Research Report in Conjunction with IVI Poster Presentation:

Strategies to Include Underrepresented Patient Populations in Patient Preference Research to Inform Open-Source Value Models

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Despite consensus across stakeholders on the need for greater inclusion of underrepresented patient populations (e.g., racial/ethnic minorities) in healthcare research, it remains challenging for research teams to recruit participants from some patient subgroups. The Innovation and Value Initiative and our research partners including the PAVE Center at the University of Maryland Baltimore, LUNGevity Foundation, and Janssen Scientific Affairs, have partnered to identify a set of best practices in establishing criteria for a representative patient population and recruiting underrepresented patient subgroups. This paper summarizes our findings and provides practical suggestions to improve representativeness in patient-centered research.

IVI **INNOVATION** AND
VALUE INITIATIVE

Strategies to Include Underrepresented Patient Populations in Patient Preference Research to Inform Open-Source Value Models

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Background

The call for greater inclusion of underrepresented populations in healthcare research, including clinical studies and health services research, has broad support across stakeholders in the health system.[1–4] Despite this, there continues to be inadequate participation in patient-centered research from some patient subgroups, defined by characteristics including race/ethnicity, age, and income level.[5–8] Thus, the unique perspectives of these groups are not captured in evidence used in a variety of decision contexts, including as inputs in value assessment (VA) models and analyses.[9]

The benefits of improving representativeness in healthcare research are manifold. Studies based on diverse and representative patient populations can generate more accurate estimates of disease burden and effectiveness of treatment options for overall patient populations and specific subgroups. In addition, sufficient subgroup sample size will allow for specific analyses and data presentation, something often lacking in medical and research journal articles.[10] In the VA context, improved inputs can account for patient heterogeneity and lead to more informed decisions, resulting in improved health outcomes and more efficient health spending.[11]

The importance of this progress transcends theory and directly applies to the ongoing research of the Innovation and Value Initiative (IVI) to improve patient-centricity in VA. As the IVI research team builds its third open-source value model focusing on major depressive disorder (IVI-MDD model), we are conducting a patient preference study with our partners. This will elicit patient-important value elements for MDD treatments and estimate associated preference weights that can be integrated into the model as inputs.[12] While IVI has prioritized representativeness of patient sampling in this effort, recruitment for the first phase revealed ongoing challenges with outreach and inclusion of individuals of color, younger age, and lower socioeconomic status

(SES). Consequently, IVI and collaborators initiated this methods study to identify best practices for including diverse patient groups in patient-centered research. IVI intends to implement the best practice strategies across its research portfolio.

This methods paper seeks to address two key questions:

- *What are specific criteria that can be used to measure patient representativeness in patient-centered research and VA?*

- *What are practical strategies and methods to recruit and engage underrepresented patient populations in patient-centered research and VA?*

The paper delineates our specific methods for defining such criteria and strategies and synthesizes related findings and feedback to develop an action plan for IVI patient preference study implementation. In sharing IVI's findings, this paper offers a transparent example of learning through action that can benefit the broader health research and VA communities.

Methods

IVI utilized a three-stage approach (**Figure 1)** to identify evidence and best practices on the two research questions, which are relevant to key stakeholders including researchers, patients, employers, payers, industry representatives, and clinicians. In the first stage, we reviewed select guidance documents (**Appendix 1)** to identify existing definitions and strategies, and synthesized learnings from continuous IVI stakeholder engagement across our research portfolio. In the second stage, we surveyed our patient advisory community to identify the relevance and priority of first-stage findings, and to highlight gaps. In stage three, we aggregated feedback from the first two stages to develop recommendations.

Stage 1

Review of Guidance Documents

IVI conducted a targeted search using the Google search engine and sought input from two patient-centered research experts to identify guidance documents on patient-centered research in the U.S. setting. Twenty-three guidance documents from nine organizations[a] with extensive patient engagement and research experience (**Appendix 1)** were reviewed to extract insights on (1) how representativeness was defined in patient-centered research, (2) barriers to recruiting underrepresented subgroups (e.g., people of color), and (3) recommended strategies and practices to overcome such barriers.

Stakeholder Engagement Fieldwork

As part of its transparent and patient-centered mission, IVI has solicited ongoing stakeholder engagement in all research and organizational initiatives. Input from three current initiatives is summarized here, including IVI's Patient Advisory Council[13], IVI-MDD model development[14], and MDD patient preference study[12]. Feedback was collected during virtual meetings (both verbally and through written online chat functions), in e-mail exchanges with individual participants, and individual conference calls with clinician and patient stakeholders.

Learnings from first-phase recruitment efforts in the ongoing MDD patient preference study were also reviewed. This project specifically aimed to recruit a sample representative of diverse patient subgroups **(Appendix 5).** As part of the project, IVI engaged an advisory group drawing

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[a] AcademyHealth, Clinical Trials and Transformation Initiative (CTTI), LUNGevity Foundation, Medical Device Innovation Consortium (MDIC), The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT), National Health Council (NHC), National Minority Quality Forum (NMQF), Patient-Centered Outcomes Research Institute (PCORI), U.S. Food and Drug Administration (FDA).

from multiple sectors, including national patient support groups, clinical sites serving primarily lower income individuals of color, and minority advocacy groups.

Stage 2

Short Survey

A short survey was developed (**Appendix 3)** and emailed to targeted individuals and organizations (N=26), selected from IVI members and partner organizations based on their experiences in patient-centered research and engagement. The survey delved deeper into the relevance and priority of issues that emerged from stage one, to identify other considerations inadvertently omitted, and to explore partnership opportunities to advance patient-centered research.

