers

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Build community and local partnerships

- [ ] Reach out to local institutions, groups, community leaders, clinics and clinicians
- [ ] Create community advisory boards to inform research design and outcomes
- [ ] Hire and train community members as staff
- [ ] Attend and integrate into community events, when possible

Provide educational activities

- [ ] Host a luncheon, health fair or expo for the community or hospital
- [ ] Provide on-site educational programs and print materials

Advertising strategies

- [ ] Create understandable, health literate study materials in languages relevant to target population
- [ ] Place study adverts in locations frequented by the target study population
- [ ] Consider all places media outlets: radio, TV, internet and social media

Integrate research into everyday life

- [ ] Consider decentralizing the trial to ease direct participation requirements
- [ ] Provide necessary provisions to encourage participation (i.e., transport or refunds) and reduce burdens
- [ ] Maintain a consistent presence in the community or with the target population.

Logic Model: Workforce Development

Audience: Sponsors/CROs, sites/investigators

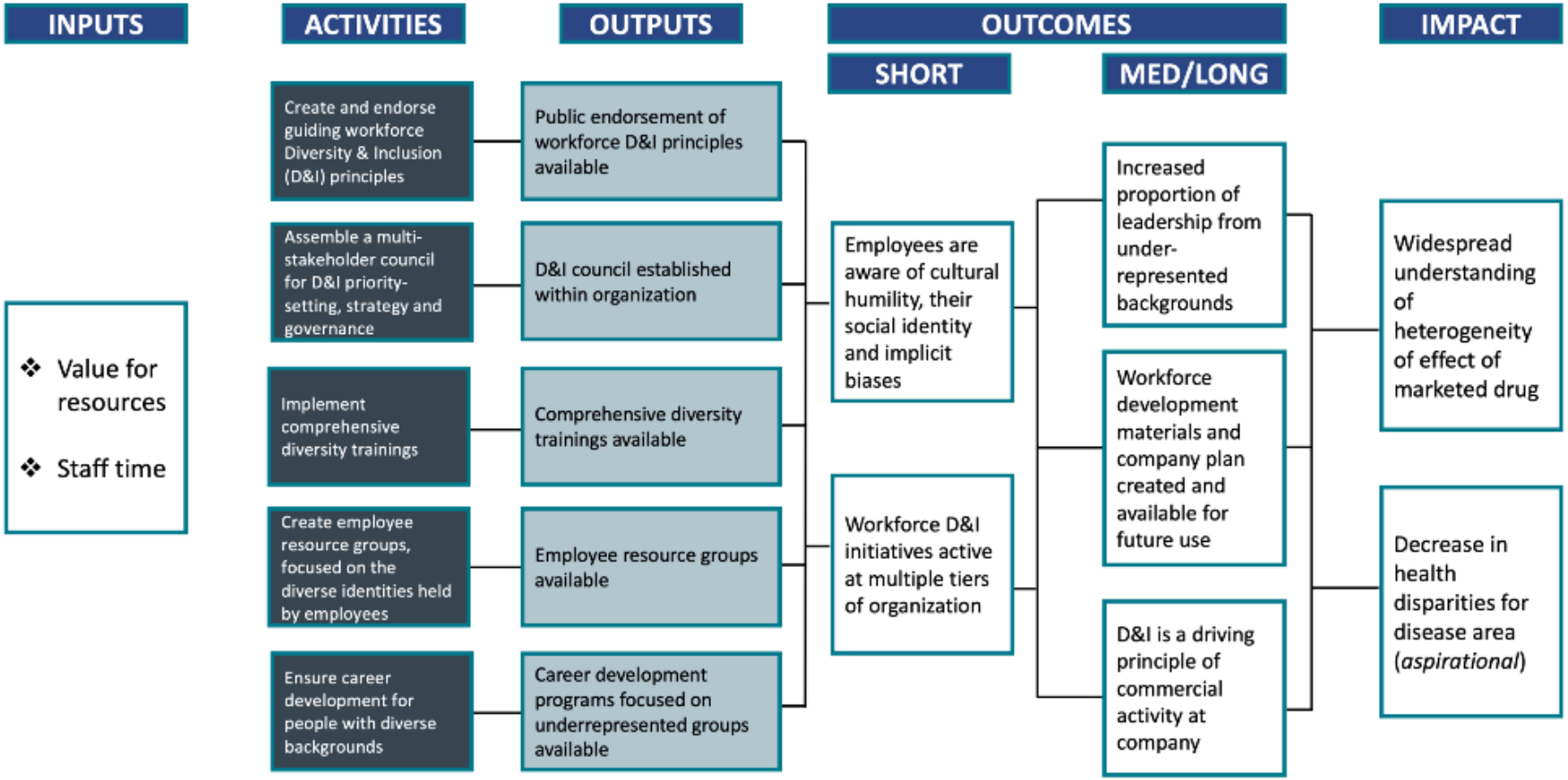
Purpose: To provide a sample of activities, linked to their intended effects (outputs, outcomes and impact), that might be included in a **workforce development strategy** within any organization. The "Measurement Mapping" schematic provides a detailed flow for translating particular activity outputs into both performance and process indicators. A non-exhaustive sample of key performance indicators for such a strategy is also provided in order to demonstrate how this logic model can be used to construct performance metrics.

Considerations for use:

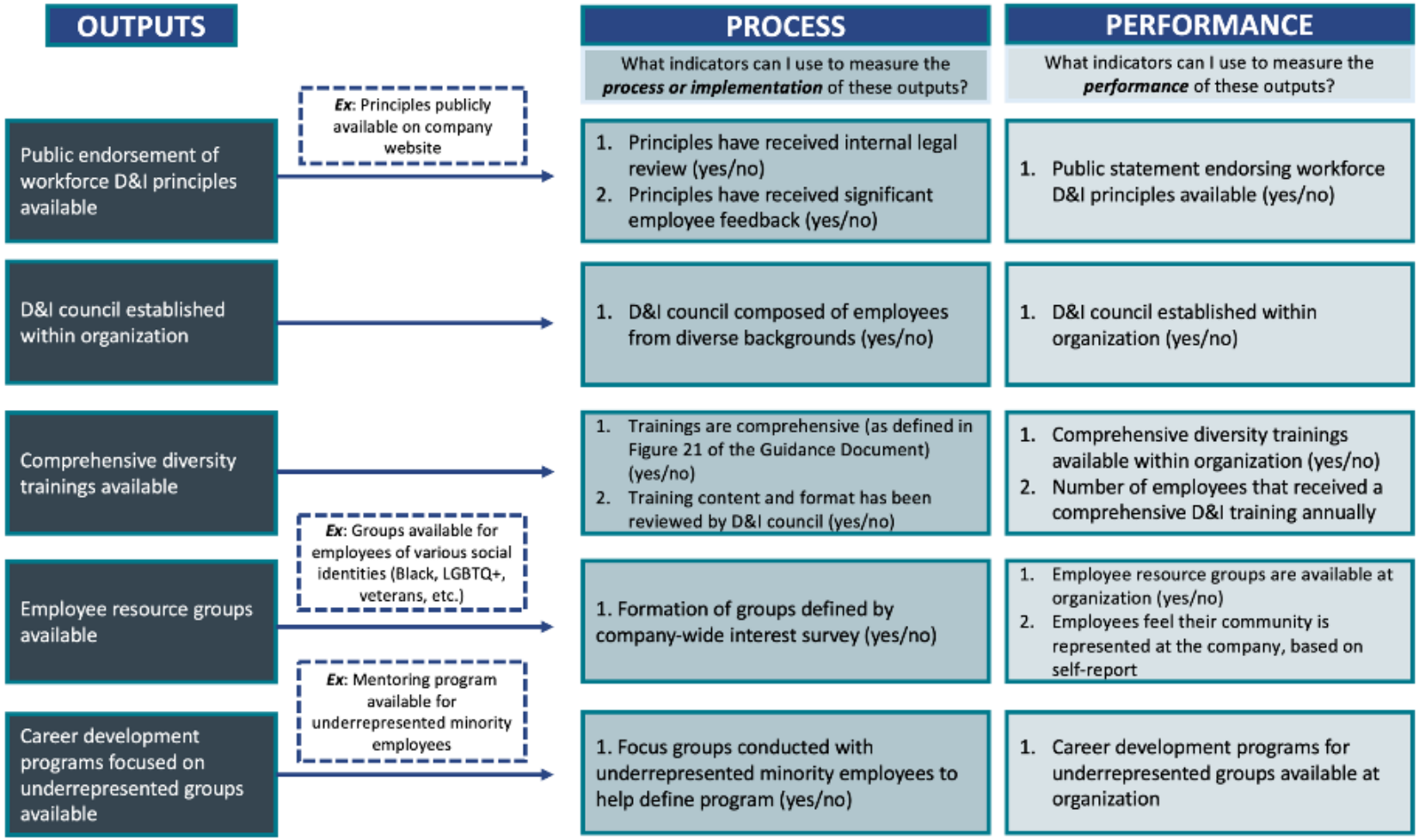
- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.
- This logic model and associated schematic captures the process that can be used to translate any of the activities from any generic logic model into specific indicators (either performance or process) and can be used for reference when adapting these tools to a particular stakeholder organization.

Logic Model: Workforce Development

Audience: Sponsors/CROs, sites/investigators



Measurement Mapping: Workforce Development



Workforce Development – Potential Key Performance Indicators (KPIs)

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Output indicators

- ☐ Public statement endorsing workforce D&I principles available
- ☐ D&I council established within organization
- ☐ D&I council develops comprehensive workforce D&I strategy
- ☐ Employee resource groups available at organization
- ☐ Number of employees that received a comprehensive D&I training annually
- ☐ Career development programs for underrepresented groups available at organization

Outcome indicators

- ☐ High attendance of D&I programs across employee type
- ☐ D&I principles cited in departmental SOPs
- ☐ Increased proportion of leadership from underrepresented demographics
- ☐ Increased self-reported understanding of cultural humility, social identity and implicit bias on company-wide survey
- ☐ D&I principles cited in commercial strategy

Data Variables Tool: Identifying and Collecting Data Variables

Currently, the collection of data variables as part of clinical research lacks uniformity, limiting the ability to capture results in a granular enough manner to accurately represent diverse populations and thus subsequently analyze within a study and compare across studies aggregate results, and assess heterogeneity of treatment effect across different subgroups. While all variables need not be collected for every research study, those that are dependent upon the nature and objectives of the research study should be collected using data standards that are as universal as possible (see *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document* Section 11.1, Data Variables and Collection, Background). The process by which data variables will be collected and the collection tool used to record data variables should be identified during study design and protocol development. This tool provides:

1) A framework to assist study designers in identifying relevant demographic/non-demographic data elements (Figures 1-3). The framework itself can be applied to any data element that will be collected as part of a research protocol.
2) A Data Collection Tool for baseline demographic variables (Figure 4). The Data Collection Tool serves as a template that sponsors and investigators can adapt and use when creating their own study specific data collection forms. The Data Collection Tool derives from previous work done by Clinical Data Interchange Standards Consortium (CDISC).[1]
3) An Aggregate Reporting Tool template (Figure 5) to be used for categorization and reporting of demographic information to regulatory authorities, oversight bodies and clinical trial registries.

Several important guiding features should be considered throughout this process:

- Data are most useful if collected at the most granular level. For example, when collecting age, a date of birth should be collected versus asking participants to categorize themselves into an age group (e.g., 20-29 years old, 30-39 years old). Data can be categorized and/or aggregated at the end of the study for different purposes, including regulatory submission or publication.
    - Some countries and regions limit the amount of personal data that may be collected. For example, in France there are limitations[2] to collecting date of birth due to privacy laws, in which case the data can be collected as year of birth (collected) and age (collected or derived).
- Demographic data variables should be self-reported. Self-report can mean that the participant completes a data collection form or that the researcher asks the participant a question and then records the answer that is given. Researchers should not assume answers regarding demographic information and should be trained on scripted, standardized methods for collection. Clear instructions in respectful, plain language should be provided to the participant.

[1] See online resources at: www.cdisc.org

[2] PHUSE Data Transparency Working Group – Recommendations for GDPR Compliancy: Version 1.0, 1-Apr-2020: https://www.phusewiki.org/docs/WorkingGroups/Deliverables/Recommendations%20for%20GDPR%20Compliancy-%20PHUSE%20Data%20Transparency%20Working%20Group.pdf [Accessed on 2020-06-10]

- Study designers should be sensitive to cultural distinctions in racial classification systems across different regions. For example, it is not allowed to collect "race" data in certain countries (see *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document* Section 11.1, Data Variables and Collection, Background), but is legally required in others.

For additional information regarding demographic variables, please see Chapter 11 of the *Achieving Diversity, Inclusion, and Equity in Clinical Research* Guidance Document.

Ultimately, standardized data collection in a common electronic format would permit data to be structured in such a way that could be uploaded directly to regulatory authorities, oversight bodies (e.g., IRBs/RECs), data repositories, and clinical trial registries (e.g. ClinicalTrials.gov, EudraCT and other national registries). We recommend a similar, defined approach be utilized for every category of data and every datum element, with particular attention to whether there may be differences in diverse populations.

A four-stage approach to data collection:

Figure 1 annotates a four-stage approach to consider: (a) **which demographic and non- demographic variables** should be collected for a specific protocol; (b) the necessary level of **granularity of the data**; (c) the standardized collection method, tool, and format for **data collection**; and (d) approaches to data aggregation for **reporting**. This framework can be used to assist study designers in identifying relevant demographic and non-demographic data elements that will be collected as part of a research protocol. Two examples of applying this approach are given (Figure 2, 3). Figure 2 (race) is representative of a demographic variable that is well delineated in CDISC standards, while Figure 3 (gender) is an example of an element that is far more sensitive, inconsistent, and dependent on the protocol itself.

Figure 1: A four stage approach to data collection

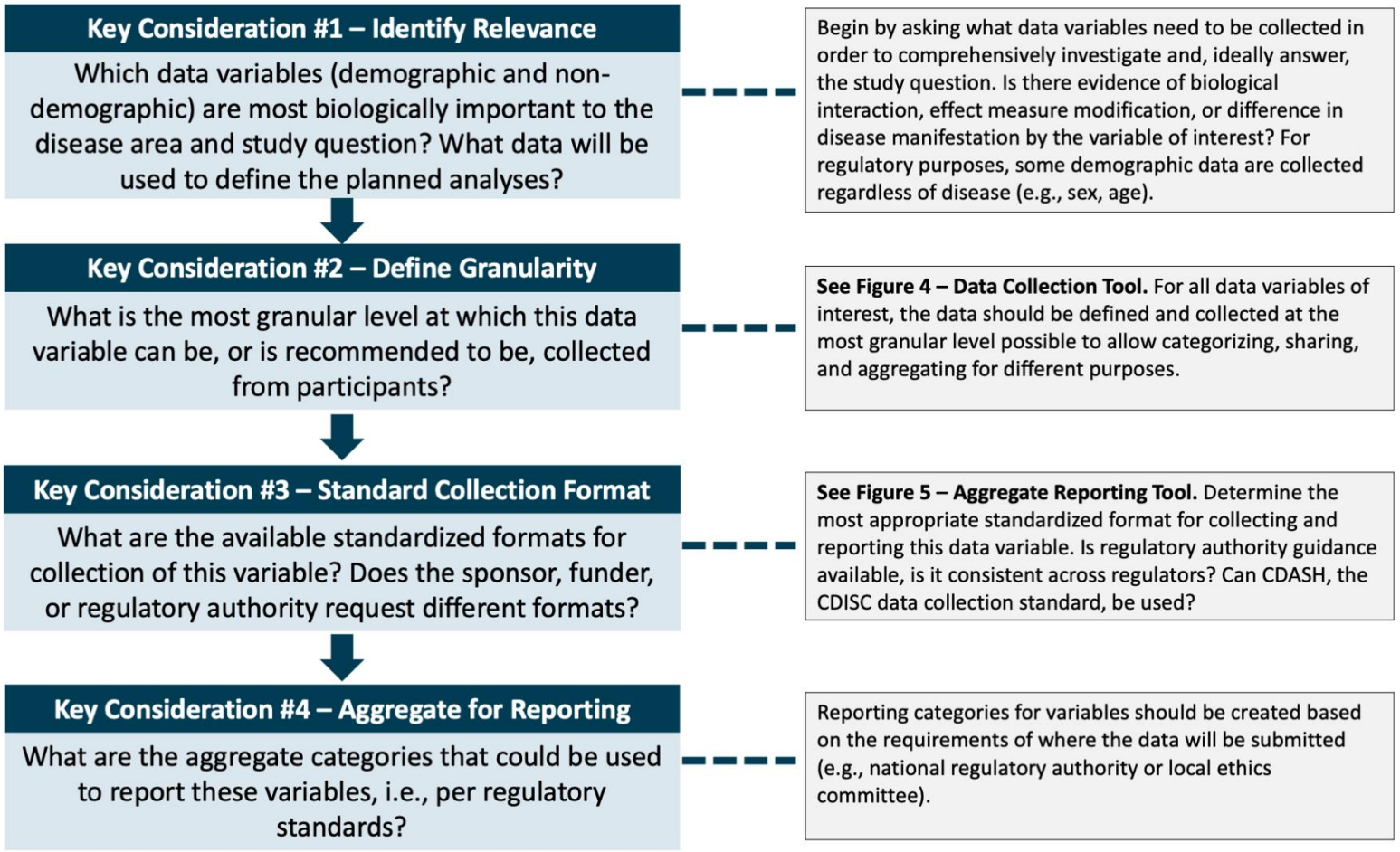


Figure 2: Key considerations for **race** as a data element during protocol development and study design

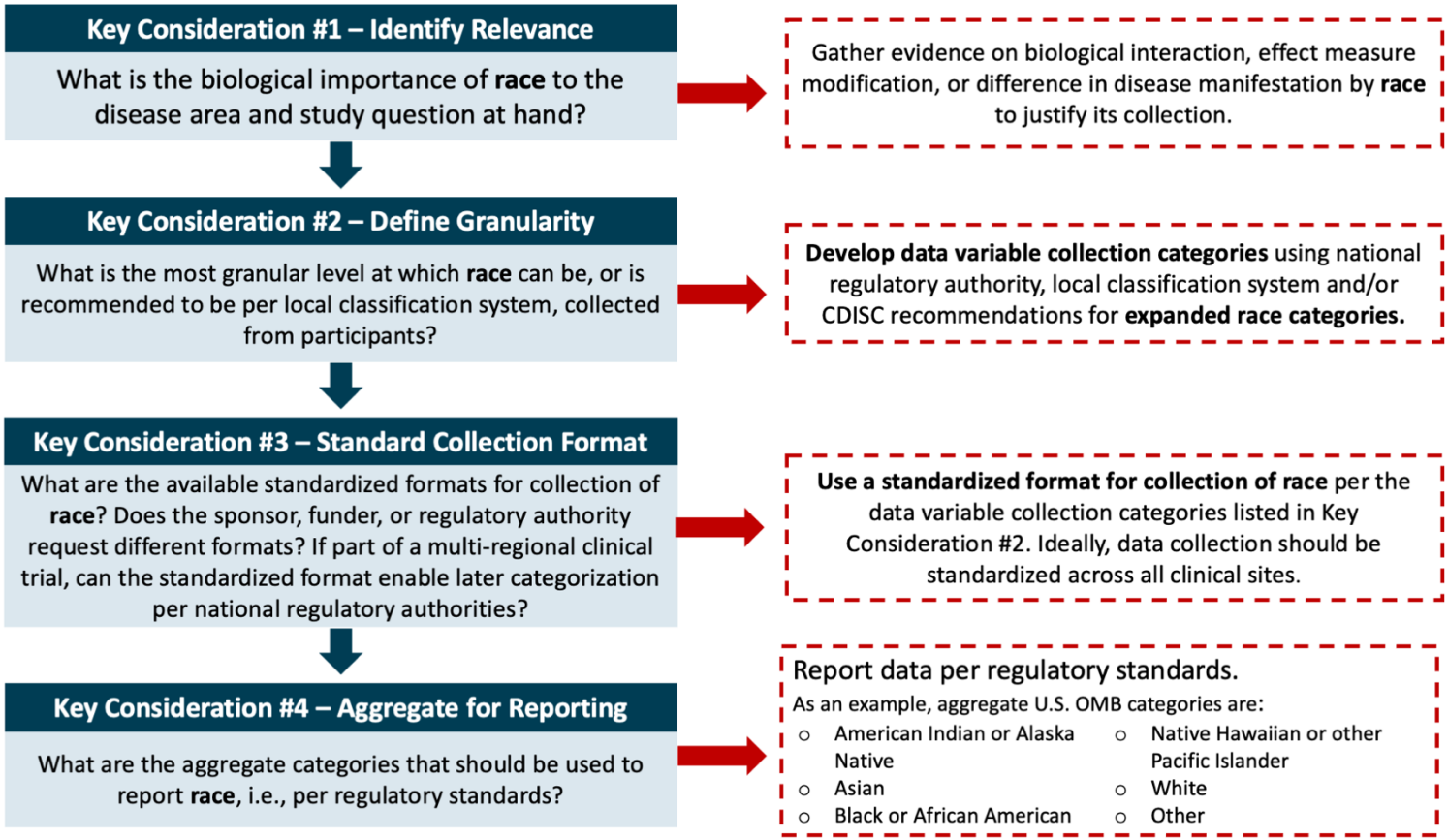
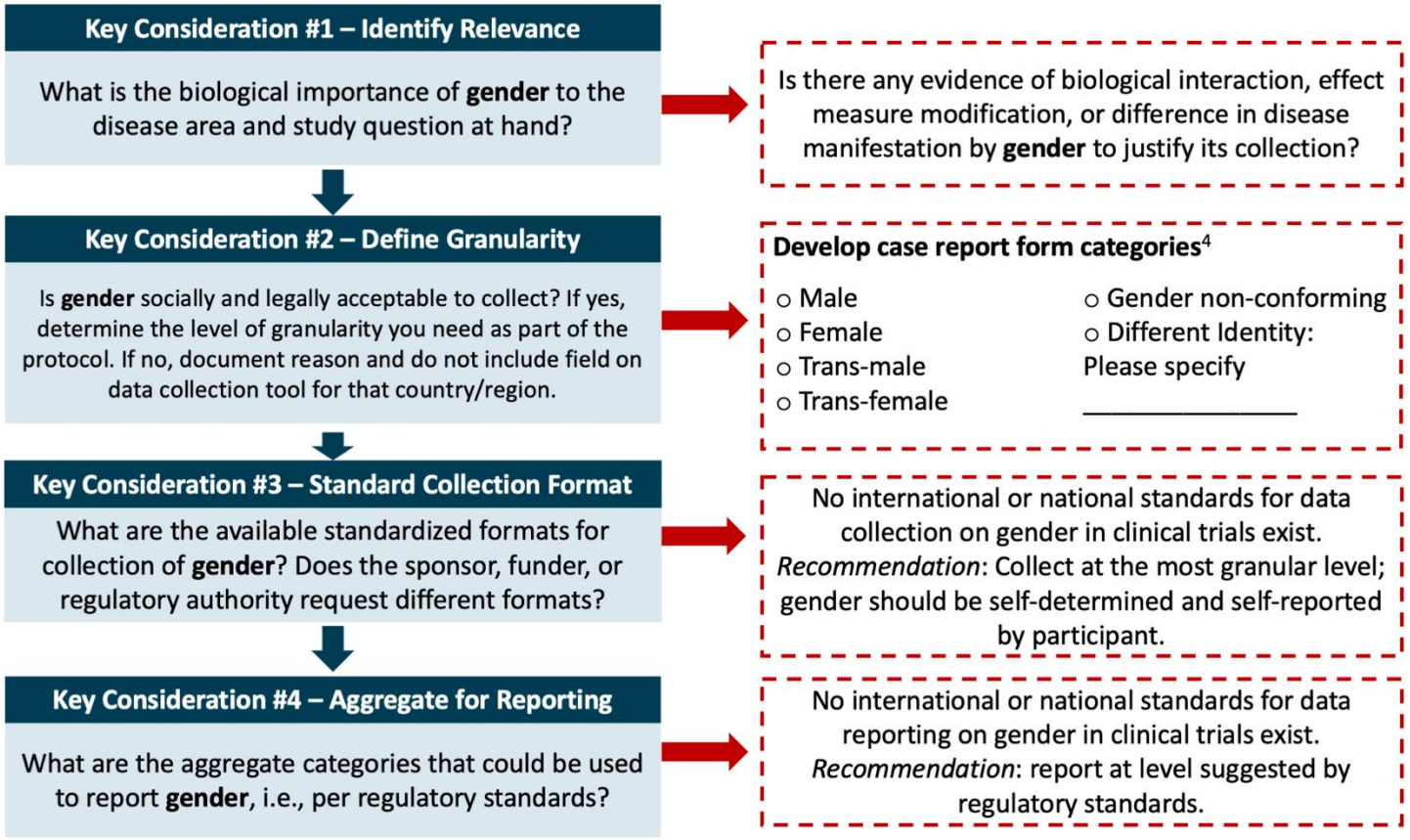


Figure 3: Key considerations for **gender**[3] as a data element during protocol development and study design



[3] Gender is defined as the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men. It varies from society to society and can be changed. World Health Organization. Glossary of terms and tools [Internet]. WHO. Available online: https://www.who.int/gender-equity-rights/knowledge/glossary/en/ (accessed May 07 2020).

[4] Bauer GR, Braimoh J, Scheim AI, Dharma C. Transgender-inclusive measures of sex/gender for population surveys: Mixed-methods evaluation and recommendations. PloS one. 2017 May 25;12(5):e0178043

The Data Collection Tool (Figure 4 below) serves as a template for study designers, including sponsors and investigators, to use when creating study specific demographic data collection forms. The demographic Data Collection Tool derives from previous work done by CDISC[5] unless noted otherwise. As noted above, data variables should be self-reported, meaning that the participant completes a data collection form or that the researcher asks the participant a specific, scripted question and then records the answer that is given. Clear instructions in plain language should be provided to the participant. Researchers should not assume answers regarding demographic information and should be trained on scripted, standardized methods for collection.