Stage 3

Based on the aggregated findings and feedback from the first two stages, IVI developed a set of recommended and prioritized strategies to guide recruitment for the patient preference study (**Appendix 5)** and other patient-centered research projects. The recommendations are based on lessons learned from fieldwork and stakeholder input, and can be used as guidance for engaging diverse and representative individuals in research that supports VA inputs.

Results

First-stage efforts yielded rich insights on the core research questions (**Appendix 2)**. In stage two, 14 complete survey responses (54%) were received from IVI members and partner

organizations (N=26). Survey responses amplified the themes identified in stage one guidance documents and provided additional strategies for recruiting a representative patient sample (**Appendix 4**). **Table 1** highlights findings associated with the research questions: defining representativeness in data samples, and specific strategies to recruit underrepresented patient populations.

In the documents and stakeholder recommendations (stage one) and short survey (stage two), near unanimous emphasis emerged on the importance of patient heterogeneity in patient-centered research, the need for continuous engagement with patients and underrepresented community leaders from the study's outset, and working with patients to understand and reduce barriers to participation. The top three strategies identified by survey respondents to improve engagement were (**Appendix A4**):

1. Partnership with organizations in the medical condition of interest (e.g., patient advocacy organizations)

2. Partnership with community-based and patient advocacy organizations serving underrepresented subgroups (e.g., community health centers)

3. Working with organizations that have engagement expertise with the underrepresented population (e.g., NMQF)

Defining Representativeness in Data Samples

The informal survey results **(Appendix 4)** indicated that "defining patient characteristics of a representative patient sample" is a key challenge. According to a consensus definition from a National Health Council (NHC) roundtable, representativeness means "a sufficient number of and types of people are included in the engagement activity to ensure that those engaged can

speak on behalf of the target population. It refers to 'who' and 'how many' individuals to include*."* [3,15] FDA and PCORI® guidelines identified a comprehensive set of characteristics in defining representativeness and identifying subgroups, including: race/ethnicity, rural vs. urban, pregnant and lactating women, gender, sexual orientation, disability status, socioeconomic status, demographic background, cultural background and specific languages, literacy and health literacy, and clinical characteristics.[1,16] Researchers are encouraged in these guidelines to develop specific criteria based on the research questions and medical condition of interest.

Given that patient characteristics vary by disease area or research question, guidance documents, stakeholder engagement, and survey recommendations **(Appendix 4)** all identified the importance of engaging early with patient and community-based organizations – or with patients directly – to understand differing perspectives and develop more specific criteria.[2,15,17–20] With early and ongoing engagement, direct patient inputs can complement existing knowledge base (e.g., the peer-reviewed articles) to inform criteria for a representative sample.[21]

Strategies to Recruit Underrepresented Patient Subgroups

Establishing a clear research objective to recruit underrepresented patient groups was a consistent recommendation in guidance documents we reviewed.[22] In developing the IVI-MDD value model, IVI operationalized this strategy by forming a multi-stakeholder advisory group that included organizations and individual representatives either from underrepresented patient communities or those who work closely with them (e.g., clinicians, patient groups).[14] Further, through continuous engagement with these advisors and with stakeholders on IVI's Patient Advisory Council, research teams were advised to include "recruiting a representative patient sample" as a research objective. Strategies to achieve this objective, discerned through our

research, include partnership and patient engagement, personnel training, focus on accessibility, cross-validation, and activation and recognition of patient participants.

Partnership Development and Patient Stakeholder Engagement

Based on review findings and stakeholder engagement, developing trusted partnerships with community leaders and targeted patient organizations is a primary strategy for recruiting underrepresented patient subgroups (**Appendix 2 + 4)**.[2,15,16,18,20,22] Multiple organizations[b] encouraged researchers to involve patients[c] and community leaders from study outset.[2,3,16,18,19,22–24] These leaders are uniquely positioned to advise researchers on inclusion/exclusion criteria, cultural appropriateness, and health literacy and linguistic appropriateness. Further, researchers can ensure that research goals are tailored to the communities' needs, thus encouraging participation.[22] Partnership with the disease state's patient organization was also prioritized by survey respondents as an effective recruitment approach (**Appendix 4).** A survey respondent further suggested that researchers identify patient representatives to serve as ambassadors for study promotion and participation. (**Appendix 4**). IVI's patient preference study experience has demonstrated that recruiting a diverse patient sample can be more time-consuming (**Appendix 5)**, as sufficient time must be dedicated to build trust with the patient community. Researchers should take this into account in study planning; they might consider developing these relationships before the study begins.

IVI's experiences further indicate that engaging with all key stakeholders may lead to a wider range of partners and organizations participating, beyond just online patient communities. During the patient preference study and IVI-MDD model development, the advisory group identified additional outreach venues including labor unions, churches and other religious

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[b] Including PCORI, MDIC, NHC, NMQF and LUNGevity.
[c] Or caregivers if patients are not able to directly participate (e.g., due to cognitive impairment).

associations, rural health centers, federally qualified health centers, state Medicaid agencies, and PCORNet partnership organizations (e.g., OCHIN Advance Collaborative). In our experience, advisory group members can help forge partnerships between researchers and prospective field partners. For example, in the first phase of patient preference work, an IVI-MDD advisory member connected research teams with a community health center that contributed directly to diverse patient recruitment.

Stage one findings suggested that research teams establish clear, regular, and open communications with partners and prospective participants to build trust and encourage ongoing participation.[2,16,19,22,25–27] Research teams should also clearly communicate study objectives, inclusion/exclusion criteria, and community benefit.[22,28] MDIC guidelines, for example, cautioned researchers not to set overly restrictive I/E criteria and to take an iterative approach in revising them based on field partner inputs.[2]

Guidance reviewed for this study encourages researchers to engage with study participants, community leaders, and field partners throughout data collection periods to ensure study completion and reduce attrition. These recommendations and the survey respondents' input (**Appendix 4**) acknowledge documented barriers to continuous participation and data collection, which include lack of trust in the medical system and research, particularly in the black community.[29,30] Hurdles to participation also include health literacy, language barriers, transportation and time costs, and site visits in addition to medical appointments. [22,31–33] Understanding specific barriers for the participant populations will enable researchers to facilitate data collection.[15,22]

Personnel Training

While not explicitly identified as a high priority, guidance documents from national experts[d] emphasize the importance of research team training, particularly with regard to cultural differences and appropriate engagement approaches with diverse populations (**Appendix 4**).[22,26,28] Areas of focus include importance of a representative patient sample, patient heterogeneity in the disease state, cultural sensitivity, and implicit bias.[16,22] Practicing humility and learning principles of respectful engagement throughout study phases have also been cited. In addition to training, the NIH and the Sullivan Commission also advocate for more diversity in the research teams.[34,35]

Technology and Language Accessibility

Guidance documents and early recruitment efforts in the patient preference study highlighted that patient access to technology (e.g., internet; smart phones) may be barriers to participants. Our first-phase efforts in the patient preference study revealed that some participants would prefer non-internet-based interactions. Guidance documents recommend that research teams work with field partners and advisors to simplify technology requirements and provide multiple channels for participation. Community-based organizations and health care providers can provide access to technologies for patients to provide input, noted in the guidance documents from NHC, NMQF, and LUNGevity.[15,19,20] Clear and accessible language at no-higher-than 5th grade reading level should be used in recruitment materials and data collection forms, with multilingual support when necessary.[2,22,36]

Online and mobile technologies such as electronic consent forms can simplify enrollment and data collection. But as shown in our patient preference study recruitment, individuals from

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[d] Including PCORI, NIH, MRCT Center, and AcademyHealth

certain groups (e.g., lower SES), may lack access to technology or prefer paper- or phone-based survey methods. Thus, IVI researchers provided multiple channels for survey enrollment and response.

Cross Validation

Guidance documents from NHC and LUNGevity advised that upon completing data collection, research teams examine the sample's patient composition against established representativeness criteria.[15,18,20] While a representative patient sample is ideal, researchers sometimes are unable to recruit a sample consistent with real-world distributions because of budget limitations or low prevalence of rare disease. In such cases, FDA guidance recommended that researchers may use statistical methods to re-weigh the data sample and derive estimates consistent with a representative patient sample.[17,37]

Activation and Recognition

IVI's engagement with its Patient Advisory Council, MDD Advisory Group, and patient partners heightened our awareness of recognizing the participation and contributions of patient communities to ensure ongoing working relationships and future research initiatives. Guidance documents and survey results **(Appendix 4)** also underscored that researchers must continue to engage with underrepresented patient communities post-study by sharing results and paying honoraria.[38] Field partners, community leaders, and advisers should be invited to help interpret study results, and researchers should explore ways that the findings can inform decisions related to the underrepresented patient. Patients can even be recognized as co-authors, and journals could begin to require demographic data or disclosure of patient engagement as part of peer-review criteria.

Discussion

There is broad consensus across stakeholder groups that a representative patient sample – consistent with disease epidemiology and proportionate participation from the underrepresented patient subgroup – be included in patient-centered research to inform population-level and subgroup analysis. Built on synthesized findings from guidance document review, a short survey, and IVI's continuous stakeholder engagement, this methods paper describes findings that apply to the wider research enterprise. It will also inform the development of an immediate action plan for IVI's second-phase patient preference study for the IVI-MDD model, which will demonstrate tangible impact of comprehensive patient engagement.

Through this study, IVI has distilled a set of guiding principles and best practices that inform our future research initiatives and serve as a model for others:

- Patient communities from diverse backgrounds should be engaged at the outset of research protocol design and invited to be active participants throughout the research process.

- Clear, deliberate, and transparent communications are key to building trust and long-term working relationships between patient communities and researchers. Attention must be paid to mode, literacy level, and cultural competency to ensure relevance and inclusiveness.

- To establish relevant criteria for a representative patient sample, researchers must reference existing knowledge base and directly engage with patients and patient entities within the disease state. Researchers must also engage with a wider community of

connectors, including sites of care, community organizations, and others with unique relationships and the ability to effectively engage.

- Recruitment is an iterative process. Researchers should establish ongoing feedback loops with patient and field partners to continually assess the representativeness of patients and impacts on research findings.

- Journals and federal agencies can incentivize stronger patient representativeness by instituting requirements for study demographic information and clear standards for patient involvement.

IVI and its research partners continue to work with the MDD Advisory Group to refine criteria for measuring representativeness and practical recruiting strategies for the patient preference study. The action plan is described in **Appendix 6**.

Limitations

There were limitations to this study. Due to time limits, a targeted literature review was not formally conducted. IVI will review additional guidance documents in the patient preference study. Second, as the patient preference study is still early-phase, the effectiveness of our proposed action plan cannot yet be evaluated. IVI remains committed to continuously sharing learnings so that partners and other research entities benefit. Third, while the research aimed to identify strategies for a wide range of disease states, some might not apply to specific disease areas or patient populations (e.g., rare diseases, incarcerated populations). Finally, stakeholder engagement to date has focused primarily on IVI members, which may limit our understanding of practice and applied efforts to improve representativeness in research. To address this, IVI is expanding its partnerships and seeking to engage with additional diverse stakeholders in the

broader health system through its advisory group process and the pursuit of novel research initiatives.