The format of this template should be modified as appropriate to the protocol. "Notes" are provided below the demographic variable fields to provide additional clarity in collecting and categorizing the variables.

Figure 4: Data collection tool for baseline demographic variables

Study ID: **Participant Study ID:** **Date of data collection:** (specify MM/DD/YYYY or DD/MM/YYYY)
AGE Instructions: Provide your date of birth to the best of your ability
Date of birth: (specify MM/DD/YYYY or DD/MM/YYYY)
Corresponding Age: (specify units: hours, days, months, years)
Note: • Collect age as a continuous variable, in order to summarize and/or report as required by the regulatory authority. • Collect age in hours, days, months, years. Age may be grouped into categories to reflect important age-related distinctions or underlying biological differences. • If there are limitations to collecting date of birth (often related to national- or region-specific privacy laws), data can be collected as year of birth and corresponding age. Specify the Age Unit (e.g., years, months). • See Section *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document* 11.2.1–11.2.3 regarding data standards for specific age categories including neonates and the elderly.

[5] CDISC: Clinical Data Acquisition Standards Harmonization (CDASH): https://www.cdisc.org/standards/foundational/cdash

<table>
<tr><td colspan="3">ETHNICITY
Instructions: Select one or more ethnicity that you most closely identify with at the high-level category or within the expanded categories. If you do not consider yourself "Hispanic or Latino," select "Not Hispanic or Latino."</td></tr>
<tr><td rowspan="3">Ethnicity</td><td>○ Hispanic or Latino</td><td>Expanded Categories:
○ Central American ○ Mexican
○ Cuban ○ Mexican American
○ Cuban American ○ South American
○ Latin American ○ Spanish</td></tr>
<tr><td>○ Not Hispanic or Latino</td><td></td></tr>
<tr><td colspan="2">○ Not Reported</td></tr>
<tr><td colspan="3">Note:
• Ethnicity terminology presented here is specific to U.S. During protocol development, a sponsor (or sponsor-investigator) should identify the classification system(s) for ethnicity, and/or national origins where trial will be ongoing. Further, understand what is legally or socially acceptable to ask.
• In the U.S., questions regarding race and ethnicity should be asked in a standard order (e.g., questions about ethnicity precede race) with scripted questions. Individuals assigned to collect personal data should be cognizant of geographic variations and cultural sensitivities, asking questions that are locally respectful and internationally meaningful for the research.
• The Ethnicity, Expanded Categories code list is expanded based on CDISC user community requests. CDISC maintains one overall ethnicity code-list that is categorized as either "Hispanic or Latino" or "Not Hispanic or Latino." The code table is available for download from the CDISC.org terminology page here: https://www.cdisc.org/standards/terminology, login required.
• See Section 11.3 of the Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document for reporting race and ethnicity to U.S. and ex-U.S. regions.</td></tr>
<tr><td colspan="3">RACE
Instructions: Select one or more race that you most closely identify with at the high-level category or within the sub-category.</td></tr>
<tr><td rowspan="2">Race</td><td>○ American Indian or Alaska Native</td><td>Expanded categories:
○ Alaska Native ○ Greenland Inuit
○ American Indian ○ Nupiat Inuit
○ Caribbean Indian ○ Siberian Eskimo
○ Central American Indian ○ South American Indian
○ Yupik Eskimo</td></tr>
<tr><td>○ Asian</td><td>Expanded categories:
○ Asian American ○ Malagasy
○ Asian Indian ○ Malaysian
○ Bangladesh ○ Maldivian
○ Bhutanese, Burmese ○ Mongolian
○ Nepalese</td></tr>
</table>

		○ Cambodian ○ Chinese ○ Filipino ○ Hmong ○ Indonesian ○ Iwo Jiman ○ Japanese ○ Korean ○ Laotian	○ Okinawn ○ Pakistani ○ Singaporean ○ Sri Lankan ○ Taiwanese ○ Thai ○ Vietnamese
	○ Black or African American	*Expanded categories*: ○ African ○ African American ○ African Caribbean ○ Bahamian ○ Barbadian ○ Black Central American ○ Black South American ○ Botswanan ○ Dominica Islander	○ Dominican ○ Ethiopian ○ Haitian ○ Jamaican ○ Liberian ○ Malagasy ○ Namibian ○ Nigerian ○ Trinidadian ○ West Indian ○ Zairean
	○ Native Hawaiian or Other Pacific Islander	*Expanded categories*: ○ Melanesian ○ Micronesian ○ Polynesian	
	○ White	*Expanded categories*: ○ Arab ○ Eastern European ○ European ○ Mediterranean ○ Middle Eastern ○ North American	○ Northern European ○ Russian ○ Western European ○ White Caribbean ○ White Central American ○ White South American
	○ Other	*Expanded categories*: ○ Unknown ○ Not reported	

Note:

- Race terminology presented here is specific to U.S. During protocol development, identify the classification system(s) based on race and/or national origins where trial will be ongoing. Further, understand what is legally or socially acceptable to ask.

<table>
<tr><td colspan="2">

In the U.S., questions regarding race and ethnicity should be asked in a standard order (e.g., questions about ethnicity precede race) with scripted questions. Individuals assigned to collect personal data should be cognizant of geographic variations and cultural sensitivities, asking questions that are locally respectful and internationally meaningful for the research.
See Section 11.3 of the Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document for regulatory guidance on reporting race and ethnicity to U.S. and ex-U.S. regions.

</td></tr>
<tr><td colspan="2">SEX
Instructions: Select your biological sex at birth. Sex is defined as the different physiological and biological characteristics of males and females, such as reproductive organs, chromosomes, hormones, etc.[6]</td></tr>
<tr><td>SEX</td><td>○ Male
○ Female
○ Unknown or undifferentiated. Intersex is included in the term undifferentiated.</td></tr>
<tr><td colspan="2">GENDER
Instructions: Select the gender you most closely identify with. Gender is defined as the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men. It varies from society to society and can be changed.[7]</td></tr>
<tr><td>GENDER[8]</td><td>○ Male
○ Female
○ Trans-male
○ Trans-female
○ Gender non-conforming
○ Different Identity: Please specify_____
○ Chose to not answer the question</td></tr>
<tr><td colspan="2">Note:

The collection of gender is sensitive. The individual collecting this information should be sensitive that this may make a participant uncomfortable and use scripted questions to ensure questions are asked in a respectful way.

</td></tr>
</table>

Figure 5: **Aggregate reporting tool**

The Aggregate Reporting Tool is used to categorize and report demographic information to regulatory authorities, oversight bodies and clinical trial registries. The specific demographic variables listed and the individual categories reported should be developed according to regulatory standards to which data will be submitted or reported and should be identified during the development of the protocol and statistical analysis. The Aggregate Reporting Tool is populated by the more granular Data Collection Tool (Figure 4), therefore development of both tools prior to study conduct is important to ensure efficient collection and categorization of demographic data. The tool created below serves as an example for

[6] World Health Organization. Glossary of terms and tools. Accessible at https://www.who.int/gender-equity-rights/knowledge/glossary/en/.
[7] World Health Organization. Glossary of terms and tools. Accessible at https://www.who.int/gender-equity-rights/knowledge/glossary/en/.
[8] Adapted from: Bauer GR, Braimoh J, Scheim AI, Dharma C. Transgender-inclusive measures of sex/gender for population surveys: Mixed-methods evaluation and recommendations. PloS one. 2017 May 25;12(5):e0178043.

categorizing previously collected demographic data and includes the demographic categories described in Chapter 11, Data Variables and Collection, of the *Achieving Diversity, Inclusion, and Equity in Clinical Research* Guidance Document. The tool is currently designed for a global study enrolling participants over the age of 18 years old. It is designed according to U.S. regulatory standards. Additional categories can be included based on the specific protocol and study population (e.g. region of enrollment, language, etc.).

Study ID: **Baseline Demographics, Aggregated Data**				
Demographic Variables	**Treatment Group(s)**		**Control Group N (%)**	**Total N**
	Group 1, N (%)	**Group 2, N (%)**		
Age				
>=18 - <65 years				
>=65 - <74 years				
>=75 - <84years				
>= 85 years				
Sex				
Male				
Female				
Unknown/Undifferentiated				
Gender				
Male Gender				
Female Gender				
Trans-Male				
Trans-Female				
Gender Nonconforming/ Unknown				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Not Reported				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Not reported/unknown				
Other/More than one				

Logic Model: Study Design

Audience: Sponsors/CROs, sites/investigators

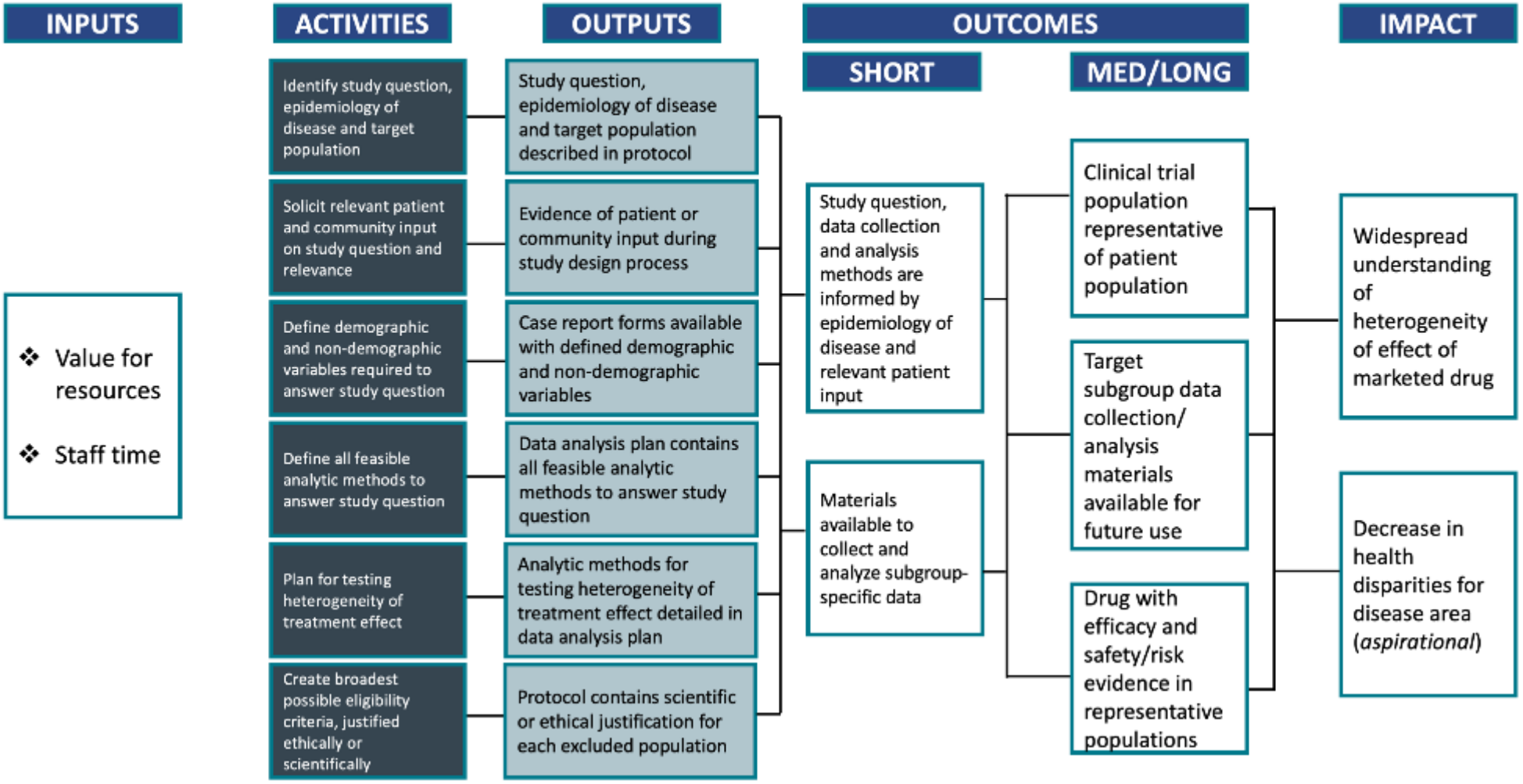
Purpose: To provide a sample of activities, linked to their intended effects (outputs, outcomes and impact), that might be considered during study design for a clinical trial aiming to enroll a representative population. A non-exhaustive sample of key performance indicators for such a study design is also provided in order to demonstrate how this logic model can be used to construct performance metrics.

Considerations for use:

- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.
- Most activities defined in this logic model are routine in a typical study design process. The logic model provides a framework for thinking about these activities through the lens of diverse enrollment.

Logic Model: Study Design

Audience: Sponsors/CROs, sites/investigators



Study Design – Potential Key Performance Indicators (KPIs)

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Output indicators

- ☐ Proportion of exclusion criteria with ethical or scientific justification within study protocol
- ☐ Protocol contains study question, epidemiology of disease, and target population
- ☐ Adjustment to protocol or data collection/analysis based on patient input
- ☐ Case report forms available at site contains all relevant data variables
- ☐ Data analysis plan contains all planned subgroup analysis
- ☐ Data analysis plan contains all planned testing for heterogeneity of treatment effect

Outcome indicators

- ☐ Granular demographic and non-demographic data collected in trial per data analysis plan
- ☐ Planned subgroup analysis performed and reported
- ☐ Planned heterogeneity of treatment effect testing performed and reported

Screen Failure Tracking Log – Trial-Level

Audience: Clinical trial staff manager

Principal Investigator:

Protocol #:

Study Title:

Sponsor:

Provided by clinical site staff conducting screening

KEY CONSIDERATIONS

1. Is the screen failure tied directly to a protocol-specified exclusion criteria?
2. Is the screen failure determined based on an objective measure of eligibility (lab value, etc.)?
3. Is the screen failure determined based on a subjective assessment or judgement (i.e., investigator discretion)?

Participant*		Date Screened	Reason for Exclusion/Screen Failure	Screen Failure Assessment**		Initials of Assessor
				Protocol-specified exclusion criteria AND/OR objective measure	Study staff or investigator discretion / judgement	
1				☐	☐	
2				☐	☐	
3				☐	☐	
4				☐	☐	
5				☐	☐	
6				☐	☐	
7				☐	☐	
8				☐	☐	
9				☐	☐	
10				☐	☐	

*Use a pre-screening number, initials, or first name to identify individuals at pre-screening, to be HIPAA compliant.

**Assessment made by clinical trial staff manager and/or investigator. Tracking these assessment data can enable an understanding of whether a particular site has justified screen failures over time. Stratifying these assessment data by participant demographics (collected on the Eligibility & Enrollment Log) can enable understanding of the demographics of screen failure, and whether objective assessments are utilized for participants of particular demographic groups.

Eligibility and Enrollment Log – Individual Participants

Audience: Clinical trial staff

All individuals enrolled must meet eligibility criteria based on the inclusion/exclusion criteria detailed in the application and approved by the IRB/REC.

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.	☐	☐	

[1] Ethnicity and race categories listed here may need to be adapted to reflect specific geographic location and populations of interest.

[2] All participant files must include supporting documentation to confirm eligibility. Methods of confirmation can include, but is not limited to, documented vitals, laboratory test results, radiology test results, subject self-report, and medical record review.

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:	

.

[3] All participant files must include supporting documentation to confirm eligibility. Methods of confirmation can include, but are not limited to, documented vitals, laboratory test results, radiology test results, subject self-report, and medical record review.

[4] The designated Principal Investigator may be required to determine eligibility for research studies involving medical/clinical care.

Logic Model: Site Selection

Audience: Sponsors/CROs, sites/investigators

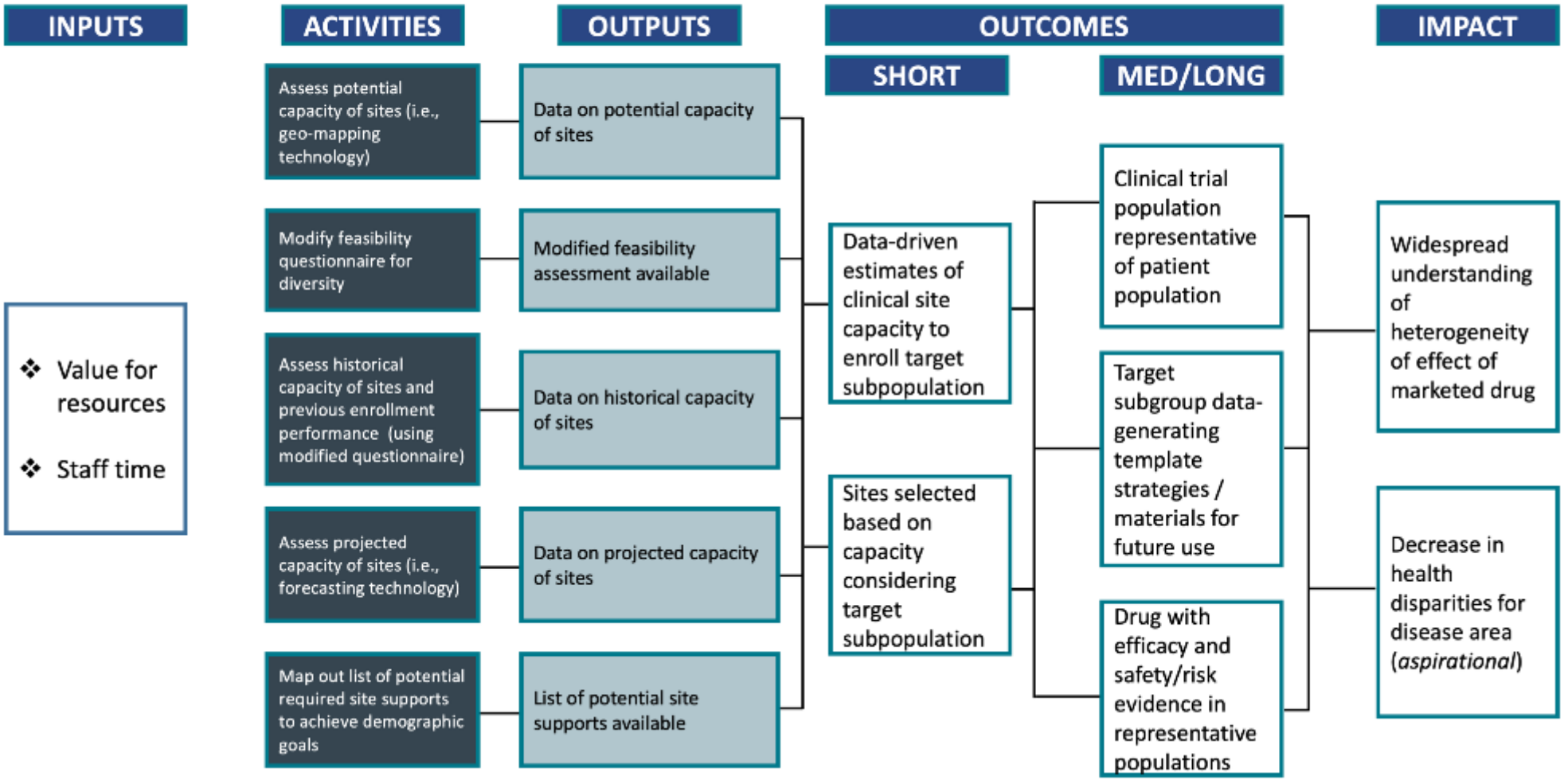
Purpose: To provide a sample of activities, linked to their intended effects (outputs, outcomes and impact), that might be included during a feasibility assessment being leveraged to enroll a representative population in a clinical trial. A non-exhaustive sample of key performance indicators for a site selection process is also provided in order to demonstrate how this logic model can be used to construct performance metrics.

Considerations for use:

- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.
- See the "Feasibility Decision Tree" tool as well the "Feasibility Questionnaire Modification Checklist" tool. Each activity presented in this logic model is explored in more extensive detail within these tools.

Logic Model: Site Selection

Audience: Sponsors/CROs, sites/investigators



Site Selection – Potential Key Performance Indicators (KPIs)

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Output indicators

- [ ] Data available on potential capacity of sites to enroll target subpopulation
- [ ] Modified feasibility assessment available for target subpopulation
- [ ] Modified feasibility assessment conducted at each site with potential capacity
- [ ] Data available on projected capacity of sites to enroll target subpopulation
- [ ] List of potential site supports to enroll target subpopulation available

Outcome indicators

- [ ] Each site selected has an estimate for its capacity to enroll target subpopulation(s)
- [ ] Each capacity estimate is derived from more than one data source
- [ ] Each site selected has a justification including reference to their capacity to enroll target subpopulation(s)

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Feasibility Decision Tree

A tool to prioritize the recruitment of a representative population during site selection

Purpose

This tool provides a high-level decision-making framework that can be used by industry or academic **sponsors and/or CROs** during the feasibility assessment and site selection process in order to select sites that can best fulfill the trial's target representative population.[1]

The overall objective of a feasibility assessment is to select sites for *"optimum project completion in terms of timelines, targets and cost."*

Rajadhyaksha, 2010

This tool aims to be

- **Supplementary**: this tool should not work against existing sponsor priorities; rather, the user should embed this tool into their existing site selection methodology.
- **Multi-regional**: the tool can and should be applied to multi-center clinical trials and/or clinical trials conducted in multiple regions or countries.
- **Capacity-building**: in order to facilitate benchmarking of site needs and capacity to enroll diverse populations, this tool incorporates "Checkpoints" where the sponsor/CRO can objectively assess the capacity of a site **and then determine whether enhancement is possible**.

Background

Despite the proliferation of multi-regional clinical trials in recent years, many groups have remained underrepresented in clinical trials globally.[2] Data generation will inherently vary across countries, for example racial and ethnic diversity applies differently in countries of context, and therefore the variable or data element of interest should be defined in advance of using this tool. In general, this tool is designed to be adapted for application across data elements, regions and countries.

Why Feasibility Assessment and Site Selection?

Clinical trial site feasibility assessment is a decision-making process that traditionally involves evaluating the possibility of conducting a particular trial in a particular region or at a particular site, "with the overall objective of optimum project completion in terms of timelines, targets and cost."[1]

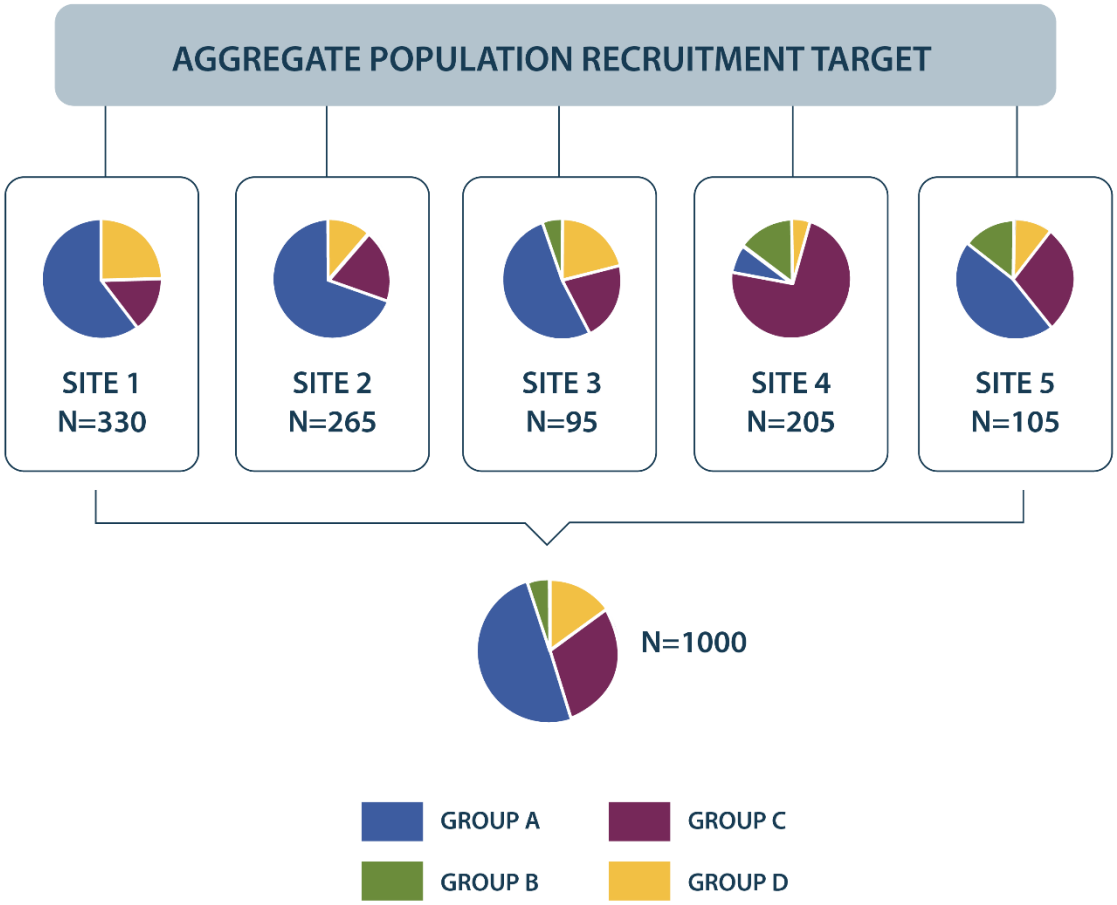
These assessments are conducted by sponsors and/or CROs, most often by requesting potential sites to complete a feasibility questionnaire that acquires data on the potential for success of the trial at that site.