Conclusion

Addressing representativeness in patient-centered research has important implications for both the validity of the upcoming IVI-MDD model and as a best practice in research design and execution to inform next-generation VA. From this methods research, IVI concludes that there is long-term benefit to improving practice in this area. Such gains include strengthening and expanding collaborative relationships with patient communities; more consistent and effective results from researchers who account for patient heterogeneity; and raising expectations for transparency and inclusion among stakeholders. By collaborating with diverse groups, IVI will continue to advance the practice and methods in patient-centered research and VA models, support patient-informed, localized decision-making, and contribute to addressing health disparities.

References

1. FDA. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders DRAFT GUIDANCE. *Draft Guid*. 2018;(June 2018). http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

2. Selig W. *MDIC Report - Maximizing Patient Input in the Design and Development of Medical Device Clinical Trials (Revised Draft)*.; 2020. Accessed January 31, 2021. https://mdic.org/wp-content/uploads/2020/02/Maximizing-Patient-Input-Public-Comment-Draft.pdf

3. National Health Council (NHC). NHC Commitment to Ensure Representativeness in all Policy Work - National Health Council. Accessed January 31, 2021. https://nationalhealthcouncil.org/blog/nhc-commitment-to-ensure-representativeness-in-all-policy-work/

4. Levin D, Greenberg R. AAMC Insight - More Minorities Needed in Clinical Trials to Make Research Relevant to All | AAMC. Published December 2016. Accessed January 31, 2021. https://www.aamc.org/news-insights/more-minorities-needed-clinical-trials-make-research-relevant-all

5. Burchard EG, Oh SS, Foreman MG, Celedón JC. Moving toward True inclusion of racial/ethnic minorities in federally funded studies: A key step for achieving respiratory health equality in the United States. *Am J Respir Crit Care Med*. 2015;191(5):514-521. doi:10.1164/rccm.201410-1944PP

6. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *J Am Med Assoc*. 2004;291(22):2720-2726. doi:10.1001/jama.291.22.2720

7. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol*. 2003;21(12):2268-2275. doi:10.1200/JCO.2003.09.124

8. Unger JM, Hershman DL, Albain KS, et al. Patient income level and cancer clinical trial participation. *J Clin Oncol*. 2013;31(5):536-542. doi:10.1200/JCO.2012.45.4553

9. Willke RJ, Neumann PJ, Garrison LP, Ramsey SD. Review of Recent US Value Frameworks-A Health Economics Approach: An ISPOR Special Task Force Report [6]. Published online 2018. doi:10.1016/j.jval.2017.12.011

10. Yancey AK, Ortega AN, Kumanyika SK. EFFECTIVE RECRUITMENT AND RETENTION OF MINORITY RESEARCH PARTICIPANTS. *Annu Rev Public Health*. 2006;27(1):1-28. doi:10.1146/annurev.publhealth.27.021405.102113

11. Lucarelli C, Nicholson S, Tilipman N. *Price Indices and the Value of Innovation with Heterogenous Patients*.; 2021. doi:10.3386/w28333

12.   dosReis S, Butler B, Caicedo J, et al. Stakeholder-Engaged Derivation of Patient-Informed Value Elements. *Patient*. 2020;13(5):611-621. doi:10.1007/s40271-020-00433-8

13.   Patient Advisory Council - Innovation and Value Initiative. Accessed January 31, 2021. https://www.thevalueinitiative.org/patient-advisory-council/

14.   IVI-MDD Value Model - Innovation and Value Initiative. Accessed January 31, 2021. https://www.thevalueinitiative.org/ivi-mdd-value-model/

15.   National Health Council (NHC). *Tackling Representativeness: A Roadmap and Rubric*.; 2019. Accessed January 31, 2021. https://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Representativeness in Patient Engagement.pdf

16.   PCORI. Strengthening Diversity in Research Partnerships: Knowledge to Action. Published 2017. Accessed January 31, 2021. https://www.pcori.org/research-results/2017/strengthening-diversity-research-partnerships-knowledge-action

17.   U.S. Food and Drug Administration (FDA). *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*.; 2020. Accessed January 31, 2021. https://www.fda.gov/media/139088/download

18.   Winkfield KM, Regnante JM, Miller-Sonet E, González ET, Freund KM, Doykos PM. Development of an Actionable Framework to Address Cancer Care Disparities in Medically Underserved Populations in the United States: Expert Roundtable Recommendations. *JCO Oncol Pract*. Published online January 18, 2021:OP.20.00630. doi:10.1200/op.20.00630

19.   Regnante JM, Richie NA, Fashoyin-Aje L, et al. US Cancer Centers of Excellence Strategies for Increased Inclusion of Racial and Ethnic Minorities in Clinical Trials. *J Oncol Pract*. 2019;15(7):E289-E299. doi:10.1200/jop.18.00638

20.   Regnante JM, Richie N, Fashoyin-Aje L, et al. Operational strategies in US cancer centers of excellence that support the successful accrual of racial and ethnic minorities in clinical trials. *Contemp Clin Trials Commun*. 2020;17:100532. doi:10.1016/j.conctc.2020.100532

21.   National Health Council (NHC). *The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric The Patient Voice in Value: The NHC Patient-Centered Value Model Rubric*.; 2016. Accessed January 31, 2021. http://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Value-Rubric.pdf

22.   PCORI. *Community-Campus Partnerships for Health - Final Report*. Accessed January 31, 2021. https://www.pcori.org/sites/default/files/Final-Report-Table.pdf

23.   Noel L, Phillips F, Tossas-Milligan K, et al. Community-Academic Partnerships: Approaches to Engagement. *Am Soc Clin Oncol Educ B*. 2019;39(39):88-95. doi:10.1200/edbk_246229