[1] Rajadhyaksha V. Conducting feasibilities in clinical trials: an investment to ensure a good study. Perspectives in clinical research. 2010 Jul;1(3):106.
[2] Knepper TC, McLeod HL. When will clinical trials finally reflect diversity?.

It is important to note that what matters in a multi-site trial is the **aggregate enrollment of the trial**. Therefore, this tool encourages sponsors to consider the potential enrollment capabilities of representative populations at each site during the site selection process, in accordance with the trial's aggregate target population. For a variety of practical reasons, not every site can enroll a representative and diverse population. As such, this tool provides a framework that can be used to assess the capacity of each site to enroll particular subgroups, addressing the overall strategic goal of achieving a diverse participant population across the study in aggregate. This becomes particularly significant in multi-regional trials where sites themselves are heterogeneous and site selection occurs across countries.

Use Figure 1 below as a visual aid for this concept. To achieve diverse representation in clinical trials in accordance with the MRCT Center's principles around diversity, studies as a whole should include a diverse population. This should be a strategic goal of sponsors and CROs aiming to achieve a population in their trials that is representative of those most likely to use the product in development. However, each site within a study will contribute its unique participant population to the overall study population (i.e., in Figure 1, Sites 1 through 5 each contribute a unique participant population to the overall study population). Therefore, the tool at hand was not built to help select sites that would each achieve diverse representation in their recruited population – a practically unfeasible goal. Rather, the tool was built to help ensure sites enroll particular subgroups at levels that will help the trial meet its strategic goals for diversity and achieve the intended population, based on the epidemiology of the disease. **In this way, the aggregate study population of the trial can achieve diverse representation.**

Figure 1: Unique site contribution to aggregate multi-site trial population achieving representative diversity across a hypothetical trial



Feasibility Decision Tree - considerations for use

It should be noted that in recent years there has been growing emphasis across the clinical research enterprise on the need for objective measures and standardization of feasibility assessments.[3] This emphasis is in part due to the traditional overreliance on subjective investigator estimates and feasibility questionnaires, common study delays and the high costs of trials.[3,4]

The Feasibility Decision Tree tool (see Figure 3: Feasibility Decision Tree **- a tool to prioritize the recruitment of a representative population during site selection** is structured to offer a comprehensive assessment of a single site's capacity at multiple tiers *(potential*, *historical*, and *future*), as discussed below. This tool is intentionally:

1. **Non-prescriptive**, in that it suggests a framework for assessing the feasibility of sites to enroll a diverse population but does not provide specific methods for that assessment. The tool can therefore be adapted to unique clinical operations approach of the sponsor/CRO user.
2. **Non-selective**, in that the framework provides thematic areas, but does not provide fixed criteria to determine a site's capacity for diverse enrollment. In fact, it incorporates multiple "checkpoints," at which the user can reconsider the capacity of a site. This provides flexibility for the sponsor/CRO in their approach to determining the capacity of a site to enroll a desired subgroup into a trial.

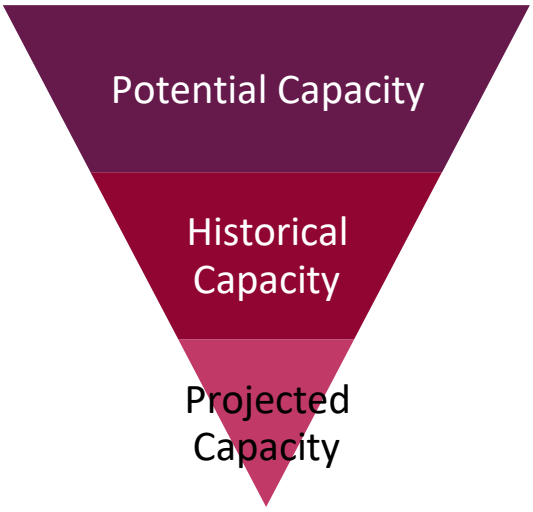
The motivation for this framework to be non-selective is rooted in the mission to build industry- wide capacity for diverse representation in clinical trials. Achieving diverse representation across trials will require strong partnerships between sites and sponsors. For this reason, this tool proposes providing feedback to those sites deemed to lack potential capacity for enrolling a particular subgroup. Further, rather than eliminate sites without historical record of enrolling a particular subgroup, sponsors and CROs should attempt to increase capacity within these sites that have potential capacity to enroll that subgroup, by means of providing feasible, evidence- based supports to achieve targeted recruitment. Note that sponsors are expected to provide recruitment materials that are adapted for the specific group and translated as needed, and that site budgets should also allow for a site's unique recruitment efforts.

[3] Hurtado-Chong A, Joeris A, Hess D, Blauth M. Improving site selection in clinical studies: a standardised, objective, multistep method and first experience results. BMJ open. 2017 Jul 1;7(7):e014796.
[4] Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. Clinical Investigation. 2015 May;5(5):491-9.

How to use this tool

This tool establishes three tiers from which to assess sites: *potential capacity*, *historical capacity*, and *projected capacity* (see Figure 2). Each tier, described in more detail below, should be assessed by the sponsor/CRO when determining whether a site ultimately has the capacity to engage a particular subgroup in a clinical trial. Embedded into these tiers are "Checkpoints" that encourage sponsors/CROs to reconsider how sites might be able to achieve capacity to successfully enroll a particular subgroup in a clinical trial (see Table 1).

Figure 2: Capacity tiers as a framework for site selection to promote diversity



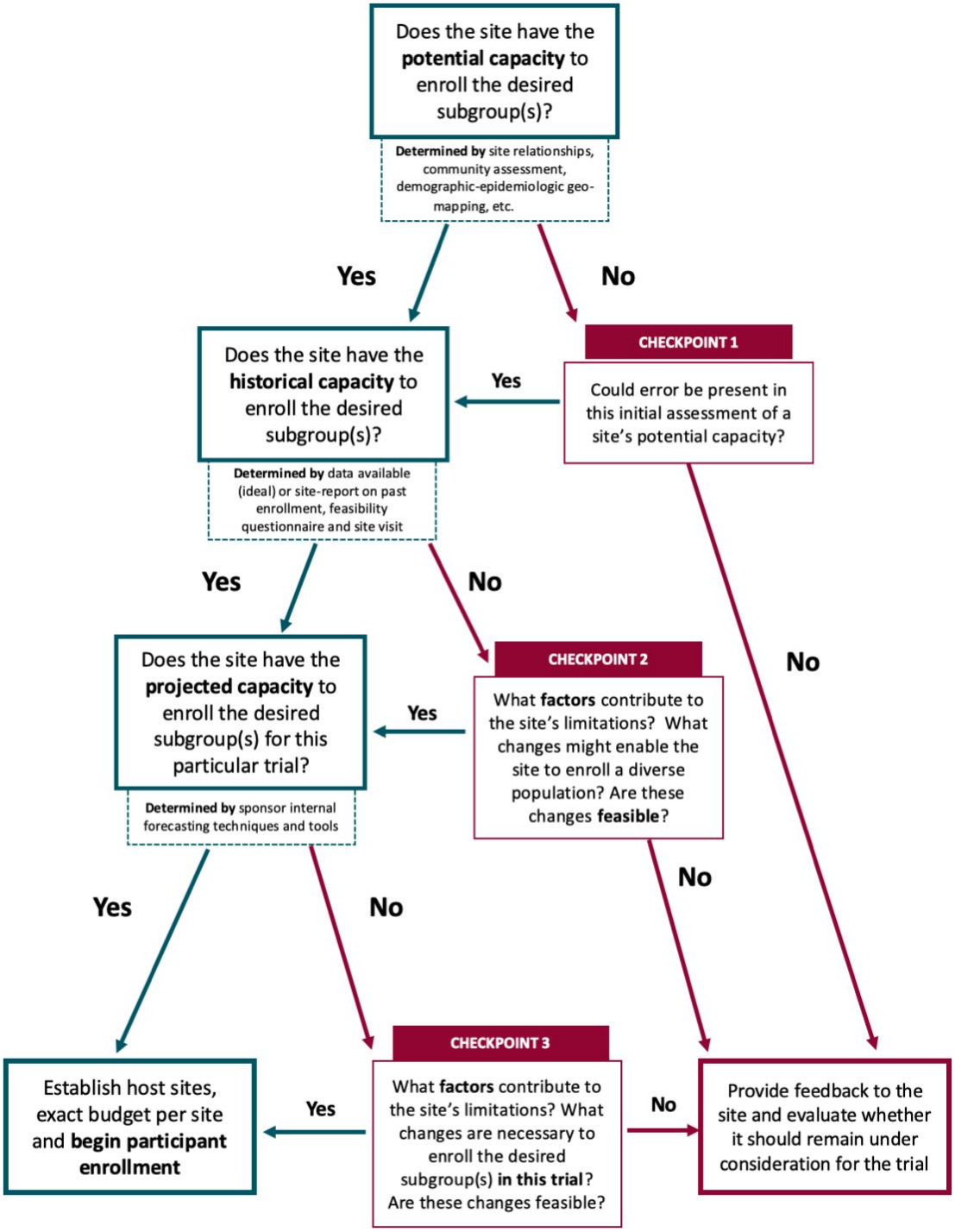
It is important to note that this tool provides a framework to assess the capacity of a single site in a field that is currently under-addressed in feasibility assessments. As such, we expect that its use will lead to iterative improvement of the tool itself.

We hope that users will share those experiences, specific applications and examples of success and challenge in its application with the MRCT Center (email: MRCT@bwh.harvard.edu).

Table 1: Summary of Checkpoints within decision tree tool

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.

Figure 3: Feasibility Decision Tree – a tool to prioritize the recruitment of a representative population during site selection



Assessing potential capacity

The potential capacity of a site can be seen as the **contextual or environmental factors** that contribute to a site's capacity to enroll a particular subgroup in a clinical trial. For example, the site's country, city, geography (urban vs. rural), and/or the demographic composition of the site's catchment area may impact potential capacity. The potential capacity of a site can be determined via existing sponsor relationships with clinical sites, community assessments, and/or geo-mapping of demographic and epidemiological data.

If this initial evidence indicates that a site does not have *potential capacity* to enroll a particular subgroup, the sponsor/CRO reaches "Checkpoint 1," and is encouraged to conduct an internal assessment of the methods used to determine that *potential capacity*. If bias or error is recognized in this initial determination, the site may still be eligible for selection.

For example, potential capacity to enroll particular subgroups can be assessed by determining whether that subgroup is available within the site catchment area (see Figure 4).[5,6] As such, if the sponsor acquires data from a geo-mapping tool that indicates a particular site's catchment area does not contain a high proportion of desired subpopulation, but that site is in fact embedded

Figure 1: An example of different patient populations at two hospitals within a similar geographic catchment area

In an urban U.S. city, despite sharing similar catchment areas with widely diverse patient populations, two hospitals do not share similar rates of diverse representation in their clinical trials.

Hospital A has a patient population primarily composed of ethnic minorities, while Hospital B has a primarily white patient population. The reasons for this disparity are complex, including:

- **Geography**: more whites live near the Hospital B
- **Cost**: some lower-cost health insurance plans do not cover high-cost care at Hospital B
- **Comfort**: ethnic minorities may not feel comfortable receiving care at primarily white institutions

Of interest is the major racial disparity in clinical trials between the two hospitals – Hospital A hosts significantly fewer clinical trials than Hospital B.[6] **Because of this, ethnic minorities in this urban city have limited access to participating in clinical trials than whites.**

Applying the proposed feasibility framework, while both hospitals in this case might have the same **potential capacity** to enroll diverse populations in a clinical trial due to a similar catchment area, in reality their capacity is quite different for the reasons demonstrated above. Users of the proposed framework should be aware of these possible nuances and limitations when assessing the capacity of sites to enroll a particular subgroup.

[5] Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. Clinical Investigation. 2015 May;5(5):491-9.
[6] Kowalczyk L. Color line persists, in sickness as in health [Internet]. Massachusetts: *Boston Globe*; 12 Dec. 2017 [accessed: Sept. 29, 2019]. Available from: https://apps.bostonglobe.com/spotlight/boston-racism-image-reality/series/hospitals.

within a community with ties to the desired subpopulation, their capacity might be higher than predicted. Alternatively, this determination could be biased by factors such as unequitable participant access to trial sites, as well as competition between sites hosting clinical trials in similar indications, in which case their capacity might be lower than predicted.[7]

The motivation of this checkpoint is to be inclusive and ensure that those sites with potential capacity to enroll particular subgroups are not being missed. Further, this checkpoint recognizes that predicting a site's capacity prior to engaging with them or collecting data from them is a known challenge during feasibility assessments.[8]

Assessing historical capacity

The *historical capacity* of a site is defined as the **site's history of enrolling particular subgroup(s)**. Evidence of historical enrollments can be obtained from past enrollment numbers by subgroup, patient population demographics, proof of relationships between the site and community leaders, and/or evidence of an implemented targeted recruitment strategy.

Figure 2: Gender, race and clinical experience (GRACE) case example

GRACE was a phase 3b study designed specifically to enroll and retain women of color for an antiretroviral clinical trial; sponsor-provided support for sites was credited as a major contributor to the success of the trial's engagement of a diverse population.[9]

The sponsor ensured diverse enrollment during site selection by **modifying their feasibility questionnaire** to include questions that ensured:

- **Potential capacity** – sites in areas of high HIV burden among women and people of color
- **Historical capacity** – sites that had a history of actively treating women of color living with HIV, whether or not they had been involved in clinical research before

Sponsor-provided strategic supports included:

- requiring sites to enroll a certain number of women before enrolling men
- hiring community advocates to advise during site selection
- pairing sites lacking capacity for diverse enrollment with more experienced sites for guidance
- granting the engaged CRO special rights to visit less experienced sites and provide technical support

[7] Rajadhyaksha V. Conducting feasibilities in clinical trials: an investment to ensure a good study. Perspectives in clinical research. 2010 Jul;1(3):106.
[8] Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. Clinical Investigation. 2015 May;5(5):491-9.
[9] Falcon R, Bridge DA, Currier J, Squires K, Hagins D, Schaible D, Ryan R, Mrus J (on behalf of the GRACE Study Group). Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. Journal of Women's Health. 2011 Jul 1;20(7):1043-50.

A sponsor or CRO can collect this information from potential sites via a feasibility questionnaire, modified specifically to generate data on diverse enrollment (see Gender, race and clinical experience (GRACE) case example, Figure 5). Consult the **"Feasibility Questionnaire Modification Checklist"** for a suggested framework on how to approach modifying a questionnaire to increase diverse participation in a trial. Note that empirical evidence has shown that sites and investigators routinely overestimate and overcommit the numbers of eligible participants available and that they are likely to recruit, and this is true prior to any consideration of diverse enrollment.[10] Adopting this multi-tier, rigorous feasibility assessment approach with multiple data sources encouraged by this decision tree tool should help to triangulate on realistic enrollment estimates.

If a site is deemed to not have *historical capacity* in enrolling diverse populations, this tool leads sponsors/CROs to "Checkpoint 2," where they are encouraged to consider what changes the site might require to reach capacity and if it is feasible for the sponsor to assist in making these changes. This consideration should be made in active collaboration with site staff.

Figure 6: Using Enrollment Prediction Software

A software company created a user-friendly, data-driven forecasting tool to help sponsors reach their targeted enrollment on time and on budget. The software allows sponsors to input any data they have (including historical site-specific data) in order to generate accurate predictions of enrollment and recruitment milestones.

> A pharmaceutical company uses this tool during feasibility assessments. In an interview, a former director of the pharmaceutical company praised the software in helping "to leverage the actual data that we had…and also to account for uncertainty by incorporating our assumptions… . The result of doing that was a much more thorough understanding of the factors that were driving enrollment."[11]

Software programs can be used to input multiple data points to predict enrollment milestones, which could include data on the diversity of the expected participant population. Users of this framework could utilize and adapt such tools to aid in predicting a site's projected capacity to enroll a particular subgroup.

[10] Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. Clinical Investigation. 2015 May;5(5):491-9.
[11] Cytel. Data-Driven Trial Planning: An Interview with Pfizer's Chris Conklin. Feb. 12, 2015. Accessed February 2020. Available from: https://www.cytel.com/blog/an-interview-with-pfizers-chris-conklin

Assessing projected capacity

The *projected capacity* of a site predicts whether a site can enroll the desired subgroup(s) for the **specific trial at hand**. As the considerations for each trial are unique, the sponsor or CRO should use relevant data available for the trial based on the competitive landscape, regulatory requirements, clinical research protocol requirements, recruitment needs, patient demographics, historical enrollments, site requirements and questionnaire-generated data in order to make this assessment. Sponsors can also create an adaptive recruitment plan that is targeted to the specific population and transparent with sites about the goals of these efforts.

In doing so, sponsors and CROs can **adapt existing forecasting techniques** (e.g., software used to generate predictions of enrollment – see Figure 6: Using Enrollment Prediction Software) used during site selection to determine whether sites will be able to engage a diverse demographic in the specific trial being conducted. With the necessary data, utilizing existing software and forecasting tools is a realistic way to assess a site's *projected capacity* to enroll the desired subgroup(s).

"Checkpoint 3" is used for assessing *projected capacity* and is similar to *historical capacity* in that it encourages sites to consider the feasibility of providing support(s) and building site capacity to enroll diverse populations, but in this case specifically for the trial at hand. At this point, a sponsor must determine the level of support available, including financial, to be provided to the site in order to evaluate whether the site should remain under consideration for the trial (see Figure 5: Gender, race and clinical experience (GRACE) case example for further details to estimate budgetary impact).

Feasibility Questionnaire Modification Checklist

A tool to evaluate clinical sites' capacity to enroll representative populations

Purpose

This tool aims to enable sponsors and contract research organizations (CROs) to improve their evaluation of clinical sites' capacity to enroll diverse and/or representative participant population, to facilitate iterative improvements to the evaluation process and of the tool itself. The Feasibility Questionnaire Modification Checklist tool proposes a particular action – modifying feasibility questionnaires to include questions on enrollment of target subpopulations – will result in improved data capture on site capabilities to enroll particular subpopulations. The outcome of this is to enable sponsors to make informed decisions around strategic site selection and to better achieve a representative trial population in aggregate. See this approach outlined in Figure 1.

We hope that users will share feedback, specific applications and examples of successes and challenges in using the tool, and suggested changes for improvement. Please share any such feedback with the MRCT Center at mrct@bwh.harvard.edu.

Background

"A critical time in a clinical trial's life cycle – the upstream planning and design phase – may be the best target for positively influencing downstream recruitment efforts."[1]

Pharmaceutical sponsors of clinical trials typically assess the capacity of potential clinical sites to enroll participants in anticipation of the trial, termed "feasibility assessments."[2] However, a gap exists in that there is no widely accepted or standardized approach to assess the capacity of sites to enroll populations of a specific demographic or subgroup. Therefore, implementation and utilization of the full potential of feasibility assessments may enhance informed decision- making by sponsors and CROs in their site selection process.[3]

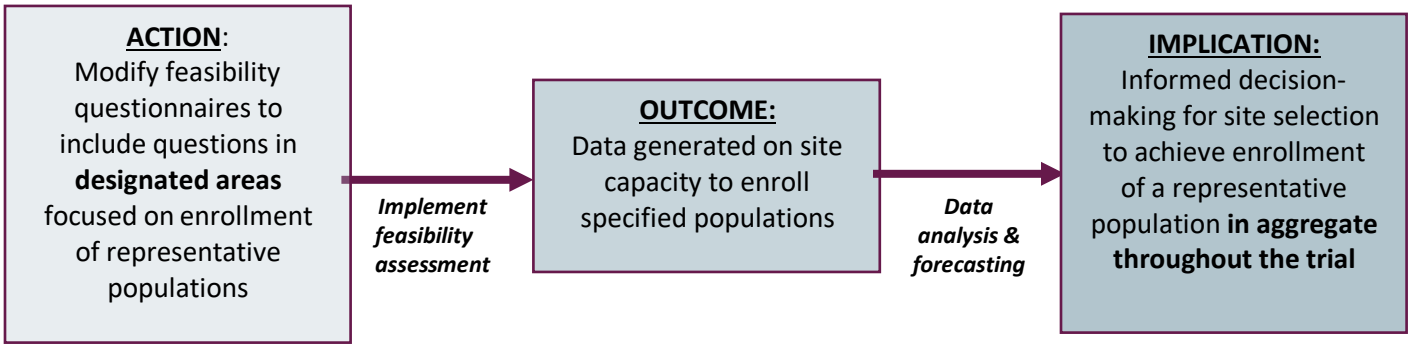
Aggregate enrollment of the trial across sites is what matters for the research. Thus, engagement of a unique clinical site need not be based on the same criteria or have the same subpopulation enrollment compared to other sites, but rather the aggregate of all sites should reflect the intended population. That said, the result will only be successful if, at the outset, site selection is planned to achieve the intended result and then actively monitored during the trial. Efforts to correct imbalance after the trial is well underway may result in expense and delay, and therefore intentional planning and mitigation measures are necessary.

[1] Huang GD, Bull J, McKee KJ, Mahon E, Harper B, Roberts JN. Clinical trials recruitment planning: a proposed framework from the clinical trials transformation initiative. Contemporary clinical trials. 2018 Mar 1;66:74-9.
[2] Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. Clinical Investigation. 2015 May;5(5):491-9.
[3] Huang GD, Bull J, McKee KJ, Mahon E, Harper B, Roberts JN. Clinical trials recruitment planning: a proposed framework from the clinical trials transformation initiative. Contemporary clinical trials. 2018 Mar 1;66:74-9.

Tool framework

- **What**: Starting point for sponsors to evaluate site capabilities for representative population enrollment.
- **Why**: Helps industry and academic sponsors of clinical trials make informed decisions about site capabilities in order to prioritize representative enrollment in trials with a standardized evaluation. Addresses gap in feasibility assessment implementation in their site selection process.
- **How**: Highlights target areas to modify existing feasibility questionnaires to collect data on the potential representative, epidemiologically aligned population to be enrolled.

Figure 1: Theoretical approach of Feasibility Questionnaire Modification Checklist tool



Tool applicability

- ***General Scope*: This tool offers a checklist of target areas in which to collect data from sites, with sample questions** that can be incorporated into existing questionnaires used by industry and academic sponsors. Wherein sponsors contract with CROs to perform this service, we recommend that the service agreement between sponsor and CRO reflect the expectation that CROs perform this service. This tool does not provide a specific modified template questionnaire, but rather guidance for how to approach this modification.

- ***Defining Representativeness*:** Note that in modifying a questionnaire to include the assessment of a site's capacity to enroll representative populations, the appropriate population must first be defined based on the demographics of the disease or condition and what is known about the populations likely to use the product or intervention. Data elements, whether demographic (e.g., race, ethnicity, ancestry, sex, gender, age at either end of the spectrum, socioeconomic status, and/or geography (urban vs. rural)) or non-demographic (e.g., comorbidities, organ function, concomitant medications) must be clearly defined in advance.

- ***Multi-Regional Studies*:** This checklist can be applied to non-demographic and demographic data elements across all countries, with the exception of race/ethnicity because significant variation exists globally in what is considered an "underrepresented population" for this element. That being said, **the broad approach offered by this checklist can be applied to any site, in any country.**

Target data areas for the Feasibility Questionnaire Modification Checklist

If feasibility questionnaires are modified to contain questions targeting the following data areas listed below, sponsors and CROs can generate data on the capacity of clinical sites to recruit particular subpopulations, thus informing their decision-making around strategic site selection to achieve representativeness in their trials (see

Figure 2: Flowchart of intended outcomes from feasibility questionnaire **modification** Checklist). The checklist provided in Figure 3 offers a *non-exhaustive* list of guidance questions that can aid relevant data generation within each key area. These questions and statements are intended to inspire the creation of targeted quantitative questions for placement on the feasibility questionnaire.

1. *Population Availability:* does the site's geographic area or catchment area contain the subpopulation of interest?
2. *Population Accessibility:* is the site accessible to the subpopulation of interest and does the site have a history of engaging this subpopulation in clinical trials?
    a. Accessible in this case is viewed as whether there is evidence of a particular subpopulation utilizing the site's resources and/or whether the site has a relationship with communities of interest.
3. *Targeted Recruitment Strategy:* does the site have the capacity to develop a targeted recruitment strategy for the subpopulation of interest?
4. *Barriers and Supports:* does the site anticipate any barriers and/or supports in developing this targeted recruitment strategy?