24.   NMQF. Research Inclusion – Center for Sustainable Health Care Quality and Equity. Accessed January 31, 2021. https://nmqf-shc.org/research-inclusion/

25. Edmunds M, Bezold C, Johnson B, et al. *The Future of Diversity and Inclusion in the Health Services and Policy Research: A Report on the Acadmey Health Workforce Diversity 2025 Roundtable*.; 2015. Accessed January 31, 2021. https://academyhealth.org/sites/default/files/AH_230DiversityReport 2015_09.15.pdf

26. Academy Health. *Making Health and Health Care Better for Everybody: A Progress Report (2015-2017)*.; 2018. Accessed January 31, 2021. https://academyhealth.org/sites/default/files/Progress_Report_Feb2018.pdf

27. Basu Roy U, King-Kallimanis BL, Kluetz PG, Selig W, Ferris A. Learning from Patients: Reflections on Use of Patient-Reported Outcomes in Lung Cancer Trials. *J Thorac Oncol*. 2018;13(12):1815-1817. doi:10.1016/j.jtho.2018.09.003

28. The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT). *Achieving Diversity, Inclusion, and Equity in Clinical Research*.; 2020. Accessed January 31, 2021. https://mrctcenter.org/diversity-in-clinical-trials/

29. Gamble VN. A legacy of distrust: African Americans and medical research. *Am J Prev Med*. 1993;9(6 SUPPL.):35-38. doi:10.1016/s0749-3797(18)30664-0

30. Corbie-Smith G, Thomas SB, St. George DMM. Distrust, race, and research. *Arch Intern Med*. 2002;162(21):2458-2463. doi:10.1001/archinte.162.21.2458

31. Perfetto EM, Oehrlein EM, Boutin M, Reid S, Gascho E. Value to Whom? The Patient Voice in the Value Discussion. *Value Heal*. 2017;20(2):286-291. doi:10.1016/j.jval.2016.11.014

32. U.S. Food and Drug Administration (FDA). FDA Insight: Minority Health and Health Equity. Published December 2020. Accessed January 31, 2021. https://www.fda.gov/news-events/fda-insight/fda-insight-minority-health-and-health-equity

33. Clark LT, Watkins L, Piña IL, et al. Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Curr Probl Cardiol*. 2019;44(5):148-172. doi:10.1016/j.cpcardiol.2018.11.002

34. The Sullivan Commission on Diversity in the Health Care Workforce. *A Report of the Sullivan Commission on Diversity in the Health Professions*.; 2016. Accessed January 31, 2021. https://campaignforaction.org/wp-content/uploads/2016/04/SullivanReport-Diversity-in-Healthcare-Workforce1.pdf

35. National Institutes of Health. *NIH Scientific Workforce Diversity Toolkit* . Accessed January 31, 2021. https://diversity.nih.gov/sites/coswd/files/images/SWD_Toolkit_Interactive-updated_508.pdf

36. Clinical Trials Transformation Initiative (CTTI). *CTTI Recommendations: Advancing the Use of Mobile Technologies for Data Capture & Improved Clinical Trials*.; 2020. Accessed January 31, 2021. https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/mobile-devices-recommendations.pdf#Pg2Ln13

37. Copeland KR, Ganesh N. Sample Weighting for Health Surveys. In: *Health Survey*

Methods. Wiley; 2014:669-694. doi:10.1002/9781118594629.ch26

38.   The Multi-Regional Critical Trial Center at Harvard (MRCT). *Return of Results Guidance Document*.; 2015. Accessed January 31, 2021. https://mrctcenter.org/wp-content/uploads/2015/11/2015-03-19_mrct_ror_guidance_1.0.pdf#:~:text=The Harvard Multi-Regional Clinical Trials Center (MRCT Center),from industry, academia, patient advocacy and non-profit centers.

Figures and Tables
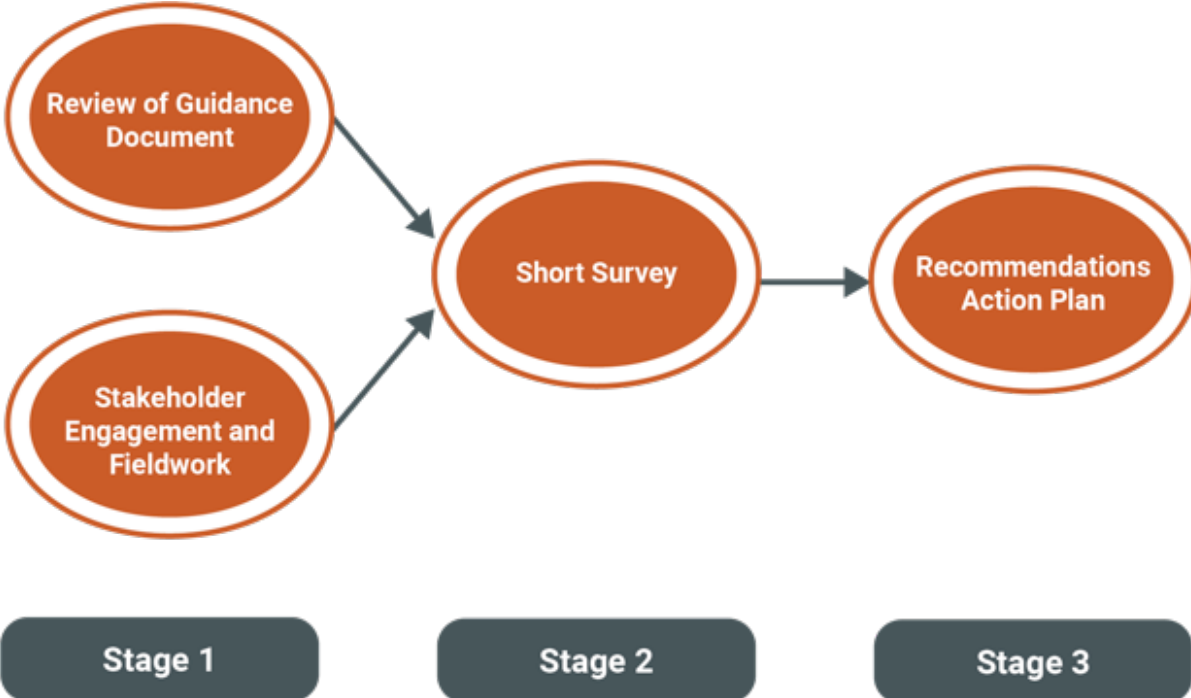
Figure 1 - Three-Stage Approach

Table 1 - Summary of Recommendations by Themes Identified

Themes	Recommendations
Defining Representativeness	- Clearly define research questions - Include "a representative sample" as a research objective - Examine existing knowledge base (e.g., peer-reviewed articles) to identify potential subgroups or gaps - Engage in conversations with patients from diverse backgrounds - Reference patient characteristics highlighted by FDA (VoP reports) and PCORI to identify potentially underrepresented patient groups
Partnership Development and Stakeholder Engagement	- Develop partnerships with community leaders and patient advocacy organizations - Engage patients from the outset and throughout the study, identify patient representatives that can serve as community ambassadors - From a multi-stakeholder advisory group that can advise on partnerships - Maintain clear, regular, and open communications with all stakeholders throughout the study phases - Understand specific barriers facing different patient subgroups and provide solutions accordingly - Avoid using overly restrictive inclusion/exclusion criteria

Personnel Training	- View training of research teams and fielding partners as an ongoing process
	- Expose research teams and fielding partners to different patient perspectives and enhance cultural sensitivity
	- Training foci can include:
	  - Engagement and partnerships with diverse patient subgroups
	  - Strategies to recruit a representative patient sample
	  - Concept of patient heterogeneity and its importance in research
	- Establish clear principles of respectful engagement and operational standards
	- Recruit research team members from diverse backgrounds

Technology and Language Accessibility	- Ensure that research instruments and materials use accessible and clear languages - Provide multilingual support (e.g., offer documents in multiple languages when possible)

	- Simplify enrollment process using strategies such as mobile technologies or through community partnerships - Provide multiple channels for survey response (online, phone, in-person) - Partner with healthcare providers to simplify technology requirements
Cross Validation	- Examine final sample against established criteria of representative sample - Apply statistical methods to re-weigh sample if needed
Activation and Recognition	- Share study results with participants - Ensure payment of honoraria - Include patient contributors as co-authors - Explore ways in which study results can inform decisions related to the underrepresented patient communities

Abbreviations: FDA, Food and Drug Administration; VoP, Voice of Patients; PCORI, Patient-Centered Outcomes Research Institute

Appendix

Appendix 1 - List of Documents Reviewed

AcademyHealth

- Making Health and Health Care Better for Everybody: A Progress Report (2015-2017). 2018 Feb. Available from: https://academyhealth.org/sites/default/files/Progress_Report_Feb2018.pdf.
- Edmunds M, Bezold C, Johnson B, Tetteh H, Barlow J, Professor A, et al. The Future of Diversity and Inclusion in the Health Services and Policy Research: A Report on the AcademyHealth Workforce Diversity 2025 Roundtable. 2015 Sep. Available from: https://academyhealth.org/sites/default/files/AH_230DiversityReport 2015_09.15.pdf.

Clinical Trials Transformation Initiative (CTTI)

- CTTI Recommendations: Advancing the Use of Mobile Technologies for Data Capture & Improved Clinical Trials. 2020 Mar. Available from: https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/mobile-devices-recommendations.pdf#Pg2Ln133.

LUNGevity Foundation

- Regnante JM, Richie NA, Fashoyin-Aje L, Vichnin M, Ford M, Roy UB, et al. US Cancer Centers of Excellence Strategies for Increased Inclusion of Racial and Ethnic Minorities in Clinical Trials. J Oncol Pract. American Society of Clinical Oncology; 2019;15:E289–99. 13.
- Regnante JM, Richie N, Fashoyin-Aje L, Hall LL, Highsmith Q, Louis JA, et al. Operational strategies in US cancer centers of excellence that support the successful accrual of racial and ethnic minorities in clinical trials. Contemp Clin Trials Commun. Elsevier Inc; 2020;17:100532. 14.
- Winkfield KM, Regnante JM, Miller-Sonet E, González ET, Freund KM, Doykos PM. Development of an Actionable Framework to Address Cancer Care Disparities in Medically Underserved Populations in the United States: Expert Roundtable Recommendations. JCO Oncol Pract. American Society of Clinical Oncology (ASCO); 2021;OP.20.00630.

Medical Device Innovation Consortium (MDIC)

- Selig W. Maximizing Patient Input in the Design and Development of Medical Device Clinical Trials (Revised Draft). 2020 Feb. Available from: https://mdic.org/wp-content/uploads/2020/02/Maximizing-Patient-Input-Public-Comment-Draft.pdf.

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT)

- Achieving Diversity, Inclusion, and Equity in Clinical Research. 2020. Available from: https://mrctcenter.org/diversity-in-clinical-trials/.
- Return of Results Guidance Document. 2015. Available from: https://mrctcenter.org/wp-content/uploads/2015/11/2015-03-19_mrct_ror_guidance_1.0.pdf#:~:text=The Harvard Multi-Regional Clinical Trials Center (MRCT Center),from industry, academia, patient advocacy and non-profit centers.