Figure 2: Flowchart of intended outcomes from feasibility questionnaire modification

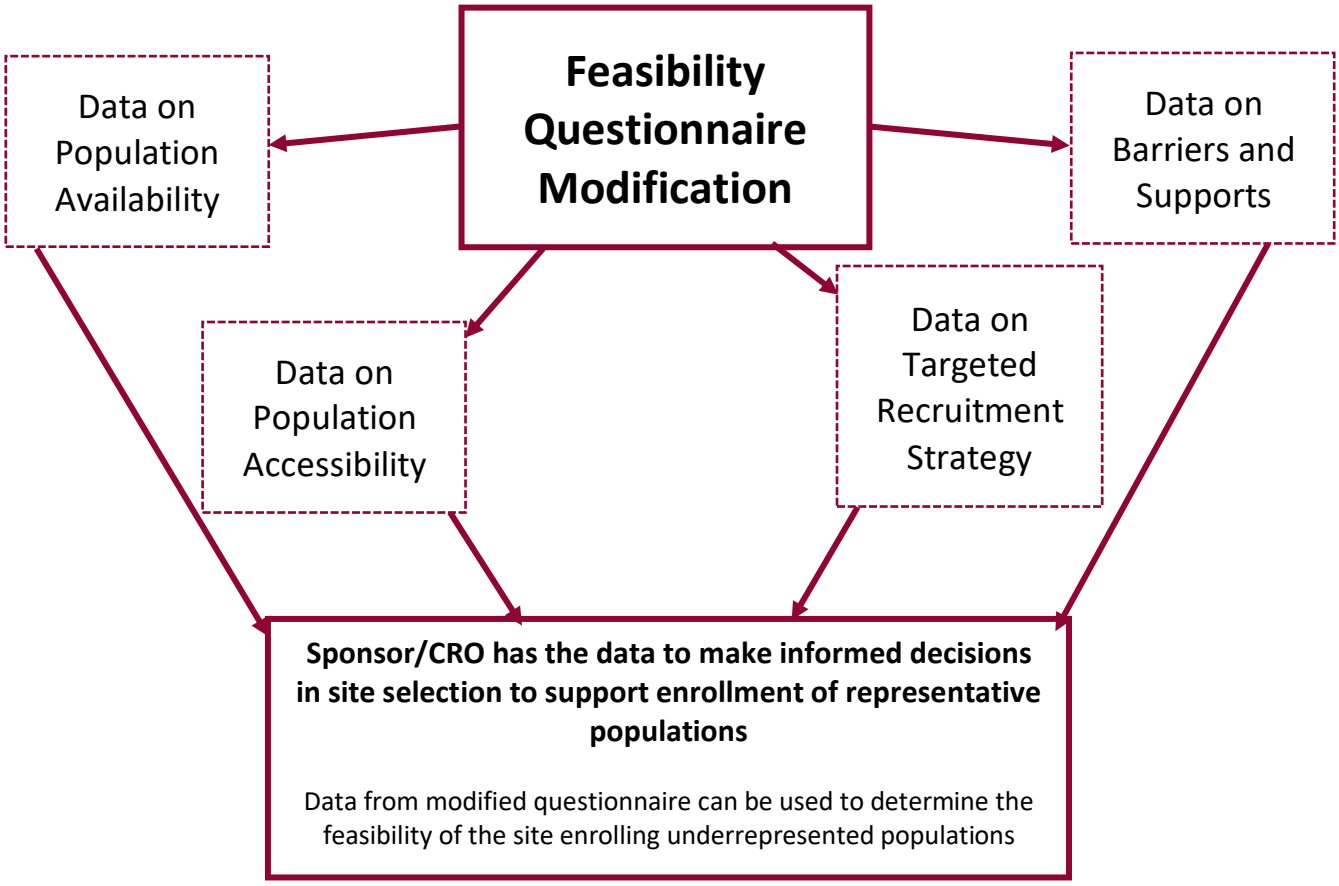


Figure 3: Checklist matrix for feasibility questionnaire modification with guidance questions toward targeted data. The intent of the "checklist" format is to ensure sponsors think through and target each key area. Not all key areas will be applicable to each research study, but the checklist is intended to ensure that decisions are deliberate and informed by information received from sites.

Sponsor Logo

CRO Logo

Recruitment Strategy Document

Study Title

Protocol #

NCT #

Study Logo

[This Recruitment Strategy Document is a template is intended to serve as a guide and all sections should be revised, as necessary, to reflect the specific objectives and challenges of a given protocol)

Document Approval Signatures

Owner/Author _____

[Name] [Date]

[Sr.] Clinical Project Manager

Approved by: _____

[Name] [Date]

Global Clinical Operations Lead

Approved by: _____

[Name] [Date]

Project Manager, CRO

Version History

Revision	Date	Author(s)	Description

TABLE OF CONTENTS

ABBREVIATIONS	
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CST	Clinical Sub-Team
EPT	Early-Stage Product Team
FAQs	Frequently Asked Questions
FPI	First Patient In
FPO	First Patient Out
FPS	First Patient Screened
GCOL	Global Clinical Operations Lead
GMA	Global Medical Affairs
HCP	Healthcare Professional
IRB	Institutional Review Board
KOL	Key Opinion Leader
LPI	Last Patient In
LPO	Last Patient Out
LPS	Last Patient Screened
LPT	Late-Stage Product Team
MSL	Medical Science Liaison
NCT	National Clinical Trial (identifier number)
PAG	Patient Advocacy Group
PR&R	Patient Recruitment and Retention Team
PST	Product Strategy Team
RSM	Remote Site Monitor
SSE	Study Site Engagement Team

RECRUITMENT PLAN OBJECTIVE

[Summarize the objective of this recruitment and retention plan. Include reference to diversity and plan to identify sites to meet diversity goals.]

STUDY QUESTION

[Briefly describe the study question and general target population. Include reference to diversity and what the study question means for diverse populations or subgroup analysis.]

STUDY CHALLENGES

[Outline the study challenges from a recruitment perspective. Consider anticipated barriers to recruitment and retention, including those related to the recruitment of diverse populations.]

STUDY OPPORTUNITIES

[Outline the study opportunities from a recruitment perspective.]

STUDY ASSUMPTIONS

[Outline the original study assumptions and milestone goals.]

Number of Patients Screened:	**[# Screened]**
Number of Patients Randomized:	[# of Randomizations]
Anticipated Screen Failure Rate:	[Screen Failure %]
Planned Randomization Rate:	[# Rand / # Sites / Enrollment Period Months]
Anticipated Drop-out Rate:	[Drop-out Rate]
Planned Complete:	[Planned number of completers]
First Patient in (FPI):	[Date]
Last Patient in (LPI):	[Date]
Number of Sites:	[# Sites]
Number of Countries:	[# Countries]

PATIENT PROFILE

PATIENT DISEASE PROFILE

*[Outline the patient profile including disease prevalence, **demographics**, symptoms, burden of disease diagnosis pathway, treating physician's treatment options, etc. Consider this with relation to the study question.]*

PATIENT JOURNEY

[Include a patient pathway visual or flow of how a patient gets diagnosed, treated and opportunities for study awareness.]

CHALLENGES OF PARTICIPATING FROM A PATIENT PERSPECTIVE

[Include a bulleted list of potential study-specific challenges and risks. Detail all anticipated challenges, e.g., how will study requirements, hours, locations, travel costs impact recruitment of specific demographic.]

OPPORTUNITIES OF PARTICIPATING FROM A PATIENT PERSPECTIVE

[Include a bulleted list of potential study-specific opportunities and benefits.]

STUDY RESPONSIBILITIES

[List the vendors involved with site engagement, recruitment, and retention. Additionally may outline the roles and responsibility of the CRO / CRAs with overall and site-based recruitment and the communication plan among all vendors.]

COMPETITIVE LANDSCAPE

[Outline/summarize the current and forthcoming competing studies, how they may impact your study recruitment, and how you are leveraging internal groups to keep up to date on competition.]

Trial Phase	Sponsor	Primary Drugs	Target Accrual	Trial Locations	Timeline

STUDY FEASIBILITY SUMMARY

[Outline who conducted study feasibility and when it was completed. List out the key learnings and how they may have been applied to protocol design and/or site selection, considering partnerships with community organizations and/or patient / advocacy input. Additionally, list out the projected randomization rate and how this rate was established / validated.]

COUNTRY SELECTION

[Outline how and why the countries were selected.]

SELECTED COUNTRIES AND PLANNED PROJECTIONS

[Include country targeted sites and patients, along with site activation schedule provided by CRO.]

Country	Randomization Target (N)	Total Number of Sites	Monthly Randomization Rate per Site (P/S/M)	Over Enrollment Allowance (%)	Screen failure ratio (% screen fail)	Sites Actively Screening (%)	Target First Site Initiated (Date)	# of days until 25% Sites Active	# of days until 50% Sites Active	# of days until 90% Sites Active	First Patient Screened (FPI) (Date)
Global	*50*	*15*	*0.230*	*15%*	*55.0%*	*40%*	*4-Apr-20*	*0*	*30*	*90*	*8-Jun-20*

BACKUP COUNTRIES

[Include a list of any backup countries in the event additional countries are required.]

COUNTRIES NOT SELECTED

[Include a list of any specific countries that were not selected or cannot participate in this study and the reasons why.]

SITE PROFILE

CURRENT SITE CAPACITY PROFILE

[Outline what the current site profile is including patient capacity, staffing/resourcing, specialty type (if any), experience, special needs/equipment, etc. Detail site capacity for recruitment of targeted demographics: age, sex, gender, race, ethnicity, etc.]

CURRENT SITE POPULATION PROFILE

{Outline the local population profile and the site population profile; use the site's completed feasibility assessment data to inform the site population profile.]

PATIENT RECRUITMENT STRATEGIES AND TOOLS

RECRUITMENT AND RETENTION STRATEGY

[Provide a high-level overview of primary and secondary patient recruitment and retention strategies. Include anticipated return on investment and recruitment funnel as appropriate. What specific approaches and techniques will be used to access and engage target populations / demographics?]

RECRUITMENT AND RETENTION MATERIALS

[Outline site, HCP, and patient materials to be developed and a brief description of how each material is to be used.]

Material	Brief Description

DIRECT TO PATIENT OUTREACH

[Outline what targeted patient outreach tactics or strategies will be used: in-clinic recruitment, patient navigators or ambassadors, website, mobile app, search engine marketing, display advertising, email outreach, trial listings, TV, radio, print, etc. What specific approaches and techniques (i.e., EHR mining) are employed to provide access to and engagement of target populations / demographics?]

REFERRING PHYSICIAN OUTREACH

[Outline HCP outreach strategy, source of data, implementation and follow up plan. Have the diversity goals been emphasized with study clinicians?]

PATIENT ADVOCACY OUTREACH

[Outline opportunities to work with relevant advocacy groups.]

Group Name	Group Contact

HEALTH CARE PROFESSIONAL SOCIETY OUTREACH

[Outline opportunities to work with professional societies and execution plan.]

INTERNAL AWARENESS

[Outline opportunities to raise awareness internally.]

PUBLICATIONS

[Outline opportunities to work with and produce publications.]

RECRUITMENT PROJECTIONS AND FUNNEL

[Insert recruitment funnels and projected total number of enrollments provided by recruitment vendor. Outline how enrollment will be measured, tracked (what specifically will be monitored), and expected timelines.]

[Detail site specific target numbers by subpopulation - age, sex, race, ethnicity etc.]

RECRUITMENT MONITORING AND MITIGATION PLAN

[Detail frequency of tracking and review of recruitment and enrollment numbers; provide suggested action steps for mitigation if recruitment and enrollment are under target.]

RETENTION MONITORING AND MITIGATION PLAN

[Detail frequency of tracking and review of enrolled participants and study follow-up; provide details on strategies that will be used to monitor retention (i.e., patient navigators or ambassadors; frequency and style of follow-up reminders, etc.) and provide suggested action steps for mitigation if retention is under target.]

SITE ENGAGMENT

[Outline strategy and plan on how to keep sites engaged throughout the enrollment period.]

SITE SPECIFIC RECRUITMENT PLANS

[Summarize the site-specific recruitment plan findings and how the team intends to hold the sites to their enrollment goals.]

SITE BOOSTER VISITS

[Outline site booster visit strategy including when, who, how, and intent of booster visits to be conducted. This includes visits by sponsor staff (study manager, MD, RSSL, MSL, etc.]

RECRUITMENT WEBINARS AND SITE COMMUNICATION

[Outline schedule and approach for site recruitment webinars, and any additional touch points around site communication.]

SITE-SPECIFIC ESCALATION PLAN

[Outline escalation plan for triggers and actions for sites.]

RISK AND CONTINGENCY MANAGEMENT

[Outline the risks associated with this study in terms of recruitment timelines and milestones, and list out the contingency strategies, triggers, and the action plan addressing those risks.]

STUDY COMMUNICATION

[Outline communication strategy and meetings among recruitment partners involved in supporting the study.]

Logic Model: Recruitment Strategy Documents (RSDs)

Audience: Sponsors/CROs, sites/investigators

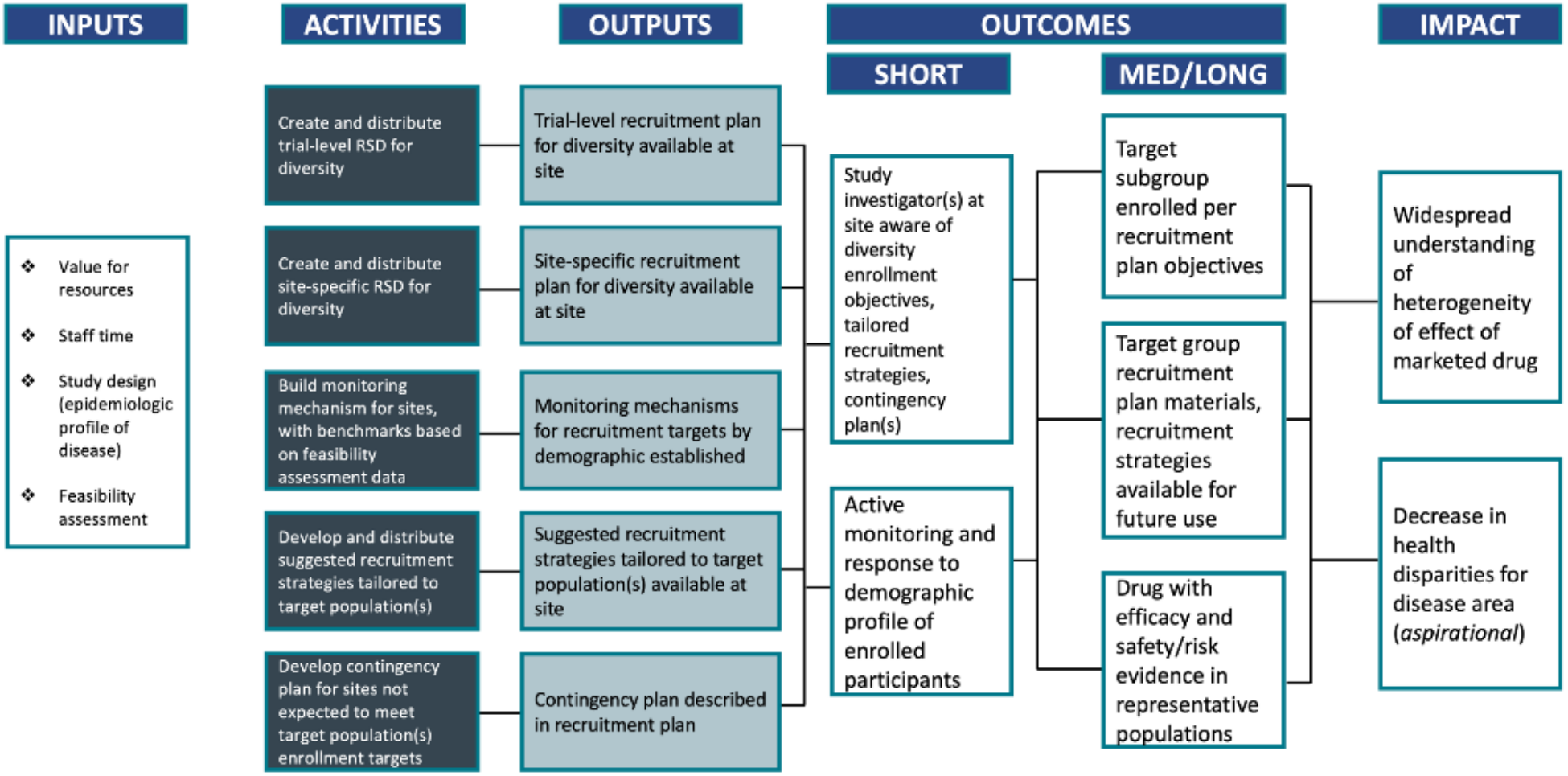
Purpose: To provide a sample of activities, linked to their intended effects (outputs, outcomes and impact), that might be included in Recruitment Strategy Documents (RSDs) aimed at achieving representative enrollment during a particular clinical trial. A non-exhaustive sample of key performance indicators for the RSD is also provided in order to demonstrate how this logic model can be used to construct performance metrics.

Considerations for use:

- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.

Logic Model: Recruitment Strategy Documents (RSDs)

Audience: Sponsors/CROs, sites/investigators



Recruitment Strategy Documents – Potential Key Performance Indicators (KPIs)

MULTI-REGIONAL CLINICAL TRIALS
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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 Contingency Action Plan*

Audience: Sponsors/CROs, sites/investigators/study teams

Purpose: To provide an operational approach to contingency planning for issues or "leaks" in recruitment of any given subpopulation. The Recruitment Contingency Action Plan offers schematics that leverage two potential "intervention points" where monitoring or oversight can occur within a clinical trial and proactive planning should be considered:

1) Intervention point 1: between sponsor/CRO and site; and

2) Intervention point 2: between the site, investigators and study teams

The schematics below provide samples for actions that can be taken by sponsors and sites when a recruitment issue or "leak" emerges for a particular subgroup. The Recruitment Contingency Action Plan is intended to guide the process in determining *context specific* contingency plans detailed within the Recruitment Strategy Document (RSD).

Considerations for use

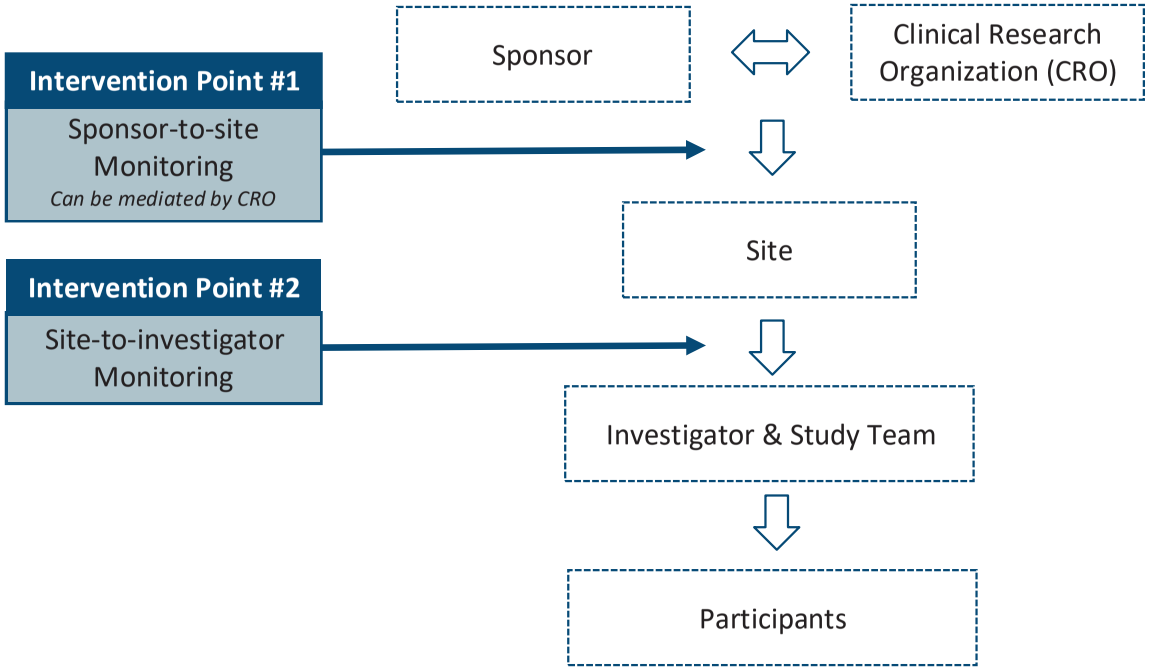
Adaptability – the schematics offer an example of an emergent issue in subpopulation-specific enrollment. However, the approach detailed is highly adaptable to whatever recruitment issues or "leaks" emerge within a particular clinical trial.

Monitoring systems – the schematics assume two intervention points within existing monitoring "intervention points" as detailed above. These "intervention points" might look different depending on the stakeholders involved, or in large, complex or multi-regional clinical trials.

*Adapted from: Harper, B. Clinical Research Recruitment & Retention Tactics. Clinical Performance Partners, Inc. 2017.

Multi-Tiered Monitoring in Clinical Trials

Intervention points for monitoring enrollment of specific populations



- Sponsors, CROs and sites can consider the following intervention points to monitor the recruitment and enrollment processes, evaluate how to enhance the pre-screening and screening processes and/or also minimize patient inconveniences, patient appointment "no-shows" or lost to follow-ups as well as consider additional areas to help support the patient education process.

Intervention Point #1:
Example of Recruitment Contingency Action Plan between **Sponsor / CRO and Site**

Issue	Action required by Site	Action required by Sponsor/CRO	Action plan status updates
Proportion of enrolled participants of a particular demographic is below target, indicating site may not achieve demographic enrollment goal	Site to further define reasons for low enrollment achievement and implement strategic programming for this demographic	Sponsor/CRO to support action chosen by site, provide strategic guidance, share resources for targeted programming, and to provide additional budget (as available) for targeted programming	1. Site met with community organization 2. Additional funding received by site from sponsor/CRO 3. Targeted programming implemented by site staff 4. Continuously track enrollment figures for demographic subgroups
Example: proportion of Black participants is lower than expected at the time of monitoring. This indicates that the site might not achieve its demographic enrollment goal for Black participants	**Example**: site staff to set up meetings with predetermined black community organizations to implement targeted pamphlet distribution for Black participant recruitment	**Example**: sponsor/CRO to provide predetermined demographic underperformance budget for targeted programming	

Intervention point #2:
Example of Recruitment Contingency Action Plan between **Site and CRA**

Issue	Action required by CRA	Action required by Site	Action plan status updates
Participants with similar demographic(s) miss appointment	Determine why these participants missed appointment and inform site	Site staff to incorporate additional retention methods to address subgroups' low rates of retention or missed visits	1. Site received additional recruitment supports from sponsor/CRO 2. Site has no more "no-shows" of target demographic(s) since reminder program
Example: 3 young Latino participants missed their appointment	**Example**: contact participant and/or their families by phone/text/email to understand reason for missed appointment	**Example:** site staff to send appointment card/email reminder one week in advance of appointment, and text message reminder day before to young Latino participants	

Participant Time Commitment Model

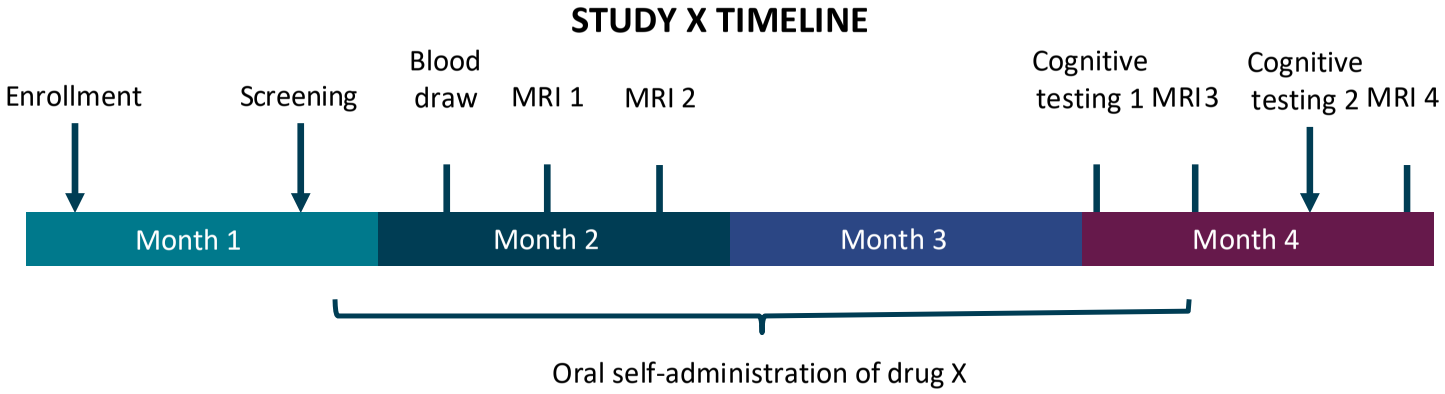
Audience: Sites/investigators

Purpose: To provide a model for a participant-centered study calendar, wherein the participant's time commitment for study participation is clearly structured and outlined in detail. The Participant Time Commitment model offers calendars and associated tables as an example for a theoretical study (Study X) investigating a treatment for Alzheimer's.

Considerations for use

- *Adaptability* – the Participant Time Commitment Model offers an example of how to integrate a participant's schedule with a study schedule to proactively plan for study visits, specimen and data collection points. Because study timelines and requirements vary significantly, this tool serves as a reference guide to be adapted further by study staff and implementation partners.
- *Unique* – each study calendar will be unique for each study participant, dependent on the commitments required by their personal life, workplace, enrollment date (the exemplar study assumes an enrollment date of September 1 for a hypothetical participant).

STUDY X: a phase 2 trial for an oral self-administered Alzheimer's drug



STUDY X REQUIREMENTS					
Month	**Appointment Purpose**	**Number of Appointments**	**Timing**	**Total Time**	**Transport Included**
Month 1	Screening	2	Non-consecutive	8 hours (4hrs/appt)	Yes
Month 2	Blood draw	1	--	2 hours	Yes
	MRIs	2	14 days apart	6 hours (3hrs/appt)	Yes
Month 3	--	--	--	--	--
Month 4	Cognitive testing	2	--	16 hours (8hr/appt)	Yes
	MRIs	2	14 days apart	6 hours (3hrs/appt)	Yes

STUDY X – Month 1

SEPTEMBER

Filled by site staff

Appointment Purpose	Number of Appointments	Timing	Total Time	Transport Included
Screening	2	Non-consecutive	8 hours (4hrs/appt)	Yes

Filled by participant

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						Appointment 1: preferred
Appointment 1: possible						Appointment 2: preferred
Appointment 2: possible						

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STUDY X – Month 2

STUDY X - OCTOBER

Appointment Purpose	Number of Appointments	Timing	Total Time	Transport Included
Blood draw	1	--	2 hours	Yes
MRIs	2	14 days apart	6 hours (3hrs/appt)	Yes

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					Blood draw appointment: possible, after 4pm	Blood draw appointment: preferred, any time
					MRI appointment 1: possible, after 4pm	MRI appointment 1: preferred, anytime
					MRI appointment 2: possible, after 6p	MRI appointment 2: preferred, after 1pm

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STUDY X – Month 3

STUDY X - NOVEMBER

Continue drug or placebo (no in-person appointments this month!)