National Health Council (NHC)

- Tackling Representativeness: A Roadmap and Rubric. 2019 Dec. Available from: https://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Representativeness in Patient Engagement.pdf.
- NHC Commitment to Ensure Representativeness in all Policy Work - National Health Council. Available from: https://nationalhealthcouncil.org/blog/nhc-commitment-to-ensure-representativeness-in-all-policy-work/.
- The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric The Patient Voice in Value: The NHC Patient-Centered Value Model Rubric. 2016 Mar. Available from: http://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Value-Rubric.pdf.

National Minority Quality Forum (NMQF)

- Research Inclusion – Center for Sustainable Health Care Quality and Equity. Available from: https://nmqf-shc.org/research-inclusion/.

Patient-Centered Outcomes Research Institute (PCORI)

- Community-Campus Partnerships for Health - Final Report. Available from: https://www.pcori.org/sites/default/files/Final-Report-Table.pdf.
- Diversity and Inclusion in PCORnet: Need and Recommendations. Available from: https://www.pcornetcommons.org/wp-.
- Gardiner P, Lestoquoy AS, Negash NL, Luo M, Gergen-Barnett K, Saper R, et al. Lessons Learned and Strategies for Recruitment of Diverse, Low-income Patients into an Integrative Medical Group Visit Clinical Trial. Explore [Internet]. Elsevier Inc.; 2019;15:215–21. Available from: https://pubmed.ncbi.nlm.nih.gov/31056423/.
- Strengthening Diversity in Research Partnerships: Knowledge to Action. 2017. Available from: https://www.pcori.org/research-results/2017/strengthening-diversity-research-partnerships-knowledge-action.

U.S. Food and Drug Administration (FDA)

- Regulatory Affairs Professionals Society. FDA lays out 2021 regulatory science areas of focus. 2021. Available from: https://www.raps.org/news-and-articles/news-articles/2021/1/harnessing-data-listening-to-patients-fdas-foci-in.
- Collection of Race and Ethnicity Data in Clinical Trials - Guidance for Industry and Food and Drug Administration Staff. 2016 Oct. Available from: https://www.fda.gov/media/75453/download.
- Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. 2020 Jun. Available from: https://www.fda.gov/media/139088/download.
- FDA Insight: Minority Health and Health Equity. 2020. Available from: https://www.fda.gov/news-events/fda-insight/fda-insight-minority-health-and-health-equity.
- Global Participation in Clinical Trials Report. 2017 Jul. Available from: https://www.fda.gov/media/106725/download.
- 2021: Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS). 2021 Jan. Available from: https://www.fda.gov/media/145001/download.

Appendix 2 - Summary from Review of Guidance Documents

1. Defining Representativeness and Diversity in Patient-Centered Research

Source / Article / URL	Findings

U.S. Food and Drug Administration (FDA).
 	
Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.; 2020.
 	
https://www.fda.gov/media/139088/download
	• Ongoing theme: How to measure diversity depends on specific research objectives.
	• Re-weighting can be used if the collected data is not a representative sample
	• Factors to consider (Figure 2 of the patient-focused drug development)
	  ○ Socioeconomic and demographic backgrounds
	  ○ Cultural background and specific languages
	  ○ Literacy and health literacy
	  ○ Clinical characteristics
	• FDA is working with academia to evaluate whether previously developed PRO measures perform differently in people living with heart failure from different demographic groups (such as racial and ethnic groups, gender groups, children, and literacy levels). FDA is exploring how these instruments may be modified to adequately capture symptoms in diverse patient groups. These PRO measures could be used to inform pre-market approvals and postmarket surveillance efforts. (**pg. 45**)

PCORI/PCORNet. *Diversity and Inclusion in PCORnet: Need and Recommendations.* https://www.pcori.org/sites/default/files/3928-PCORnet-Engagement-Committee-Diversity-Inclusion-Needs-Recommendations.pdf	• Study participants/governance representatives reflecting the population demographics they represent. • Voices of all stakeholders are heard and incorporated throughout the process through genuine power sharing and decision-making authority. • All audiences impacted by the research question/health topic are included. • Underrepresented groups impacted by the outcomes of research are included and prioritized (i.e., people of color, rural/inner city populations, pregnant and lactating women, gender and sexual minorities2, individuals with disabilities, and other audiences commonly underrepresented in clinical research).

NHC	

The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric The Patient Voice in Value: The NHC Patient-Centered Value Model Rubric.; 2016.
 	
http://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Value-Rubric.pdf
 	
Commitment to Ensure Representativeness in all Policy Work - National Health Council.
 	
https://nationalhealthcouncil.org/blog/nhc-commitment-to-ensure-representativeness-in-all-policy-work/
	● Diversity of Patients/Populations. The value model should account for differences across patient subpopulations, trajectory of disease, and stage of a patient's life.
	  ○ High: Thoughtful consideration was given to differences in patient perceptions of value across relevant patient subpopulations, including populations at-risk and those with early- and late-stage disease
	  ○ Low: The model assumed the patient population is homogenous and takes a 'one-size-fits-all' approach

NHC	● "'Representativeness' means a sufficient number of and types of people are included in the engagement activity to ensure that those engaged can speak on behalf of the target population. It refers to 'who' and 'how many' individuals to include in an interaction in order to, as closely as possible, engage with individuals that represent the broader, target patient population."
Tackling Representativeness: A Roadmap and Rubric.; 2019.	
https://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Representativeness in Patient Engagement.pdf	**Consider "representativeness" as a process involving a minimum target (or targets)** ● Define - Clearly define objective for engagement effort ● Understand - Understand as much as possible about the full population and subpopulation and their challenges ● Specify - Develop a description of the minimum target(s) for representativeness for the engagement activity ● Plan - Develop a plan to achieve the minimum target(s) defined ● Evaluate - Develop an evaluation plan to assess progress on achieving target(s) ● Document - Record how patient representativeness was defined, targeted, achieved, and assessed