Appointment Purpose	Number of Appointments	Timing	Total Time	Transport Included
--	--	--	--	--

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

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STUDY X – Month 4

STUDY X - DECEMBER

Appointment Purpose	Number of Appointments	Timing	Total Time	Transport Included
Cognitive testing	2	--	16 hours (8hr/appt)	Yes
MRIs	2	14 days apart	6 hours (3hrs/appt)	Yes

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					MRI appointment 1: possible, after 4pm	Cognitive testing appointment 1: possible, any time
					MRI appointment 1: preferred, after 4pm	Cognitive testing appointment 1: preferred, any time
					MRI appointment 1: possible, after 4pm	Cognitive testing appointment 2: possible, any time
					MRI appointment 2: preferred, after 4pm	Cognitive testing appointment 2: preferred, any time

Logic Model: Recruitment, Conduct and Retention

Audience: Sponsors/CROs, sites/investigators

Purpose: To provide a sample of activities, linked to their intended effects (outputs, outcomes and impact), that might be included during study recruitment, conduct and retention of a trial that is aiming to achieve representative enrollment. A non-exhaustive sample of key performance indicators for these study implementation activities is also provided in order to demonstrate how this logic model can be used to construct performance metrics.

Considerations for use:

- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.

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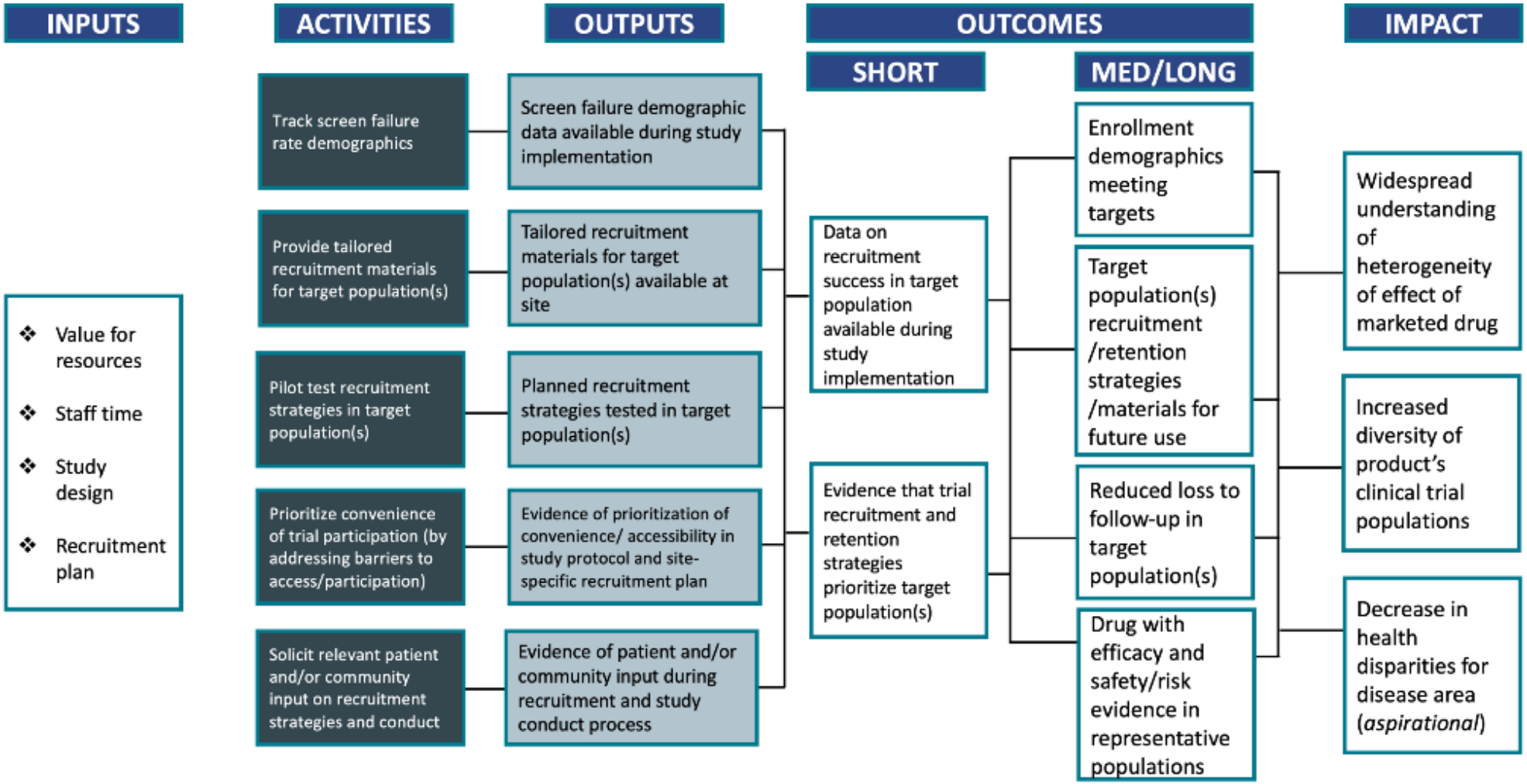
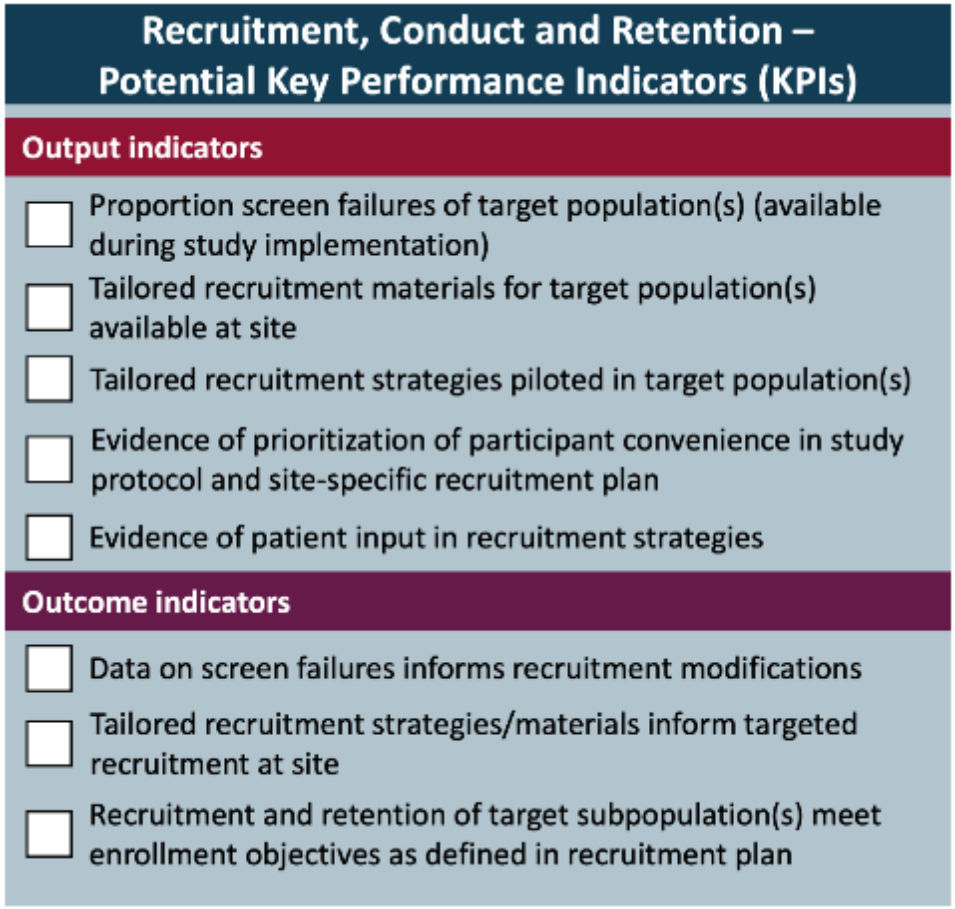
Logic Model: Recruitment, Conduct and Retention

Audience: Sponsors/CROs, sites/investigators





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Logic Model: Accountability

Audience: Sponsors/CROs, sites/investigators

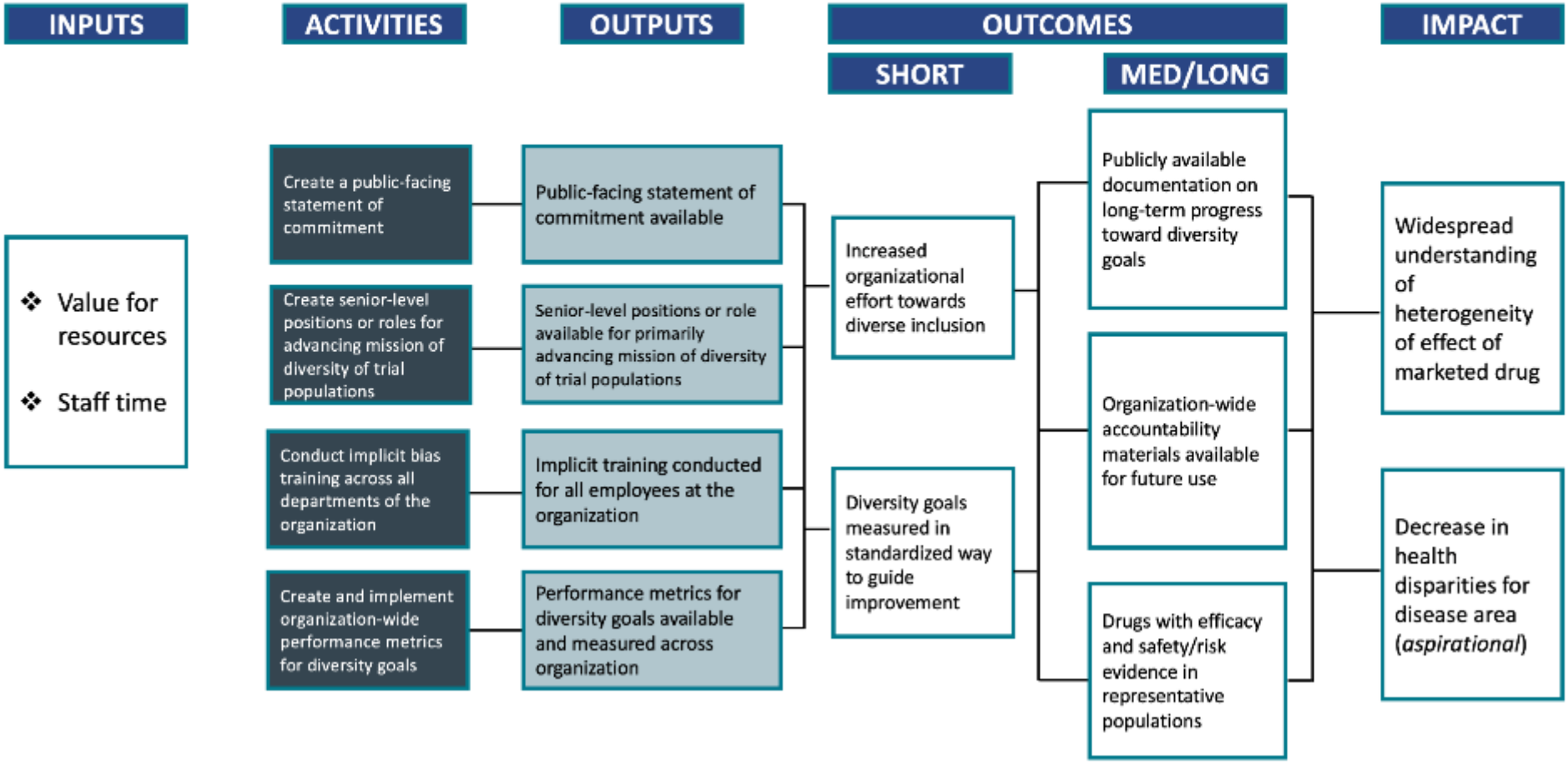
Purpose: To provide a sample of activities, linked to their intended effects (outputs, outcomes and impact), that might be included in any organization's strategy for being accountable to the mission of increasing diverse enrollment in clinical trials. A non-exhaustive sample of key performance indicators for such a strategy is also provided in order to demonstrate how this logic model can be used to construct performance metrics.

Considerations for use:

- See *Introduction to Logic Models* for detailed instruction on the use of logic models in general and as related to the *Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document*.
- Note that in Part F of the Guidance Document ("Stakeholder Commitments and the Future"), the accountability for diverse representation is placed on multiple unique stakeholders. This logic model does not aim for this level of granularity, and rather provides generic activities that could be pursued by any stakeholder organization.

Logic Model: Accountability

Audience: Sponsors/CROs, sites/investigators



Accountability – Potential Key Performance Indicators (KPIs)

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Output indicators

- ☐ Public-facing statement of commitment available on website
- ☐ Proportion of senior-level positions/roles with diversity focus
- ☐ Performance metrics available internally for diversity goals
- ☐ Proportion of employees participated in implicit bias training

Outcome indicators

- ☐ Organizational diversity goals measured using predetermined performance metrics
- ☐ Increased organizational effort towards diverse inclusion, as measured by company-wide survey self-report
- ☐ Diversity language in contracts with CROs informs diversity-related study implementation measures
- ☐ Proportion of clinical trial populations achieving epidemiologically representative demographics increased

Diversity & Inclusion Organizational Strategy

A model checklist for any clinical research stakeholder*

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Priority-setting, governance and monitoring strategies

- ☐ Establish organization-wide Diversity & Inclusion policy
- ☐ Assemble a multi-stakeholder council for Diversity & Inclusion priority-setting, strategy and governance
- ☐ Create performance indicators to measure each Diversity & Inclusion initiative implemented
- ☐ Identify demographic diversity profile for the intended population of each therapeutic area. Strategic initiatives should focus on key subpopulations identified
- ☐ Ensure Diversity & Inclusion is prioritized in every work stream. If the organization is for-profit, ensure that Diversity & Inclusion is integrated into commercial activities

Internal workforce development strategies

- ☐ Create and publicly endorse a set of workforce Diversity & Inclusion principles to guide workforce development activities
- ☐ Create employee resource groups, focused on the diverse demographic identities held by employees (i.e., groups connecting and empowering LGBTQ+ employees, Black employees, older employees, etc.)

External community development strategies

- ☐ Engage in political advocacy around contemporary, relevant Diversity & Inclusion issues
- ☐ Create community initiatives addressing demographic disparities in Science, Technology, Engineering and Mathematics (STEM) education

*Adapted from Biogen's Diversity and Inclusion strategy, available at: https://www.biogen.com/en_us/diversity-inclusion.html

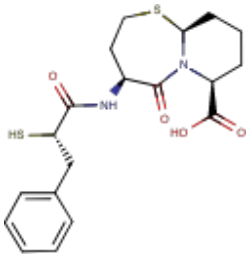
Case Study: Omapatrilat

Key lessons learned

- The safety profile of a medication may differ among different subpopulations of participants and the possibility of differences in adverse events—and efficacy—is good reason to include participants of diverse backgrounds in clinical trials and post- marketing research studies.
- Safety of a drug must be measured with regard to benefit, both which may vary by subpopulation.
- Often the biological basis of any difference in safety or efficacy based on demographics is poorly understood.

Disease background

High blood pressure, also known as hypertension, is a common condition whereby the blood that flows through veins or arteries is at a higher than normal pressure.[1] An estimated 1.13 billion people worldwide have hypertension, the majority of which live in low- and middle- income countries.[2] Having high blood pressure puts one at risk for heart disease and stroke. In 2017, nearly half a million deaths in the United States listed hypertension as a primary or contributing cause.[3] Furthermore, rates of high blood pressure vary by sex, race, ethnicity and geography,[4] all variables that may complicate treatment and medication management.



Drug development and clinical findings

Treatment for high blood pressure involves a combination of different therapies, lifestyle changes and medications. One of the more common anti-hypertensive drug class used to treat hypertension is angiotensin- converting enzyme (ACE) inhibitors. ACE inhibitors work by blocking the hormone (angiotensin II) responsible for narrowing blood vessels. Other drug classes control levels of proteins in the blood to help high blood pressure. Omapatrilat, a drug developed by Bristol-Myers Squibb, was initially heralded as a far more effective anti-hypertensive treatment because it lowered blood

[1] National Heart, Lung, and Blood Institute. High Blood Pressure [Internet]. National Institutes of Health. Available online: https://www.nhlbi.nih.gov/health-topics/high-blood-pressure [Accessed April 15, 2020].

[2] World Health Organization. Hypertension [Internet]. World Health Organization. Sept 13, 2019. Available online: https://www.who.int/news-room/fact-sheets/detail/hypertension [Accessed April 15, 2020].

[3] Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. Available online: https://wonder.cdc.gov [Accessed April 15, 2020].

[4] Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. Available online: https://wonder.cdc.gov [Accessed April 15, 2020].

pressure in two ways – by inhibiting the hormones that cause blood vessels to constrict and also by changing proteins levels in the blood.

Clinical trials with omapatrilat were promising. They showed that omapatrilat was much more effective in lowering blood pressure than another common, marketed drugs.[5,6,7] However, these studies also showed an increase in a side effect called angioedema – a condition where there is localized swelling of the skin particularly on the face, lips, mouth, and throat.[8]

Studies pursued the use of omapatrilat to control high blood pressure;[9] the *OCTAVE* (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) study[10] was a multicenter, randomized, double-blind, active-controlled trial that aimed to enroll approximately 25,000 patients to better characterize the risk–benefit relationship of omapatrilat compared with another ACE inhibitor. Findings showed that omapatrilat significantly reduced blood pressure as compared to the other drug and those who received omapatrilat did not require as much antihypertensive therapy overall. This was true for all subgroups analyzed (e.g., age, sex, ethnicity, race, type of and severity of hypertension, comorbidity).

The incidence of adverse events, however, was imbalanced as rate of angioedema was increased approximately threefold in Black patients as compared to others.[11] Smokers also had an increased risk for angioedema. Notably, given the risk of serious cardiovascular disease, the calculated reduction in potential cardiovascular events by treatment with omapatrilat would outweigh the risk of clinically significant angioedema in all patient groups, although the increased risk in Black patients and smokers would need to be considered prior to prescribing the drug.

Bristol-Myers Squibb (BMS), the developer of omapatrilat, voluntarily halted drug development in the United States in 2000 following the early reports regarding the risk of angioedema.
Clinical development proceeded elsewhere; however, in 2002, results from the OCTAVE study led to a non-approval vote by a U.S. FDA advisory committee and clinical development was stopped completely. To date, the biological cause of angioedema remains unexplained and the pathophysiological explanation for the increased risk in Black patients remains elusive.

[5] Asmar R, Fredebohm W, Senftleber I, Chang PI, Gressin V, Saini RK. A085: Omapatrilat compared with lisinopril in treatment of hypertension as assessed by ambulatory blood pressure monitoring. American Journal of Hypertension. 2000 Apr 1;13(S2):143A.

[6] Campese VM, Lasseter KC, Ferrario CM, Smith WB, Ruddy MC, Grim CE, Smith RD, Vargas R, Habashy MF, Vesterqvist O, Delaney CL. Omapatrilat versus lisinopril: efficacy and neurohormonal profile in salt-sensitive hypertensive patients. Hypertension. 2001 Dec 1;38(6):1342-8.

[7] Neutel J, Shepherd A, Pool J, Levy E, Saini R, Chang PI. D054: Antihypertensive efficacy of Omapatrilat, a vasopeptidase inhibitor, compared with lisinopril. American Journal of Hypertension. 1999 Apr 1;12(S4):124A.

[8] Gang C, Lindsell CJ, Moellman J, Sublett W, Hart K, Collins S, Bernstein JA. Factors associated with hospitalization of patients with angiotensin-converting enzyme inhibitor–induced angioedema. In Allergy and asthma proceedings. 2013 May (Vol. 34, No. 3, p. 267). OceanSide Publications.

[9] Coats AJS. Omapatrilat—the story of Overture and Octave. International Journal of Cardiology. 2002: 86: 1-4.

[10] Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. American Journal of Hypertension. 2004 Feb 1;17(2):103-11.

[11] Coats AJS. Omapatrilat—the story of Overture and Octave. International Journal of Cardiology. 2002: 86: 1-4.

Case Study: *All of Us* Research Program

Background

Representation of diverse populations is important in clinical trials, in part to understand whether drug efficacy or effectiveness, dosage, and safety are equivalent across populations as well as for reasons of appropriate access to cutting edge therapies. The *All of Us* Research Program (https://allofus.nih.gov/) is a large observational research study, part of the Precision Medicine Initiative (PMI) and supported by National Institutes of Health (NIH).[1] The All of Us Research Program, launched nationally in May 2018, serves as a repository that is collecting data from a diverse and representative U.S. population and across a variety of health conditions. As of April 2020, the program has over 350,000 participants enrolled and plans to provide access to de-identified and encrypted data to researchers.[2]

The mission of the *All of Us* Research Program is to enable and accelerate health research and medical breakthroughs. One of its strategic priorities is to ensure that the program recruits a diverse group of participants – focusing on participants of every race, ethnicity, sex, gender, and sexual orientation who live in United States, and inclusive of individuals in rural and urban settings, with and without health insurance. A 2019 review of the *All of Us* Research Program indicated that more than 80% of participants in the *All of Us* Research Program are from groups that have been historically underrepresented in biomedical research and data repositories or clinical trial data to date.[3]

[1] Devaney S. All of Us Research Program. National Institutes of Health. National Advisory Child Health and Human Development Council. Jan. 31, 2017. Available online: https://www.nichd.nih.gov/sites/default/files/about/advisory/council/archive/201701/Documents/201701_devaney.pdf [Accessed Aug. 8, 2018].

[2] National Institutes of Health. Data Snapshots - All of Us Research Hub [Internet]. Available online: https://www.researchallofus.org/data-snapshots/?_ga=2.23730355.827964377.1586792768-646145407.1586544775 [Accessed April 13, 2020].

[3] All of Us Research Program Investigators. The "All of Us" Research Program. New England Journal of Medicine. 2019 Aug 15;381(7):668-76.

Pre-launch stage: Considerations and steps taken

During the early planning process for the *All of US* Research Program, the NIH conducted public workshops on issues of design and vision for the cohort and issued two Requests for Information.[4,5] One of the workshops concluded that continued engagement of a broad range of stakeholders would be needed to plan, execute, and sustain the PMI cohort program. As part of this larger public engagement effort, a survey of U.S. adults was conducted to measure support for such a study, acceptability of various design features, and to identify and prioritize concerns from the public.[6]

In addition to hosting public workshops, the NIH also conducted a preliminary pilot study,[7] sponsored focus groups,[8] sent out surveys,[9] and held listening sessions with people about their hopes, ideas, and concerns regarding the collection of detailed and sensitive health information from a million or more people over their lifetimes.[10] The listening sessions targeted LGBTQI groups,[11] vulnerable groups (sexual and gender minorities[12]) and others to understand their specific concerns and foster public engagement. In addition, online surveys were conducted to determine preferences of potential participants of the program. Seventy-nine percent of the U.S. adults who responded to the survey were supportive of a large national cohort study.[13] Levels of support for the study as well as willingness to participate were consistent across most demographic groups.

[4] National Institutes of Health. Summary of Responses from the Request for Information on Building the Precision Medicine Initiative National Research Participant Group [Internet]. Bethesda: National Institutes of Health; May 28, 2015. Available online: https://www.nih.gov/sites/default/files/research-training/initiatives/pmi/pmi-workshop-20150528-rfi-summary.pdf [Accessed Aug 21, 2018].

[5] National Institutes of Health. Request for Information: NIH Precision Medicine Cohort—Strategies to Address Community Engagement and Health Disparities [Internet]. Bethesda: National Institutes of Health; June 22, 2015. Available online: http://www.nih.gov/precisionmedicine/rfi-announcement-06022015.htm [Accessed Aug. 21, 2018].

[6] Kaufman DJ, Baker R, Milner LC, Devaney S, Hudson KL. A survey of US adults' opinions about conduct of a nationwide Precision Medicine Initiative® cohort study of genes and environment. PLoS One. 2016;11(8).

[7] Beasley, D. Verily, Vanderbilt to test enrollment in U.S. Precision Medicine Pilot. Health News. Feb 25, 2016. Available online: https://www.reuters.com/article/us-health-us-precisionmedicine-idUSKCN0VY1BL [Accessed Aug 20, 2018].

[8] Kaufman D, Murphy J, Scott J, Hudson K. Subjects matter: a survey of public opinions about a large genetic cohort study. Genet Med. 2008;10(11):831-839.

[9] Murphy-Bollinger J, Bridges JF, Mohamed A, Kaufman D. Public preferences for the return of research results in genetic research: a conjoint analysis. Genet Med. 2014;16(12):932-939.

[10] Dishman, E. "I handed over my genetic data to the NIH. Here's why you should, too." Stat News. June 13, 2018. Available online: https://www.statnews.com/2018/06/13/entrusted-my-genetic-data-nih/ [Accessed Aug. 20, 2018].

[11] The Montrose Center. The LGBTQI Health Community Listening Sessions – All of Us Research Survey. Huston. Available online: http://www.montrosecenter.org/all-of-us-research-survey/ [Accessed Aug 20, 2018].

[12] Baker, M. UCSF to Develop National Network for Health. Data of Sexual, Gender Minorities. University California San Francisco. Aug 22, 2017. Available online: https://www.ucsf.edu/news/2017/08/408116/ucsf-develop-national-network-health-data-sexual-gender-minorities [Accessed Aug. 20, 2018].

[13] Kaufman D, Murphy J, Scott J, Hudson K. Subjects matter: a survey of public opinions about a large genetic cohort study. Genet Med. 2008;10(11):831-839.

The opportunity to learn about one's own health information from the study appeared to be a strong motivation to participate.[14]

The *All of Us* Research Program continues to successfully engage people and provide them with information about participation.[15] From the outset, the program embodied the following recruitment and enrollment ideas and marketing strategies to encourage diverse inclusion in clinical research:

Recruitment and enrollment ideas

- Eligibility criteria: The *All of Us* Research Program considered how to address barriers for certain groups. Minorities are more likely to be un- or under-insured, to seek care at under-resourced hospitals, and to have concerns about the cost of participating in a clinical trial.[16] Lack of or inadequate health insurance can act as a barrier to enrollment in clinical trials for several under-represented populations, including racial and ethnic minorities.[16] Language complexity and translation are also considered to be barriers for certain populations.[16] Enrollment as a participant in *All of Us* Research Program encourages inclusion of diverse participation by stipulating that:[17]
  - No health insurance is required.
  - Joining the program and any appointments or activities that are part of the study are free of costs.
  - Participation is irrespective of one's nationality or health status.
  - Spanish speaking advisors are provided. Plans are underway to add additional languages.
  - No computer, tablet or smartphone devices are required to join.

[14] National Institutes of Health. Request for Information: NIH Precision Medicine Cohort—Strategies to Address Community Engagement and Health Disparities [Internet]. Bethesda: National Institutes of Health; June 22, 2015. Available online: http://www.nih.gov/precisionmedicine/rfi-announcement-06022015.htm [Accessed Aug. 21, 2018].

[15] Ross, B. Precision Communication for Precision Medicine: How NIH's All of Us Is Tackling Patient Recruitment [Internet]. Clinical. Research News Online. Aug 2, 2018. Available online: https://www.clinicalresearchnewsonline.com/news/2018/08/02/precision-communication-for-precision-medicine-how-nihs-all-of-us-is-tackling-patient-recruitment.aspx [Accessed Sept. 11, 2018].

[16] Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, Tilburt J, Baffi C, Tanpitukpongse TP, Wilson RF, Powe NR. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2008 Jan 15;112(2):228-42.

[17] National Institutes of Health. Who can join, All of Us Research Program [Internet]. 2020. Available online: https://www.joinallofus.org/en/who-can-join [Accessed Sept. 11, 2018]

- Benefits to encourage participation: Participants are offered a one-time payment of $25 in the form of cash, gift card, or electronic voucher if they agree to provide blood, urine, saliva samples and to have physical measurements such as height, weight, blood pressure and heart rate recorded.
- Building trust: Building trust across the diverse population and understanding concerns/feedback through community partnerships is critically important.[18] The *All of Us* Research Program utilizes community advocacy groups and participant advisory boards at participating health care organizations provide reports on participant feedback to better understand what was successful and what continues to be a challenge. Privacy and security of the information collected are considered important issues.
- Privacy Safeguards: The data that participants give to the *All of Us* Research Program are personal, and the program is designed to follow strict security protocols and processes to ensure protection.[19] All the data that are received by the *All of Us* Research Program are encrypted and de-identified before they are deposited on the secure platform. In anticipating of opening access to the data for research, the *All of Us* Research Program plans to require requesting researchers to undergo ethics training and to abide by a code of conduct for data use. In addition to this, the platform tracks researcher activity and no data can be downloaded from the platform.
- Legal Protections: Participant data in the *All of Us* Research Program are afforded special legal protections and the program has U.S.-issued Certificates of Confidentiality to protect the privacy of research participants.

Marketing strategies

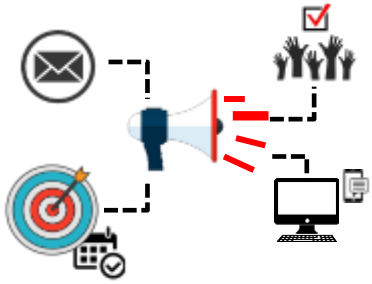
- *Community Resources*: The *All of Us* Research Program produced brochures and documents as resources to potential participants. These resources are available on the *All of Us* Research Program website (https://allofus.nih.gov) as free, downloadable material to assist community members explain and disseminate information about the program. These brochures are customized based on communities, and include:
  - National Brochure - General Community
  - National Brochure - African American Community
  - National Brochure - Asian American Community
  - National Brochure - Hispanic American Community
  - Program FAQ (Document with 60 answers to common questions) and National Program FAQ (7 most frequently asked questions)

[18] Sankar PL, Parker LS. The Precision Medicine Initiative's All of Us Research Program: an agenda for research on its ethical, legal, and social issues. Genetics in Medicine. 2017 Jul;19(7):743-50.
[19] National Institutes of Health. Privacy Safeguards - Join All of Us [Internet]. Available online: https://www.joinallofus.org/privacy-safeguards [Accessed Aug. 8, 2018].

- *Multi-media educational resources*: In addition to available brochures, the message about the *All of Us* Research Program is disseminated through short videos that include information about the program, its benefits, and the importance of diverse participation. The videos are posted online (https://allofus.nih.gov/news-and-events/all-us-sharable-resources) and also on a designated YouTube channel (https://www.youtube.com/channel/UCQId1TfpwPaYiDIGlxEhlkA) accessible to the public. Videos are also available in Spanish.
- *Additional informational resources:* Workshops, webinars, and a 37-week national tour were held to invite community members to join the cohort. The events were free and open to the public, assisted by volunteers that, additionally, offered other interactive sessions: CPR trainings, face painting and balloon art for the children, photo booth, live music, and art, all to promote the *All of Us* Research Program.[20]
- *Representative Considerations:* Marketing strategies, documents, and pictures consciously represent diverse populations and promote inclusion. All resources are freely accessible, translated and customized based on the targeted community.

What will success look like?

The *All of Us* Research Program invested considerable time and resources from its vision in 2015 to national launch in spring 2018 to understand and ensure diverse recruitment. To be successful, the *All of Us* Research Program will need to add value to its stakeholders: participants, health care providers, researchers and communities. Recruitment into the study is estimated to continue into 2024 with new sites adding to the weekly recruitment rate of 3,000+ participants.21 As participants are longitudinally followed over decades to come, the All of Us Research Program should help researchers better understand health and disease of underrepresented populations, and as a result, improve accuracy of diagnoses, disease- prevention strategies, treatment selections and targeted therapies. We will all continue to learn from analyses of the All of Us Research Program's successful strategies.



[20] National Institutes of Health. Journey and Events - Join All of Us [Internet]. Available online: https://www.joinallofus.org/journey-and-events [Accessed Aug., 20, 2018.]

[21] All of Us Research Program Investigators. The "All of Us" Research Program. New England Journal of Medicine. 2019 Aug 15;381(7):668-76.

Case Study: Multiple Sclerosis Research Mythbusting Series

Summary

While multiple sclerosis (MS) affects all races and ethnicities, minority populations may bear an unequal burden from the disease. Blacks may not only have a higher risk of developing MS, but it may be more aggressive, with more severe effects and faster progression.[1,2,3,4,5,6,7,8,9] Latinos may have an earlier onset of disease and may be more prone to lesions located in the spinal cord and optic nerve.[10,11]

Genetic, environmental, and social factors may contribute to the development of MS and the treatment received for the disease. In fact, minorities in the U.S. have higher rates of MS compared to people living in their ancestral communities.[12] Additional disparities relating to access to health services, differing cultural beliefs, and distrust of the medical profession may also contribute to worse outcomes.

[1] Khan O, Williams MJ, Amezcua L, Javed A, Larsen KE, Smrtka JM. Multiple sclerosis in US minority populations: Clinical practice insights. Neurology: Clinical Practice. 2015 Apr 1;5(2):132-42.
[2] Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosis in multiple racial and ethnic groups. Neurology. 2013 May 7;80(19):1734-9.
[3] Wallin MT, Culpepper WJ, Coffman P, Pulaski S, Maloni H, Mahan CM, Haselkorn JK, Kurtzke JF, Veterans Affairs Multiple Sclerosis Centres of Excellence Epidemiology Group. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. Brain. 2012 Jun 1;135(6):1778-85.
[4] Kimbrough DJ, Sotirchos ES, Wilson JA, Al-Louzi O, Conger A, Conger D, Frohman TC, Saidha S, Green AJ, Frohman EM, Balcer LJ. Retinal damage and vision loss in African American multiple sclerosis patients. Annals of neurology. 2015 Feb;77(2):228-36.
[5] Howard J, Battaglini M, Babb JS, Arienzo D, Holst B, Omari M, De Stefano N, Herbert J, Inglese M. MRI correlates of disability in African-Americans with multiple sclerosis. PloS one. 2012 Aug 10;7(8):e43061.
[6] Naismith RT, Trinkaus K, Cross AH. Phenotype and prognosis in African-Americans with multiple sclerosis: a retrospective chart review. Multiple Sclerosis Journal. 2006 Nov;12(6):775-81.
[7] Kister I, Chamot E, Bacon JH, Niewczyk PM, De Guzman RA, Apatoff B, Coyle P, Goodman AD, Gottesman M, Granger C, Jubelt B. Rapid disease course in African Americans with multiple sclerosis. Neurology. 2010 Jul 20;75(3):217-23.
[8] Ventura RE, Antezana AO, Bacon T, Kister I. Hispanic Americans and African Americans with multiple sclerosis have more severe disease course than Caucasian Americans. Multiple Sclerosis Journal. 2017 Oct;23(11):1554-7.
[9] Weinstock-Guttman B, Ramanathan M, Hashmi K, Abdelrahman N, Hojnacki D, Dwyer MG, Hussein S, Bergsland N, Munschauer FE, Zivadinov R. Increased tissue damage and lesion volumes in African Americans with multiple sclerosis. Neurology. 2010 Feb 16;74(7):538-44.
[10] Amezcua L, Oksenberg JR, McCauley JL. MS in self-identified Hispanic/Latino individuals living in the US. Multiple Sclerosis Journal-Experimental, Translational and Clinical. 2017 Sep;3(3):2055217317725103.
[11] Rivas-Rodríguez E, Amezcua L. Ethnic Considerations and Multiple Sclerosis Disease Variability in the United States. Neurologic clinics. 2018 Feb;36(1):151.
[12] Amezcua L, Lund BT, Weiner LP, Islam T. Multiple sclerosis in Hispanics: a study of clinical disease expression. Multiple Sclerosis Journal. 2011 Aug;17(8):1010-6.

Minority populations are severely underrepresented in scientific research in general, and this is true of MS as well. According to FDA Drug Trials Snapshots[13] reports showing the demographic characteristics of clinical trials for four recently approved MS drugs, fewer than 6% of the combined participants for these trials belonged to a race other than White. Without the participation of minority populations in MS research studies, it is impossible to understand how the disease manifests and which treatments work best in all people with MS.

People affected by MS from underserved populations may be reluctant to participate in research due to misconceptions about what participation entails, the benefits of research to individuals and their communities, and the risks and demands of participation. To address these needs and concerns, two advocacy organizations that serve the MS community decided to join forces and develop an educational event series, focused on providing current, factual information about research participation and study opportunities that may be of interest to individuals with MS.

Program approach

Building upon the work of the established MS Minority Research Engagement Partnership Network (MS MREPN),[14] Accelerated Cure Project (ACP) and the Multiple Sclerosis Association of America (MSAA) joined together to create and conduct a "Research Mythbusting Series" of events planned and held across the span of one year. The "Research Mythbusting Series" was designed to educate and inform people with multiple sclerosis and their care partners on topics related to participation in research. Four in-person educational events and one broadly accessible webinar were held to address the misconceptions (i.e., "myths") associated with participation in, regulations around, and goals of research.

The desired outcome of the "Research Mythbusting Series" was that people living with MS and their care partners, particularly those from racial and ethnic minority populations, would be interested in and open to participation in research as a result of an improved understanding of the role research plays in improving the health and quality-of-life of people affected by MS, and the benefits that a diverse research participant base could provide to underserved communities.

[13] U.S. Food and Drug Administration. Drug Trials Snapshots. 07/15/2020. Available at https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots. [Accessed 17 July 2020].
[14] For more information, see https://www.acceleratedcure.org/ms-minority-research-network

The specific educational objectives included:

1. An understanding of what participation in research entails including addressing misconceptions;
2. The regulations in place to provide protection to research participants;
3. The role research plays in providing evidence for treatment and quality-of-life decisions;
4. The importance of participating in research so that the evidence generated is applicable to the diverse population of people affected by MS;
5. How to assess the benefits and risks of participation; and
6. How to learn about research opportunities that are available to individuals with MS.

The in-person educational events were held in population centers where there is significant racial and ethnic diversity (i.e., Atlanta, GA; Houston, TX; Chicago, IL; and Pasadena, CA). The webinar was scheduled to accommodate both the eastern and western parts of the U.S. and was also recorded for access by those unable to attend the live event.[15,16] Each event was facilitated by a Black or Latino MS specialist using a common set of slides developed by ACP with input from MSAA and the presenters. MSAA led the recruitment efforts and managed the meeting and webinar logistics. Financial support for the series was provided by Biogen and Genentech.

Most attendees were Black and Latinos living with MS and their care partners. The live events were very interactive, with participants encouraged to ask questions throughout the events. Comments made during and after the presentations supported earlier findings by the MS MREPN that people with MS belonging to minority groups support and recognize the value of clinical research to enable future breakthroughs but are not necessarily aware of the issues arising from the lack of diversity in research studies.

Learnings from ACP and MSAA's "Research Mythbusting Series" illustrate that patient advocacy organizations working in a disease area can help to make their communities aware of the need for all groups to participate in clinical research in order for the benefits of research to be distributed more fairly. Following their joint Mythbusting series, MSAA and ACP are each continuing to communicate with underrepresented groups about research awareness and participation in order to expand the reach and impact of their message.

Points to consider

- Interactive engagement strategies, such as educational events, can help organizations identify gaps in community knowledge about clinical research more broadly
- Engagement of communities from diverse backgrounds requires intentional selection of sites and population demographics
- Community engagement works best when organizations commit to sustaining relationships and partnership through outreach activities
- Patient advocacy organizations can be an important and critical partner in building and sustaining community engagement

[15] Available online at: https://www.youtube.com/watch?v=oWMcx1BLz7c
[16] Available online at: https://mymsaa.org/videos/ms-research-mythbusting/

Case Study: Diverse Patient Engagement at a Pharmaceutical Company

Sanofi Genzyme's approach to involve patients in clinical trial development

Summary

In 2011 Sanofi acquired Genzyme, a mid-sized pharmaceutical company focused on rare diseases and one that routinely engaged patients in study planning and design. Appreciating that everyone with a condition, whether its diabetes or Duchenne Muscular Dystrophy, has their own experience and narrative, Sanofi began to apply this practice to other therapeutic areas, implementing Patient Advisory Panels to obtain input on aspects of planned clinical trials from the perspectives of potential participants. Sanofi has made listening to and incorporating patient perspectives a consistent practice throughout the clinical trial lifecycle. As a demonstration of its importance, Sanofi made the integration of patient perspectives into clinical projects one of Research & Development (R&D) priorities in 2019.

Approach

Patient Advisory Panels are a major component of prioritizing the patient perspective as a means to provide feedback on feasibility and design of clinical trials. Sanofi identifies the patients to serve on advisory panels through contracts with various patient advocacy groups. In addition to the panel itself, participants provide feedback through surveys enabling the company to use feedback for continuous improvement.

The company leverages advisory panels to enable an understanding of the diversity of patients to be enrolled in the trial. Specifically, Sanofi works to find patients for these panels that share demographic profiles with potential participants of the upcoming trial. In this way, study design and implementation are guided by relevant and informed perspectives reflecting the lived experience of the patients themselves.

Examples of patient advisory panels

Sanofi held a series of panel sessions in 2018 and 2019 with the Susan G. Komen (SGK) Foundation to integrate perspectives of a demographically diverse patient community into the study design for a phase 2 breast cancer treatment trial. The first engagement consisted of two dedicated face-to-face patient panel sessions during which women with metastatic breast cancer provided feedback on study design. Importantly, one of the sessions was facilitated by a Spanish-speaking SGK patient navigator and held for Spanish-speaking women. Navigation programs are associated with improved breast cancer survival rates and may be especially helpful for medically underserved women who lack insurance or adequate resources to see themselves through treatment.[1]

[1] Baik SH, Gallo LC, Wells KJ. Patient navigation in breast cancer treatment and survivorship: a systematic review. Journal of Clinical Oncology. 2016 Oct 20;34(30):3686.

Leadership commitment

A multi-stakeholder team of upper-and mid-level managers at Sanofi drove the effort to endorse and implement diverse patient engagement strategies. Leaders included the Senior VP of Scientific Platforms, R&D; Global Head, Clinical Sciences & Operations; Global Head, Clinical Operations Lead Office, Strategy & Collaboration; Head of Compliance Risk Assessment, Policies & Education; Public Affairs; and Patient Advocacy Groups.

Successes

Patient centricity has been identified as strategic and integral to Sanofi's culture, translating into the systematic integration of patient perspectives during study design and implementation. The company is committed to hiring staff to focus on patient engagement, and all employees attend corporate-wide global training on how to interact with patients and patient groups. Patient engagement has helped Sanofi simplify study designs in a number of tangible ways, including:

> Sanofi's approach underscores that studies are designed for people in real life-- and therefore real-life input is necessary.

- reducing the number of procedures within a protocol, thus lessening patient burden
- reducing the number of required visits to the study sites and clinics
- broadening eligibility criteria, enabling greater participant access to research
- extending the dosing window from a **required time** to a **time range,** increasing flexibility and compliance
- consideration of logistical support mechanisms in protocols, including mobile health technologies and home administration where feasible

Sanofi exemplifies an organization that has established patient engagement as a strategic priority. It has implemented an operational patient engagement process that threads through legal review and compliance (e.g., contracting, confidentiality and privacy provisions), and clinical trial operations, and has dedicated a budget to support fair inclusion of patient input in research studies.

Challenges

Although patient engagement is integral to Sanofi's clinical development process, implementation takes time. Contract negotiation and relationship management with patient advocacy groups requires time, persistence, and effort. Another challenge was the culture shift from a posture of "we cannot talk to patients or participants" to one that seeks to learn from patients, participants, and their families. Further, managing patient advisor expectations is complex when these advisors are not yet participants in the trial upon which they are advising. Sanofi informs members of the patient advisory panel that they will not be solicited for participation in future trials and that the investigational medication is not discussed for promotional purposes to avoid "false hope" with potential treatments.

Points to consider

- The perception and adage that sponsors cannot engage or talk to patients is false. A framework that is compliant and feasible to support patient engagement is possible.
- Contracting with patient advocacy groups provides appropriate access to the constituency to create patient advisory panels.
- Organizations can develop a collaborative approach to patient and patient organizations, providing financial and other support, including patients in the development process, and enabling the organization to understand and respond to patient needs and priorities.
- Emulating the process requires companies to confirm leadership commitment; identify responsible individuals; engage with patients and advocacy groups; provide training, reference materials (e.g., Patient Focused Drug Development guidance by FDA), and compensation to patient advisors; and plan and conduct patient and family advisory councils. Metrics of progress and of success are helpful.

Case Study: Diverse Recruitment at Yale Center for Clinical Investigation

Yale School of Medicine's Integrative Approach to
Recruit a Diverse Patient Population for Research

Summary

The Yale Center for Clinical Investigation (YCCI) was established in 2005 as one of the first recipients of NIH's Clinical and Translational Science Awards (CTSA) and serves as a hub for clinical and translational research at Yale School of Medicine. As an institution, the Yale School of Medicine has been focused on building an integrated approach to clinical research and clinical research participation aimed to create a partnership that included both the University health system and the larger community. Since YCCI was formed in 2005 and Yale's CTSA grant was awarded in 2006, both Yale School of Medicine (YSM) and the Yale-New Haven Health System (YNHHS) have greatly expanded their clinical practices. Supported by their CTSA, this expansion has made possible a more than 850% growth in industry-sponsored clinical trials, with NIH funding IRB-approved research requiring informed consent growing from less than 25% in 2006 to more than 70% in 2019.

The YCCI utilized a multipronged approach that included: (1) Cultural Ambassador Programs intended to foster a partnership with community leaders, and investigator teams; (2) leveraging patient portal in research by developing innovative ways of utilizing Electronic Health Records (EHRs) to house research activities; and (3) incorporating clinical research recruitment call centers with extended hours to accommodate patients interested in research outside of business hours.

Approach: Cultural ambassador program

One of the key objectives of the YCCI was to diversify clinical trials and research. In 2010 the Center, based on recommendations from a focus group, committed to diversifying clinical trials and research and initiated the Cultural Ambassador Program. The goal of the program is to partner with community leaders to engage community members to participate in research.

Partnerships were formed with the Connecticut African Methodist Episcopal Zion Churches (AME Zion), one of the oldest African American Congregations in the U.S. and Junta, one of the first Latino community-based non-profits in New Haven. Connecticut AME Zion and Junta partners select the Cultural Ambassadors, who then receive about 200 hours in research training. The Ambassador program roles include bidirectional collaboration, expressing community needs, ideas, and interest. They provide assistance in recruitment campaigns. They meet with YCCI investigators and research teams to assess protocols during the design phase, provide input on the recruitment plan, host activities in the community to raise awareness about ongoing research, translate study material and informed consent forms, and participate in community grand rounds that are held monthly.

Through this effort, YCCI has seen an increase in the participation rates of underrepresented populations across the health system each study engaging the Cultural Ambassadors has had participation of underrepresented groups ranging from 22% - 91%, with one exception at 12% underrepresented participation.

Leveraging patient portals for research

In March of 2015, Yale's *"Help Us Discover program"* was enhanced through an integration effort with Epic, Yale's enterprise-wide electronic health record. The integration, created as an opt-out enterprise, helped Yale to focus on many direct to patient innovations using Epic EHR, including the conversion of the "*Help Us Discover"* volunteer profile from a paper to an electronic profile available from a locally constructed Yale research tab in the MyChart patient portal.

Without any direct advertisements, the MyChart research profiles resulted in more than 3,329 new volunteers for clinical trials, with 2,603 individuals actually referred to and screened for a study. In addition, YCCI rolled out new direct to patient recruitment functionality through MyChart. This functionality allows the EHR to automate high level matching of patients based on study inclusion/exclusion criteria and sends alerts directly to the patient's MyChart. Yale was the first Epic site in the country to utilize this new functionality in its live environment to aid recruitment. The platform has been used in 40 studies and data from those screened and enrolled showed that: 1) underrepresented minorities made up 35% of the interested respondents; 2) 40% of all responses came after business hours or on weekends; and 3) 57% of the underrepresented minority respondents came after hours as compared with 38% non- underrepresented minorities, suggesting that the digital outreach may enhance underrepresented minority recruitment by being available 24 hours a day.

These combined efforts have enabled Yale to recruit more than 26,000 patients to research studies in FY19, with underrepresented populations making up 31% of all participants in clinical research at Yale. YCCI efforts have improved not only improved broad participation in clinical trials but improved participation by underrepresented minorities by ~29%.

Points to consider

- This case study illustrates that creating long-term community partnerships with local organizations has extensive overarching benefits. The value of this includes building trust among historically underserved communities, improving the biomedical research landscape by incorporating diverse voices into shaping research questions, and increasing recruitment and retention efforts for clinical trials.
- It also highlights the importance of having an integrative multi-pronged methodology that links healthcare to research through patient portals.
- Additionally, having after hour and weekend services for patients interested in research eliminates the burden for patients having to take time off of work to explore their options around participating/volunteering for research.

Case Study: Bucindolol

Key lessons learned

- The safety profile of a medication may differ among different subpopulations of participants and the possibility of differences in adverse events—and efficacy—is good reason to include participants of diverse backgrounds in clinical trials and post- marketing research studies.
- Prior experience and data arguably inform future trials.
- Efficacy of beta-blockers, specifically bucindolol, appeared to differ between White and Black patients, a finding that was in part revealed by sufficient representation of the populations to permit *post hoc* subgroup analysis.
- Genetic polymorphisms, and the different background rates of the polymorphism in different race and ethnic populations, may have contributed to different efficacies in response.
- Often the biological basis of any difference in safety or efficacy based on demographics is poorly understood.

Disease background

Heart failure, also known as congestive heart failure, occurs when the heart either fails to fill with enough blood (right sided heart failure) and/or is unable to pump enough blood to support other organs in the body (left sided heart failure).[1] Heart failure affects 26 million people worldwide[2] and despite significant advances in therapies and preventions, people still suffer from complications and treatment challenges.

Drug development and clinical findings

A combination of different therapies and medications are used in the treatment of heart failure. Beta-blockers are one class of drugs used to control the symptoms of heart failure caused by activity of certain hormones.[3] Bucindolol is a beta-blocker that was tested in clinical trials for heart failure.[4]

[1] National Heart, Lung and Blood Institute. Heart Failure [Internet]. National Institutes of Health. Available online: https://www.nhlbi.nih.gov/health-topics/heart-failure [Accessed 15 April 2020].
[2] Savarese G, Lund LH. Global public health burden of heart failure. Cardiac failure review. 2017 Apr;3(1):7.
[3] National Heart, Lung and Blood Institute. Heart Failure [Internet]. National Institutes of Health. Available online: https://www.nhlbi.nih.gov/health-topics/heart-failure [Accessed 15 April 2020].
[4] Givertz MM, Cohn JN. Pharmacologic management of heart failure in the ambulatory setting. In Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease 2007 Dec 1 (pp. 331-362). Elsevier Inc.

In the BEST (Beta-Blocker Evaluation Survival Trial) clinical trial, bucindolol was given as an additional therapy at the same time as two other drugs to see if it provided any added benefit.[5] The trial specifically recruited selected subgroups (e.g., women, ethnic and racial minority populations) as it was known that Black patients have a higher rate of death from heart failure in the United States.[6,7] Treatment groups were divided not only by the severity of their heart failure symptoms, but also by sex and self-reported race.

Findings from trials initially suggested good effect: death from cardiovascular causes was significantly lower in the bucindolol group; and bucindolol reduced the average number of hospitalizations and average number of inpatient days per patient.[8] However, while the addition of bucindolol to treatment for heart failure reduced the number of times patients had to go to the hospital, it did not appear to change the risk of death from heart failure.

Careful study of the results and further subgroup analysis, however, showed that "non-black" patients—that is, patients other than those who described themselves as Black—did better on bucindolol than without it. And that advantage was seen in each way bucindolol was first thought as being beneficial—the rate of death from heart disease, the number of times that patients had to go back into the hospital for heart problems and how long they stayed, and overall outcomes. Black patients, however, did not experience the same level of survival benefit. [9]

The reason that Black patients did not benefit—and that non-black patients did benefit—was further studied. Different forms of one gene change whether or not a person responds to the drug, and one form of that gene is more common (but certainly not always present) in Black patients than non-black patients.[10,11] The drug response does not relate to *race*—it relates to the fact that one form of the gene is more common in one population than another. However, given the lack of impact on overall mortality in the Black population, and the general availability of effective beta-blockers and other therapies, the development of bucindolol in the United States was abandoned. Whether genetic testing would be helpful to drive the choice of therapy has not yet been examined.

[5] BEST Steering Committee. Design of the beta-blocker evaluation survival trial (BEST). The American Journal of Cardiology. 1995 Jun 15;75(17):1220-3.
[6] Gillum RF. Epidemiology of heart failure in the United States. Am Heart J 1993;126:1042-1047
[7] Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. New England Journal of Medicine. 1999 Feb 25;340(8):609-16.
[8] Torp-Pedersen C, Køber L, Ball S, Hall A, Brendorp B, Ottesen MM, Berning J, Jensen G, Hampton J, Zilles P, Eberle S. The incomplete bucindolol evaluation in acute myocardial infarction Trial (BEAT). European journal of heart failure. 2002 Aug;4(4):495-9.
[9] Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. New England Journal of Medicine. 2001 May 31;344(22):1659-67.
[10] Bristow MR, Murphy GA, Krause-Steinrauf H, Anderson JL, Carlquist JF, Thaneemit-Chen S, Krishnan V, Abraham WT, Lowes BD, Port JD, Davis GW. An a2C-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the β-Blocker bucindolol in chronic heart failure. Circulation: Heart Failure. 2010 Jan 1;3(1):21-8.
[11] Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT. A polymorphism within a conserved β1-adrenergic receptor motif alters cardiac function and β-blocker response in human heart failure. Proceedings of the National Academy of Sciences. 2006 Jul 25;103(30):11288-93.

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Case Study: Data-driven Diversity Assessments at a Medical Device Company

Boston Scientific utilizes data to systematically prioritize racial and ethnic diversity in cardiovascular treatment and clinical trials

Summary

Through their health equity initiative, *Close the Gap*, Boston Scientific developed straightforward data-based tools to call attention to demographic disparities in cardiovascular treatment and clinical research. At partner hospitals, the company used a novel application on a mobile Salesforce® platform to highlight demographic subgroups being missed in cardiovascular treatment. At selected clinical study sites, the initiative collected demographic data, actively monitoring disparities in study enrollment on their 'Catalyst Clinical Trial Scorecard.' Boston Scientific's data-based tools for combatting disparities demonstrate a tangible approach for sponsor companies to contribute to diverse representation in clinical research and care.

Background: Close the gap

Close the Gap is Boston Scientific's health equity initiative created to eliminate disparities in care across the United States.[1] *Close the Gap* focuses on awareness, advocacy and education in order to help close the proverbial gap in treatment between White men and other underserved demographic communities.[2]

The *Close the Gap* initiative was established in 2004, at a time when cardiovascular disease in women was gaining widespread attention. Although implantable cardioverter defibrillators (ICDs) had been recently approved for primary prevention of sudden cardiac death (SCD) in high risk heart failure patients, women and ethnic minorities at-risk for SCD were more than 60% less likely to receive ICDs than their White male counterparts. Boston Scientific, in conjunction with other advocacy organizations, acted on the disturbing emerging trend.[3] Since its inception, the initiative has expanded to include other therapeutic areas such as coronary artery disease, atrial fibrillation, and, recently, colon cancer.

> Dr. Paul Underwood, Boston Scientific Interventional Cardiology Medical Director noted, "the disconnect between the burden of illness observed in the community and who is actually being treated in the hospital **makes obvious that some of the people needing treatment are being missed.**"[4]

[1] Close the Gap. Boston Scientific. Available at https://www.knowyourhealth.com/en-US/About-Close-the-Gap.html
[2] Mezu U, Halder I, London B, Saba S. Women and minorities are less likely to receive an implantable cardioverter defibrillator for primary prevention of sudden cardiac death. Europace. 2012 Mar 1;14(3):341-4.
[3] Gauri AJ, Davis A, Hong T, Burke MC, Knight BP. Disparities in the use of primary prevention and defibrillator therapy among blacks and women. The American Journal of Medicine. 2006 Feb 1;119(2):167-e17.

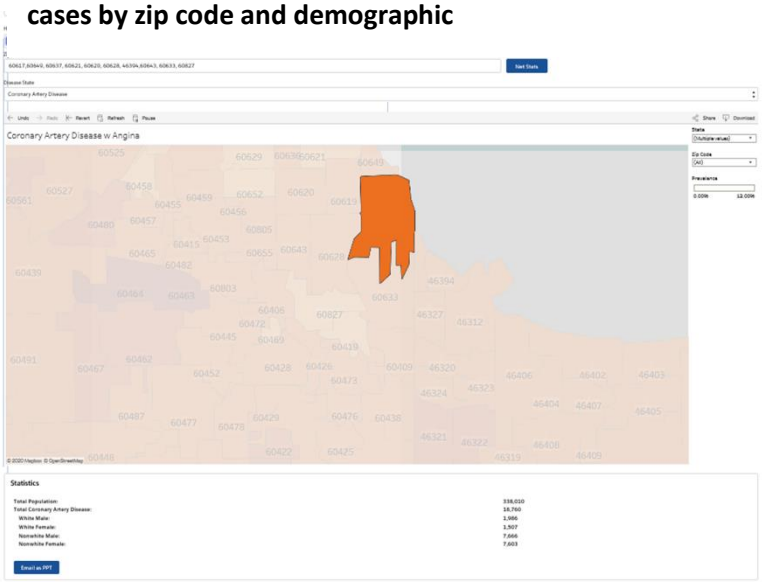
For Boston Scientific, the ICD implant disparity became apparent with the observation that the number of patient defibrillator implants was not consistent with number of patients known to have heart failure with indications for the device. Further analysis revealed that minority patients were being underserved. The company quickly recognized that bridging this gap demanded social equity and access to care, as well as physician awareness of the new indication and the referral pathway for a device implant.

> Dr. Underwood explained that after using the app to inform sites of their current performance, "hospitals would be encouraged…to **establish a task force** to understand better where some of the demographic gaps are and then develop a plan that would help mitigate some of the identified barriers to care."[4]

Boston Scientific responded to this treatment disparity by creating the awareness-raising and education-oriented *Close the Gap* initiative. The initiative networks client hospitals with community partners and professional/patient advocacy organizations to spread awareness regarding demographic disparities in cardiovascular care. The initiative also links the providers' understanding of disparities with the provider's experience. Often, hospitals don't address disparities in a meaningful way; although 'community engagement' activities are common, they are often not targeted and limited in scope leading to ineffective impact on treatment disparities in the long term.

> In cardiology, "providers generally know that disparities exist, but not in **their clinics** or **their practices.**"[5]

Figure 1: Hospital service area coronary disease burden visualization on the mobile app, indicating number of cases by zip code and demographic



Quantifying treatment inequities: Disparity Index mobile application

The Boston Scientific *Close the Gap* Disparity Index mobile app was designed to initiate conversations around health disparities between Boston Scientific's local sales teams and partner hospitals. Using a mobile app, hospitals can be provided with a graphic analysis of their clinical coverage regarding treatment access for patients within their service area.

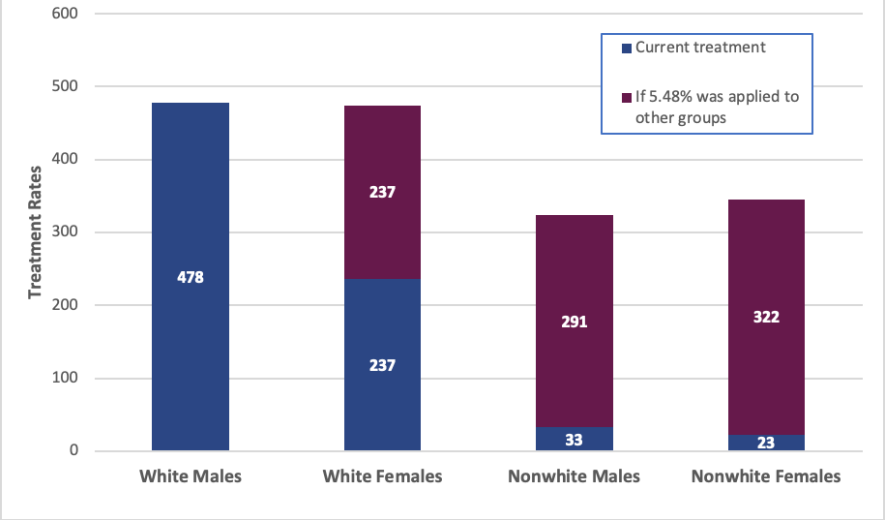
How it works: Claims data from partnering hospitals is collected to calculate treatment rates by demographic group in the therapeutic area of interest. The claims data is matched to publicly available census data at the zip code-level to project disease prevalence by demographic subgroup (see Figure 1). A customizable hospital service area map is created using zip codes derived from the hospital's community health needs assessment (CHNA). The CHNA is a publicly accessible document dictated by the Affordable Care Act to accompany an

[4] Dr. Paul Underwood. Close the Gap. [Personal interview, 8 August] Telephone; 2019 (unpublished).
[5] Lurie N, Fremont A, Jain AK, Taylor SL, McLaughlin R, Peterson E, Kong BW, Ferguson Jr TB. Racial and ethnic disparities in care: the perspectives of cardiologists. Circulation. 2005 Mar 15;111(10):1264-9.

Implementation Plan for hospitals to maintain their non-profit tax status. Using matched data, visualizations can be generated on the app, presenting scenarios of selected disease states by demographic subgroup within the hospital's service area (see Figure 1).

These visualizations can help hospitals understand their patients' demographics and the quantitative impact on disease burden in order to facilitate establishing long term goals and monitoring metrics.
These matched data also enable hospitals to quantify the treatment disparities in a given disease. By comparing treatment rates of patients at the hospital to cases present in the hospital's catchment area by demographic, the *Close the Gap* Disparity Index app effectively quantifies and visualizes the facility-level demographic 'gap' in treatment for certain therapeutic areas (see Figure 2). The *Close the Gap* team is constantly identifying additional spaces where health and treatment inequities exist. The next data update of the Index will include diabetes, prostate cancer and benign prostate hyperplasia.

Figure 2: PCI treatment rates in select groups



'Gaps' figure on the mobile app, indicating treatment disparities at the hospital for Percutaneous Coronary Intervention (PCI) in particular demographic subgroups. Data was derived from 2016 Medicare data to estimate the number of individuals who were diagnosed with disease in the selected catchment area.

In addition to providing a quantitative snapshot for the hospital, the Boston Scientific initiative then encourages the hospital to form an internal hospital-based task force to identify specific groups that are undertreated within their service area and address their unique barriers to care. While not a central focus of the task force, *Close the Gap* can maintain relationships with the task forces to share data in addition to patient and physician educational resources relating to cardiovascular treatment and outcome disparities. As a result, groups such as African Americans, who already carry a higher baseline burden of heart failure,[6] began receiving the care they needed.

[6] Carnethon MR, Pu J, Howard G, Albert MA, Anderson CA, Bertoni AG, Mujahid MS, Palaniappan L, Taylor Jr HA, Willis M, Yancy CW. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation. 2017 Nov 21;136(21):e393-423.

Monitoring diverse enrollment: Clinical Site Scorecard

In addition to using demographic data to highlight cardiovascular treatment disparities at a given hospital, Boston Scientific also uses demographic data to promote diverse enrollment in their clinical studies.

By utilizing real time enrollment demographic data from all clinical sites, project teams can develop a 'Clinical Site Scorecard' for each investigative site. The dashboard displays demographic data by gender and race. By collecting the data in real-time, enrollment of diverse populations can be actively monitored in conjunction with other trial performance indicators such as query response time and protocol compliance.

Figure 3: Boston Scientific 'Catalyst Clinical Site Scorecard' quantifying enrollment demographics of any clinical trial in real-time

Catalyst

Site Scorecard | Definitions | ↓ Export

Project | PLATINUM DIVERSITY ▼ | Performance | Demographics

SITE	CENTER CODE	INVESTIGATOR	LOCATION	ACTIVATION DATE	PATIENTS ENROLLED	FEMALE SHARE OF ENROLLMENT	NON-WHITE SHARE OF ENROLLMENT
Baptist Health Medical Center	0111	Brown, Roxanne	United States	17-Nov-2014	101	86.1%	23.8%
Memorial Regional Hospital	0222	Blue, Fredrick	United States	14-Oct-2014	95	37.6%	91.5%
Mount Sinai Medical Center	0333	Grey, Luis	United States	10-Oct-2014	81	48.5%	50.4%
Union Memorial Hospital	0444	White, John	United States	06-Nov-2014	83	74.2%	62.2%
Wake Medical Center	0555	Red, Maria	United States	01-Dec-2014	75	54.3%	12.8%
Bay Medical Center	0666	Black, Mary	United States	27-Oct-2014	48	81.7%	50.7%

The dashboard and scorecard ensure the aggregate population being enrolled in the study is representative of the population most likely to use the study device (see Figure 3).[7]

> "If in a certain disease state, half the affected people will be women, you should expect half the subjects in the clinical trial to be women. But in reality, it's often more complex…"[8]

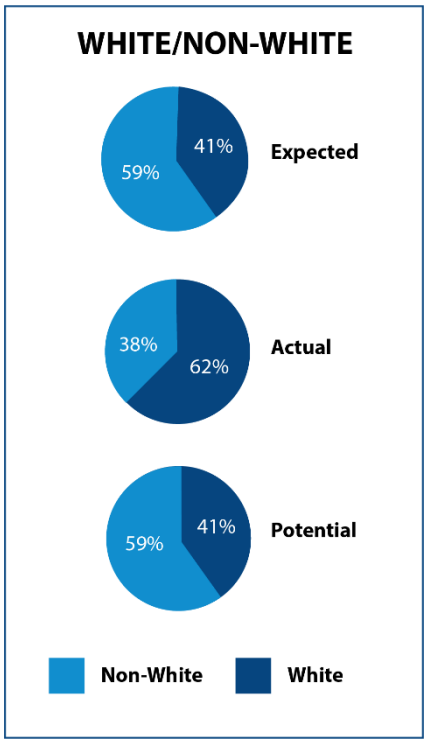
By mapping the demographic pages from the electronic case report forms through a centrally accessible Catalyst dashboard, clinical trial project teams can develop a real-time Clinical Site Scorecard to understand the demographic composition of the patients sampled in the study. These data are used to assure sites are enrolling patients reflective of their clinical practice and the disease prevalence in the hospital's patient community. Manual combination of real-time enrollment data with investigative site catchment area data enables assessment of the clinical site's ability to match the available treatment with the disease prevalence demographics in the hospital service area community (See Figure 4).

[7] Data in Figure 3 have been modified to protect identity of sites and investigators.
[8] Dr. Paul Underwood. Close the Gap. [Personal interview, 8 August] Telephone; 2019 (unpublished).

The combined data are then used internally by clinical project teams and the *Close the Gap* team to drive diverse enrollment in their clinical program.

Close the Gap's data driven quantification and visualization of demographic data enables Boston Scientific clinical project teams to monitor site performance and understand the diversity of a clinical study population in aggregate and in real-time. The tools have also been used to support recommendations during clinical study site selection.

Figure 4: Example of Clinical Site Scorecard



Combined data from a hypothetical trial's 'Clinical Site Scorecard' by race (white, non-white) 'Expected' represents the hospital treatment rate at the clinical site; 'Actual' represents the real-time enrollment demographics seen on the Catalyst dashboard; 'Potential' represents is the demographic prevalence in the hospital service area.

Scaling up and next steps

In conversation around the future of the *Close the Gap* Disparity Index mobile application and the Catalyst Clinical Site Scorecard, Underwood noted many opportunities to scale the tools within Boston Scientific:

- **Expand data areas to include more therapeutic areas** – currently only available for a limited number of cardiovascular conditions
- **Expand demographic subgroups -** currently only provides male/female and white/non-white data
- **Increase interoperability of data –** complete migration from iPad to Salesforce® application platform
- **Catchment area discrepancies** – target geocoding to more accurately reflect catchment area geography and demographics
- **Census-based data limiting targeted catchment areas –** current data sources exclude 'Federal' populations such as Veterans Administration, American Indian reservations, and prisons
- **Incorporating other important data elements–** such as comorbidities and age
- **Broadening clinical scorecard functionality –** to assist clinical sites to use current enrollment data to promote diverse study enrollment
- **Automate linking demographic enrollment data to hospital/clinical site service area –** currently combined data is created manually for visualization; automation would provide real-time comparisons useful for sites

Points to consider

- Clinical project teams should think critically about the data they have available to them to gain actionable insight and, optimally, use an approach as highlighted in this case study.
- Real-time monitoring of clinical trial enrollment and utilization of clinical trial scorecards enable an understanding of the diversity present across a trial population
    - Real-time monitoring helps to ensure that the intended distribution of enrolled populations is on target.
    - Real-time monitoring may be particularly useful for adaptive clinical trials.
- Quantitative assessment of treatment disparities and clinical trial diversity are necessary components to ensure clinical trial data are generalizable to the entire population.
    - Clinical sites ideally would have the capacity to generate actionable data that promotes health equity and diverse participation in clinical studies. Site metrics enable them to inform sponsors/CROs of their capacity for diverse subject enrollment.
    - These data can assist sites to perform feasibility assessments focused on diversity (i.e., assessments that target treatment rates in specified subgroups).

Case Study: Achieving and Exceeding Clinical Trial Participant Diversity Targets

Using Customized Tools, Applications and a Dynamic Enrollment Tracker [1]

Summary

Hepatitis C Virus (HCV) infection is a potentially curable chronic liver infection that can cause cirrhosis, liver cancer, and even death. HCV affects approximately 170 million individuals worldwide and disproportionately impacts Blacks and Latinos.[2,3] Blacks demonstrate lower responses to some treatments (i.e., interferon-alpha) compared to other racial subgroups.
Also, the major HCV genotypes vary in prevalence (based on regional and ethnic/racial demographics), severity, and treatment response (see Section 16.2.2 "Hepatitis C, genomics, geographic region, ethnicity" in *MRCT Center Diversity Guidance Document*), thus amplifying the importance of participant diversity in clinical trials of the treatment for Hepatitis C.[4]

In its pivotal phase 3 "C-EDGE" program evaluating the combination of two products, elbasvir/grazoprevir (Zepatier®), Merck[5] demonstrated that enrolling a diverse population can be improved and targets exceeded through the use of customized tools and applications, and by utilizing a dynamic participant enrollment tracker. Although there were significant program challenges (short enrollment period, competitive landscape, aggressive timelines, managing enrollment on a global basis, and requirement for reliable, real-time reporting and site communication), the goal for minority enrollment of 20% was exceeded.

The activities of Merck to increase clinical trial diversity include a 'Diversity in U.S. Clinical Trials Core Team' that supports company efforts to develop a sustainable process to ensure inclusion of underrepresented diverse patient populations with regard to sex, age, race, and ethnicity in its research and clinical trials. An overall objective of the team is to support the development and implementation of sustainable solutions aimed to make diversity a standard part of the company's commitment to conducting research to develop innovative medicines and vaccines that address important, unmet medical needs to help improve the quality and quantity of life for all people and communities. In 2015 Merck collaborated with the Association of Black Cardiologists, academia and others, to complete an intensive research effort, involving patients, investigators, referring physicians, and study coordinators,

[1] This Case was developed by utilizing the information provided in the webinar hosted by DrugDev. https://www.drugdev.com/uncategorized/merck-improved-clinical-trial-patient-diversity-using-dynamic-enrollment-tracker/

[2] Melia MT, Muir AJ, McCone J, Shiffman ML, King JW, Herrine SK, Galler GW, Bloomer JR, Nunes FA, Brown KA, Mullen KD. Racial differences in hepatitis C treatment eligibility. Hepatology. 2011 Jul;54(1):70-8.

[3] Vutien P, Hoang J, Brooks Jr L, Nguyen NH, Nguyen MH. Racial disparities in treatment rates for chronic hepatitis C: analysis of a population-based cohort of 73,665 patients in the United States. Medicine. 2016 May;95(22).

[4] Reddy, K. Rajender, et al. "Racial differences in responses to therapy with interferon in chronic hepatitis C." *Hepatology* 30.3 (1999): 787-793.

[5] For simplicity, we use "Merck" to reference the company's full legal name, Merck & Co., Inc., Kenilworth, NJ, USA.

to investigate the barriers to minority participation in U.S. clinical trials and to identify potential solutions with respect to implementation, recruitment, retention, and communication.[6] Key barriers were identified including mistrust and lack of comfort with the clinical trial process. Referring physicians were recognized as key drivers of minority patients' participation in clinical trials. They represent the most trusted source of medical information for their patients, and need to feel engaged, informed, and appreciated by study teams.

Challenges and approach

The C-EDGE Program presented the Clinical Trials Core team with a short enrollment period in a competitive landscape. The Core Team had only eight weeks to activate sites and an additional eight weeks to enroll participants. Further, it was necessary to have flawless and reliable medication adherence by the participants. An additional challenge was managing enrollment at a global level in all the sites, across different time-zones, holidays, etc. A reliable, real-time reporting and site communications tool was needed to provide multiple status updates per day, accessible across all sites in different countries, and specifically available for headquarter teams involved in the program management of the trial.

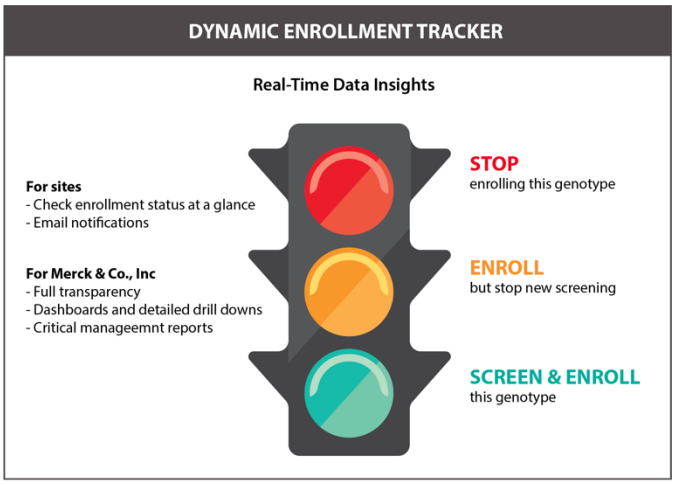
The C-EDGE phase 3 program committed to a certain percentage of minority enrollments as a goal and that goal was set to be higher than those of earlier trials. The program used targeted site selection and made the difficult decision to work only with those centers and sites that were confident in their ability to meet the recruitment goals in the aggressive timelines set. The program partnered with The Center for Information and Study on Clinical Research Participation (CISCRP) to develop customized tools and minority patient education materials. These resources included tools for sites to use such as cultural pointers for healthcare professionals, implementation guides for sites, and bi-lingual consumer materials and brochures that emphasized how patients had been part of the healthcare team designing the trial and not just as recipients of healthcare treatment. The tools highlighted the values of clinical research, the rights of patients and participants in research, and expectations of the participants.

The program developed a communication strategy focused on community building and site engagement using the DrugDev Spark[7] platform. This portal was used as a central cloud-based platform that allowed all staff conducting a study to access materials securely and efficiently. It had multiple features including study dashboards, enrollment update emails, educational videos, team photos, electronic newsletters, and operational spotlights with key materials and best practices. The tools in the platform helped sites trust and rely on the content and the extended network.

[6] Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, Jamerson B, McCullough C, Pierre C, Polis AB, Puckrein G. Increasing diversity in clinical trials: overcoming critical barriers. Current Problems in Cardiology. 2019 May 1;44(5):148-72.

[7] For more information, see http://drugdevspark.com/

Figure 1: High-level dynamic enrollment tracker



The dynamic enrollment tracker (see Figure 1) provided real-time data feedback by leveraging the integrated platform system. The tracker was used in tandem with targeted email blasts in addition to an automatic document notification system that deployed a “stop-light" method. This transparent and identifiable visual imagery allowed study leads to check enrollment status and critical management reports quickly.

The enrollment tracker was designed and configured to meet specific study needs. Functionalities were adjusted for specific protocols depending on the study as were subgroups that were important to include and track. The platform was designed to be visually appealing so that sites and other staff members would be comfortable and engage with the tracker. The dashboard within the platform had clear and direct messaging to internal and external study stakeholders, as well as a virtual protocol guide so all information required by a coordinator would be available. Further, the platform contained a ‘Document Exchange’ – a secure repository of all the study documents with a uniform folder structure that was applied to all studies in the program. The standard configuration made it easier for all staff to locate and access necessary information in a timely fashion and decreased barriers to uptake and implementation.

Key components of the program

- **Targeted site selection** including only those sites confident in their ability to meet the diversity recruitment goals;
- **Partnering with CISCRP** to develop customized education materials and resources for healthcare professionals, implementation guides for sites, and bi-lingual communication materials for patients;
- **A communication strategy** focused on community building and site engagement using a central cloud-based platform that allowed all staff access to materials securely and efficiently;
- **A dynamic enrollment tracker** that provided real-time data feedback by leveraging the integrated platform system and transparently allowed study leads to check enrollment status and critical management reports quickly.

Results and key takeaways

- The C-EDGE program exceeded the minority enrollment goals of 20%. The actual number screened was 26.6% and the actual randomized minority population was 26.5%.
- Creating a plan with diversity goals that are clear is key.
- Monitoring execution against plan is a critical element for success.

- Building a clinical trial community is essential.
- Celebrating and sharing those successes continuously promote utilization.
- Engaging sites requires easy, direct, and focused communication to align partners.
- Execution entails partner awareness and tracking through customized tools and applications.

Case Study: PCSK9

Key lessons learned
• In a number of large observational studies, reduced low-density lipoprotein (LDL) is associated with decreased coronary heart disease. • Early studies on families with very high cholesterol levels in the blood helped identify a link between LDL levels and PCSK9, a protein (proprotein convertase subtilisin kexin- type 9) that controls the number of receptors for LDL on the surface of cells. Genetic sequencing[1] was able to identify mutations expression of PCSK9 in individuals with very high and low levels of LDL. • While race is generally considered to be only a surrogate marker for genetic differences, race has been associated with a number of biological differences (e.g., salt sensitivity, hypertension, renin activity, and nitric oxide response). With regard to PCSK9, racial differences were associated with the likelihood of different genetic variants of the protein. • Racial and ethnic diversity can, in some instances, lead to identification of important genetic variants that may prove important in drug discovery and development.

Disease background

Low-density lipoproteins (LDL) are a well-studied risk factor associated with heart disease, mediated through “hardening of the arteries," or atherosclerosis. A number of studies have shown that lowering the concentration of LDL in the blood can reduce the risk of cardiovascular diseases, specifically those related to coronary heart disease (CHD).[2] There are a number of ways to lower LDL concentrations in the blood including modifying one’s diet by lowering saturated fat consumption or by using cholesterol-lowering therapies such as statins.

[1] There is a difference between genotyping, genetic sequencing, and genetic expression. Genotyping is the process of determining which genetic variants an individual has; genetic sequencing is the method used to determine the exact sequence the four chemical building blocks of DNA are within a certain cut of DNA; genetic expression is a result of how DNA is transcribed into different cells and therefore how genes may be expressed.
National Human Genome Research Institute. DNA Sequencing Fact Sheet [Internet]. National Institutes of Health. Dec. 18, 2015. Available online: https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Fact-Sheet (accessed May 8, 2020).

[2] Rosenson RS, Hegele RA, Fazio S, Cannon CP. The evolving future of PCSK9 inhibitors. Journal of the American College of Cardiology. 2018 Jul 9;72(3):314-29

In 2002, research on families with high cholesterol (i.e., familial hypercholesterolemia) found that certain individuals with high LDL levels also have an increased amount of a protein, termed PCSK9 (or proprotein convertase subtilisin kexin-type 9), in their blood.[3] PCSK9 impacts the metabolism of LDL by occupying and degrading the LDL receptor on cells that would have otherwise bound and digested LDL.[4] Therefore, high levels of PCSK9 result in elevated levels of LDL- cholesterol.

Discovery to genetic variation

Shortly after the initial findings from the familial high cholesterol studies,[5] a series of genetic analyses were done to investigate PCSK9 gene mutations; it was discovered that individuals may either express less (i.e., loss-of-function [LOF]) or more (i.e., gain-of-function [GOF]) of the protein PCSK9.[6,7,8] Research on gene expression found different variations of the gene in different individuals. Populations of self-reported Black participants had a higher frequency of two of the three most common PCSK9 loss-of-function mutations; both of these variations were rare in White participants.

The higher frequency of the LOF mutations in Black patients in earlier studies[9] correlated with the relationship that had been observed between reduced LDL-C and reduced CHD, leading to further study of the role and function of PCSK9. Discovery and the understanding of the function of PCSK9 led to the development of therapeutic PCSK9 inhibitors, thereby offering treatment for individuals with high cholesterol levels and heart disease.

[3] Leren TP. Cascade genetic screening for familial hypercholesterolemia. Clin Genet. 2004;66:483–487.

[4] Glerup S, Schulz R, Laufs U, Schlüter KD. Physiological and therapeutic regulation of PCSK9 activity in cardiovascular disease. Basic research in cardiology. 2017 May 1;112(3):32.

[5] Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derre A, Villeger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34:154–156.

[6] Leren TP. Cascade genetic screening for familial hypercholesterolemia. Clin Genet. 2004;66:483–487.

[7] Shioji K, Mannami T, Kokubo Y, Inamoto N, Takagi ST, Goto Y, Nonogi H, Iwai N. Genetic variants in PCSK9 affect the cholesterol levels in Chinese. J Hum Genet. 2004;49:109–114

[8] Timms KM, Wagner S, Samuels ME, Forbey K, Goldfine H, Jammulapati S, Skolnick MH, Hopkins PN, Hunt SC, Shattuck DM. A mutation in PCSK9 causing autosomal-dominant hypercholesterolemia in a Utah pedigree. Hum Genet. 2004;114:349–353.

[9] Cohen JC, Boerwinkle E, Mosley Jr TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. New England Journal of Medicine. 2006 Mar 23;354(12):1264-72.

Case Study: Clopidogrel (Plavix®)

Key lessons learned
• Clinically significant differences in treatment response indicates a need for further investigation. • Differences may be attributable to metabolic or genetic variation. Genetic variation results from different forms (termed "alleles"} of the same gene. • Allelic frequency differs between racial and ethnic populations. • Therefore, observed differences in treatment response between different racial or ethnic subgroups can, in some instances, indicate important genetic variants that may lead to important observations in drug discovery and development. • The importance of determining differences in treatment response or disease prevalence between patients in clinical trials is dependent on accurate and detailed demographic and clinical data collection.

Disease background

Blood clotting, the process of platelets clumping, is an important response to the control of bleeding, such as after cuts, injury, or surgery. Problematic blood clots, however, can also form within the blood stream and can cause serious health and cardiovascular events such as heart attack, stroke, difficulty breathing and other problems. People who have experienced a cardiovascular event are sometimes placed on medications to prevent blood clotting and those include anti-platelet therapy drugs.

Treatment for cardiovascular events has historically focused on aspirin therapy,[1] which reduces inflammation and helps block platelets from clotting. Additional therapeutic interventions beyond aspirin, especially for patients allergic or for those who are high risk for clotting, are sometimes needed. Clopidogrel, originally marketed under the trade name Plavix®, is a drug that inhibits platelet activation and aggregation and was initially approved in the U.S. in 1997 as a treatment for cardiovascular disease and atherosclerosis.

Discovery to genetic variation

The efficacy and safety of clopidogrel was investigated in clinical trials, leading to its emergence as an alternative therapy to aspirin, especially among individuals allergic to aspirin,[2] as well as in combination

[1] Angiolillo DJ, Bhatt DL, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. The American journal of cardiology. 2009 Feb 2;103(3):40A-51A.

[2] CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). The Lancet. 1996 Nov 16;348(9038):1329-39.

therapy with aspirin.[3] Results from initial large-scale clinical trials suggested that clopidogrel, alone and also when combined with aspirin, reduced the occurrence of death, heart attacks, and stroke by 20% as compared to aspirin alone.[4] By 2010, clopidogrel was the world's second best-selling medicine – contributing $9.6 billion to the drug market.[5]

The mechanism by which clopidogrel works, however, was not discovered until after the drug was marketed; dosing was largely determined by clinical experience and changing therapeutic strategies.[5] Because of this, there were wide variances in drug response with a notable number of "non-responders." [5] While clinical utilization of clopidogrel was still being adjusted, biomolecular research on the difference in patient treatment responses also continued. Clopidogrel was discovered to be inactive until it is metabolized in the liver by proteins of the cytochrome P450 family, namely CYP2C19; this process results in the production of an active small molecule that then irreversibly blocks the P2Y12-receptor on platelets, a receptor that normally signals platelet activation and aggregation (i.e., clotting).[4] Any alteration, or genetic defect (e.g., loss-of-function [LOF]), in the availability or function of the liver protein CYP2C19 would reduce the conversion of clopidogrel to its active form and could explain "non- responders." These bio-mechanistic findings helped clarify the variability of treatment response to clopidogrel.

Further analysis of results from clopidogrel trials investigated populations with a genetic variation in CYP2C19 and discovered that the majority of individuals with LOF for CYP2C19 were Asian.[6] In fact, more than 50% of Asians carry this variation as compared to only 28% of Whites.[6] This is a critical clinical finding since reduced function of CYP2C19 results in a reduced response to clopidogrel and, therefore, an increased risk for a cardiovascular event. Genotyping individuals can aid in the development of therapeutic guidelines and will ultimately help clinicians and prescribers understand their patients' profiles and therapeutic response in advance of treatment.[7]

[3] Rezkalla SH, Benz M. Antiplatelet therapy from clinical trials to clinical practice. Clinical medicine & research. 2003 Apr 1;1(2):101-4.
[4] Angiolillo DJ, Bhatt DL, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. The American journal of cardiology. 2009 Feb 2;103(3):40A-51A.
[5] Fitzgerald DJ, FitzGerald GA. Historical lessons in translational medicine: cyclooxygenase inhibition and P2Y12 antagonism. Circulation research. 2013 Jan 4;112(1):174-94.
[6] Sorich MJ, Rowland A, McKinnon RA, Wiese MD. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis. Circulation: cardiovascular genetics. 2014 Dec;7(6):895-902.
[7] Cresci S, Depta JP, Lenzini PA, Li AY, Lanfear DE, Province MA, Spertus JA, Bach RG. Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. Circulation: Cardiovascular Genetics. 2014 Jun;7(3):277-86.

Case Study: Embedding Diversity & Inclusion within a Pharmaceutical Company

Biogen's approach to D&I across the organization's culture and strategy

Summary

Biogen, a multinational biotechnology corporation dedicated to neuroscience and neurological disease, endeavored to embed a philosophy of Diversity & Inclusion (D&I) within the organizational mission and corporate culture. Recognizing the value of diversity, Biogen developed an organization-wide strategy to reflect and operationalize this philosophy in the workplace, within its research and development priorities, and as an expectation for their external ventures and partnerships.

Biogen offers an important example of how a sponsor can prioritize the goal of health equity in its research vision through efforts to emphasize and support diversity and inclusion in its business functions, and it has been recognized globally for developing and applying inclusive practices. The company has achieved a score of 100% on the Human Rights Campaign Corporate Equality Index[1] since 2014, and was named best Workplaces for Women Italy,[2] and Forbes Best Employers for Diversity in 2019.[3]

Approach to Diversity & Inclusion at Biogen

Biogen's emphasis on D&I stems from an appreciation for the diverse patient populations that use their products as well as the value of the diversity within their workforce. Biogen's executive leadership considered how to build supportive organizational structures to ensure that inclusivity was weaved throughout Biogen's business practices.[4] As such, leaders at Biogen established the Diversity and Inclusion Strategic Council (DISC), tasked with addressing how diversity, inclusion, and equity can intersect and enhance the company's strategic priorities (see Figure 1). The DISC offers a governance structure to guide the coordination and implementation of diversity initiatives and to ensure accountability and ownership throughout this arm of the organization's overall commitment to Corporate Responsibility (CR).

[1] Human Rights Campaign Foundation. Corporate Equality Index 2020. Rating workplaces on lesbian, gay, bisexual, transgender, and queer equality. Available at https://assets2.hrc.org/files/assets/resources/CEI-2020.pdf?_ga=2.185370346.2142529676.1586941402-1623098796.1586941402. [Accessed 15 April 2020].

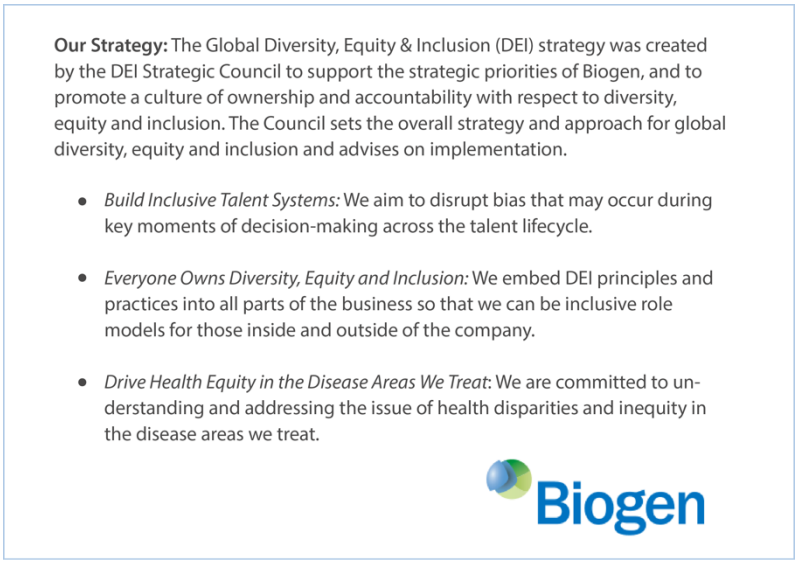
[2] The Best Workplaces for Women 2018 ranking. Available at https://translate.google.com/translate?hl=en&sl=it&u=https://www.greatplacetowork.it/best-workplaces-italia-2018-for-women&prev=search. [Accessed in translation 15 April 2020].

[3] Forbes. Biogen (BIIB). Available at https://www.forbes.com/companies/biogen-idec/#209df0ce1823. [Accessed 17 April 2020].

[4] Biogen. Global Diversity and Inclusion. Available at https://www.biogen.com/en_us/diversity-inclusion.html.

For example, one part of Biogen's product portfolio is treatment for multiple sclerosis and Alzheimer's disease, two diseases that disproportionately affect women.[5,6] And whoever the patient, the majority of caregivers are women.[7] These realities drive Biogen's diversity priority setting, and they work to promote women's voices within the company, and embed this consideration of gender equity into their governance structures.

Figure 1: Biogen's three-tiered Global D&I strategy governed by the Diversity & Inclusion Strategic Council (DISC)



Biogen honors and respects the fact that differences and inclusivity sometimes demand difficult conversations about identities, backgrounds, and experiences. In their work, exploring and leveraging the differences among employees and customers translates into an awareness of the characteristics that make each individual unique. Biogen's efforts toward inclusivity translate into an environment where everyone has a voice, creates a culture of respect and trust, and drives creativity by asking for alternate perspectives. The commitment to D&I generates employee ownership and responsibility to the principle, as well as company-wide accountability for its successful execution.

The stated mission of D&I at Biogen is "to create, nurture and sustain a global, inclusive culture, where differences drive innovative solutions to meet the needs of our patients and employees,"[8] and conceptualizing diversity as the combination of differences and similarities that make up individuals, groups, and organizations within and associated with the company. It includes, but is not limited to cultures, backgrounds, behaviors, beliefs, perspectives and characteristics. In developing their strategy,

[5] Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, Ebers GC, Canadian Collaborative Study Group. Sex ratio of multiple sclerosis in Canada: a longitudinal study. The Lancet Neurology. 2006 Nov 1;5(11):932-6.
[6] Mazure CM, Swendsen J. Sex differences in Alzheimer's disease and other dementias. The Lancet. Neurology. 2016 Apr;15(5):451.
[7] Sharma N, Chakrabarti S, Grover S. Gender differences in caregiving among family-caregivers of people with mental illnesses. World journal of psychiatry. 2016 Mar 22;6(1):7.
[8] Biogen. Global Diversity and Inclusion. Available at https://www.biogen.com/en_us/diversity-inclusion.html.

the company understood that these differences vary in relevance and importance among the regions where they do business.

Through its organizational structure and governance, Biogen is able to employ both internal, workforce-related D&I strategies as well as external strategies focused on business operations, all as a preliminary step towards a broader aim of increasing diversity in clinical research.

Internal strategies

Internally, Biogen worked to integrate the Workforce Development, Diversity, & Inclusion principles (WDDI) adopted by the Biotechnology Innovation Organization (BIO).[9] A number of Employee Resource Networks (ERNs), internal groups for employees that share life experiences and/or interests, have been established. These groups enable knowledge exchange, mentorship and support.[10] Biogen's ERN offerings are displayed in Table 1 below.

Table 1: Biogen Employee Resource Networks (ERNs)

Employee Resource Network (ERN)	Focus area
AccessAbility	Disability (particularly Alzheimer's Disease and Multiple Sclerosis)
Biogen Veterans Network	Veterans
Ignite	Early-career professionals and their advocates
Mosaic	Multiculturalism (cultural heritage and identity differences)
ReachOUT	LGBTQ
Women's Innovation Network (WIN)	Gender equality

[9] Biotechnology Innovation Organization (BIO). Principles on Workforce Development, Diversity & Inclusion for the Biotech Industry. Available at https://archive.bio.org/sites/default/files/bio-principles-wddi-for-the-biotech-industry.pdf [Accessed 3 May 2020] and https://www.bio.org/workforce-development-diversity-inclusion [Accessed 3 May 2020].
[10] Biogen. Global Diversity and Inclusion. Available at https://www.biogen.com/en_us/diversity-inclusion.html. [Accessed 15 April 2020].

External strategies

Biogen engages responsibly with the external community, both commercially and philanthropically, through a number of D&I initiatives described below.[11]

Advocacy and Community Engagement

- *Public policy advocacy* – Biogen takes an active role in political advocacy. For example, the company supported the Massachusetts campaign to maintain legal protections for the transgender community and denounced the repeal of the Deferred Action for Childhood Arrivals (DACA) program.

- *Underrepresented Scientific, Technology, Engineering, and Mathematics (STEM) education* – Biogen addresses STEM education through its Science, Teacher support, Access and Readiness (STAR) program. The STAR program tackles demographic disparities in STEM careers by providing access to STEM resources for low-income students with limited access to educational opportunities or professional networks that would enable a career in STEM.

- *Underrepresented student engagement* – *Biogen's Community Lab* hosts students from the greater Boston area of Massachusetts and Research Triangle Park in North Carolina hands-on science learning. Designed to foster a passion for science, the program accepts students from lower income households and groups historically underrepresented in science and provides them with the opportunity to meet and interact with Biogen employees and get an inside view of a biotech company. In 2020, Biogen partnered with the Lemelson-MIT Program at the Massachusetts Institute of Technology (MIT) to launch the Biogen-MIT Biotech in Action: Virtual Summer Lab. This is a state-of-the-art, virtual program to continue to inspire and empower a new generation of young scientists.

Supply chain diversity

Another way Biogen integrates D&I philosophy into their commercial operations is through their supplier diversity initiative.[12] Through this program, Biogen's procurement procedures ensure that small and diverse suppliers have an equitable opportunity in competing for Biogen's tenders. Small businesses, as defined by the U.S. Small Business Administration, as well as enterprises owned by underrepresented groups (including women, veterans, disabled, LGBTQ+, etc.) partner with Biogen through this initiative.

[11] Biogen. Global Diversity and Inclusion. Available at https://www.biogen.com/en_us/diversity-inclusion.html. [Accessed 15 April 2020]

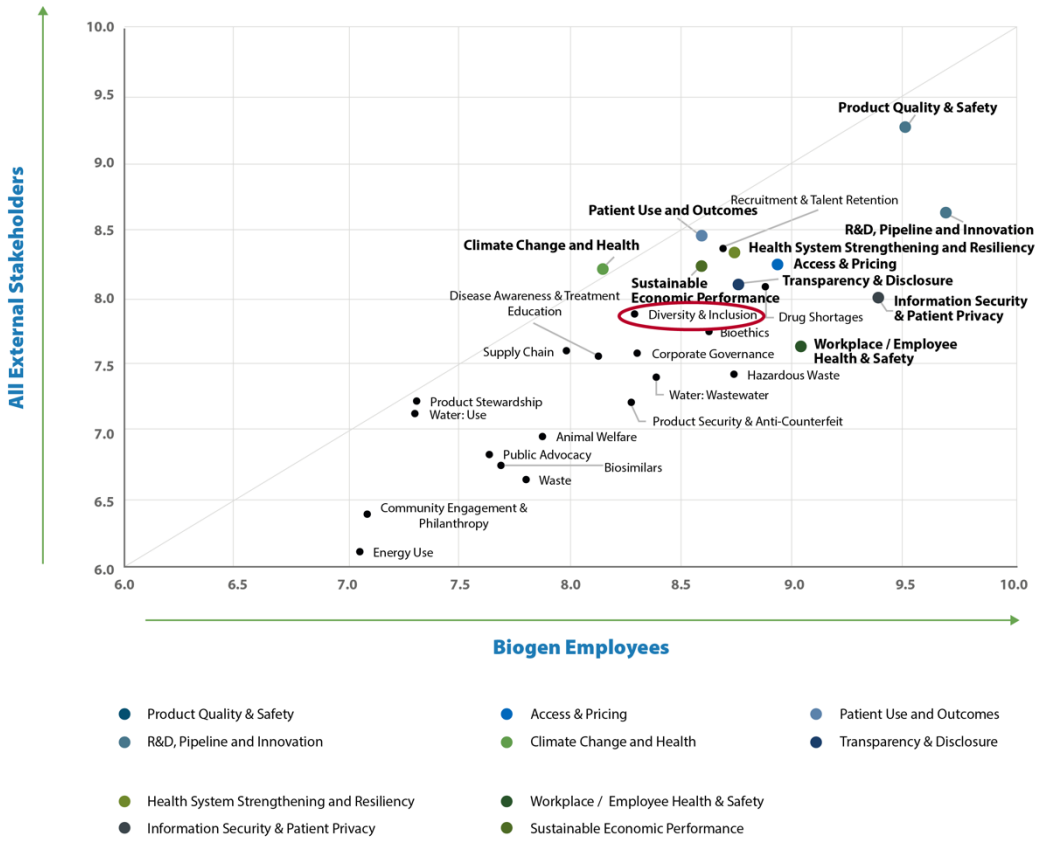
[12] Biogen. Working with us. Available at https://www.biogen.com/en_us/diversity-inclusion.html. [Accessed 15 April 2020]

The supplier diversity program is a case where Biogen integrates its commercial and social goals. The company believes partnering with a diverse network fulfils a social responsibility and also spurs economic growth, fosters innovation and provides Biogen with competitive advantage.

D&I accountability at Biogen

Biogen measures D&I objectives using performance indicators, highlighted in their Year in Review which demonstrates the company's commitment to Corporate Responsibility (CR).[13]

Figure 2: 2019 Importance of Issues - External vs Internal



Corporate Responsibility (CR) issues of significance to external stakeholders and Biogen employees, determined per the 2019 Materiality Assessment. Diversity & Inclusion is circled in red.

[13] Biogen. Reporting. Available at https://www.biogen.com/en_us/yearinreview/reporting.html. [Accessed 11 June 2020]

The company creates indicators based on a formalized process called "materiality assessments," conducted every few years through desk review[14] and stakeholder interviews in order to identify corporate responsibility issues most important to the business and its stakeholders.[15] They correlate these issues against those issues deemed a priority internally, by Biogen employees. This is a strategic process involving external stakeholders and occurs at a higher level than DISC priority-setting. See Figure 2 for a display of key issues identified in the 2019 Materiality Assessment, visualized as a scatter plot comparing the importance of a set of issues internally and externally. Note that "Diversity and Inclusion" was identified as a key issue for Biogen employees (Score=~8.4) and external stakeholders (Score=~7.8).

Key performance indicators used to measure D&I issues were included as part of Biogen's 2019 Year in Review are displayed in Table 2 below.[16]

Table 2: Biogen 2019 D&I-related indicators

Theme	Material Issue	Indicator
Supply Chain	Procurement Practices - Supplier Diversity	204-1: Proportion of spending on local suppliers
	Supplier Social Assessment	414-1: New suppliers that were screened with social criteria
		414-2: Negative social impacts in the supply chain and actions taken
Workforce Diversity & Inclusion	Diversity & Equal Opportunity	405-1: Diversity of governance bodies and employees
		405-2: Ratio of basic salary and remuneration of women to men

Points to consider

- Governance structures, accountability, and commitment at the highest levels of an organization are critical in driving D&I at a strategic level.
- Integrating D&I principles into the core of a business requires both:

[14] A desk review entails activities such as a review of active projects and activities, literature review, analysis of secondary data, and creation or update of references and resources.
[15] Biogen. GRI Materiality Assessment. Available at https://www.biogen.com/en_us/yearinreview/materialityassessment.html. [Accessed 11 June 2020].
[16] Biogen. GRI and SASB Content Indices. Available at https://www.biogen.com/en_us/yearinreview/griandsasb.html. [Accessed 11 June 2020].

  - Internal strategies focused on workforce development and inclusive employee initiatives.
  - External strategies focused on research, business operations and strategy (for example, considering health equity in R&D priority setting and supply chain management, as well as patient and community engagement).
- Creating a comprehensive D&I portfolio focuses on equity elements such as the demographics of corporate leadership, on the one hand, and as access to STEM education to enhance the pipeline, on the other.
- Diversity initiatives might be viewed to have a "trickle down" effect, wherein implementing workforce-based strategies can be seen as a preliminary step in addressing the broader goal of increasing diversity in clinical research populations.
- Weaving together commercial strategy and social D&I objectives can result in financially sustainable, socially impactful programs.
- Creating and utilizing key performance indicators (KPIs) around D&I are essential in tracking and accelerating progress.