MRCT
 	
Achieving Diversity, Inclusion, and Equity in Clinical Research.; 2020.
 	
https://mrctcenter.org/diversity-in-clinical-trials/
	● Sample size and sampling techniques depend on the desired representativeness based on the research question and objective
	
	● Sample size is influenced by:
	  a. Aim of the study
	  b. Sample specificity
	  c. Use of established theory
	  d. Analysis strategy

2. Barriers to Recruiting Underrepresented Patient Subgroups

Source / Article / URL	Findings
U.S. Food and Drug Administration (FDA). *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.*; 2020. https://www.fda.gov/media/139088/download	Rare Diseases: Very few patients and are often difficult to recruit. Technology: The use of technology may make it *more difficult* for some patients to participate, and may make it difficult to verify the patient identity or clinical and demographic characteristics. However, not using technology may make it more difficult to reach younger demographics. Health literacy, language, health state, cognitive abilities can all impact the ability to participate.
U.S. Food and Drug Administration (FDA). FDA Insight: Minority Health and Health Equity. Published December 2020. https://www.fda.gov/news-events/fda-insight/fda-insight-minority-health-and-health-equity	**Transcript Extract:** **RADM Araojo:** *Advancing diverse participation in clinical trials is a priority for the Office of Minority Health and Health Equity. We know that racial and ethnic minority populations continue to be underrepresented in clinical trials.* *This is due to factors including a lack of trust in the medical system—in part due to past historical abuses—as well as other barriers like a lack of transportation, time, or knowledge about clinical trials and research opportunities.* *And while great strides have been made to build trust, confidence and access, many health disparity issues continue to need attention. Over the coming years we will continue our work to broaden knowledge of clinical trials through expansion of successful initiatives such as our ongoing clinical trial diversity campaign in which we are always adding new tools and resources like the most recent addition to this campaign that we developed in collaboration with the Center for Devices and Radiological Health on the importance of diverse participation in medical device clinical trials.*

U.S. Food and Drug Administration (FDA). *Global Participation in Clinical Trials Report*.; 2017. https://www.fda.gov/media/106725/download	Participation in clinical trials varies widely across disorders. For example: Psychiatry (24.18 percent black or African American), Oncology (2.74 %), and Cardiovascular Disease.
PCORI Gardiner P, Lestoquoy AS, Negash NL, et al. Lessons Learned and Strategies for Recruitment of Diverse, Low-income Patients into an Integrative Medical Group Visit Clinical Trial. *Explore*. 2019;15(3):215-221. doi:10.1016/j.explore.2019.01.003	Cited for low participation in research include: mistrust of research studies or the medical system, time commitment to the study, possible loss of income from participation and transportation difficulties. Other barriers emerging from qualitative literature include not having enough information about clinical research or potential harmful consequences of the clinical trial. Due to these obstacles, strategies to recruit diverse participants often include resource and time intensive methods

PCORI *Community-Campus Partnerships for Health - Final Report*. https://www.pcori.org/sites/default/files/Final-Report-Table.pdf	By listing researcher recommendations first, we reflect a key issue that emerged across the listening sessions and community forums – to make research more culturally responsive,researchers must do better. Many of the concerns and desires were framed in terms of how researchers have caused harm to the community, as well as ways in which researchers worked in equitable partnerships to ensure community benefits. Ultimately, we list community recommendations prior to researcher recommendations for several key reasons. Across the community forums, participants spoke to the importance of: - Honoring community voices. The table reflects what community members shared regarding their lived experiences specific to research, but also the context in which research happens. - Ensuring our materials were community-centered. While the materials are intended to increase researchers' abilities to be more culturally responsive (i.e. how to be a better ally to communities), the intent is also to provide communities support on how to advocate for more culturally responsive research. Ideally this will lead to more equitable partnerships that increase community health and well-being. (**pg. 1**) **Community-Campus Relationship building barriers:** 1. Researchers do not understand communities (history, historic trauma, geo-political context, socio-demographic, institutional racism) 2. Treat people and communities as homogeneous 3. Use communities for their own benefits 4. Focus on topics that are important to other stakeholders, but not to the communities 5. Create processes that make sense to themselves (researchers, but not to the communities). Also do not account for cultural context, not the reality of the complexity of the community in any way 6. Negatively portrays communities that perpetuate stereotypes 7. Effective community dissemination (findings etc.)

PCORI Strengthening Diversity in Research Partnerships: Knowledge to Action. Published 2017. https://www.pcori.org/research-results/2017/strengthening-diversity-research-partnerships-knowledge-action	*Project Summary* *In the last decade there has been much growth in the involvement of patient and family advisors in improvement and research. IPFCC recognizes that many organizations struggle to build advisory programs that reflect the diversity of the population they serve. In order to see improved health equity and reduced health disparities, we must strengthen the capacity to create partnerships with individuals and families living in diverse and underserved communities; better involve them in their own care; and engage them in the improvement of care processes, interprofessional education, and research.*

NHC
The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric The Patient Voice in Value: The NHC Patient-Centered Value Model Rubric.; 2016.
 	
http://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Value-Rubric.pdf
	Potential burdens to participation in trials/studies:
	  e. Requiring participants to make frequent visits to specific sites may burden the elderly, children, disabled, and cognitively impaired individuals who require transportation or caregiver assistance, or participants who live far from research facilities
	  f. Financial costs (e.g., travel, missing work), including study visits that interfere with work and family responsibilities
	  g. Added clinical trial study visits for patients receiving regularly scheduled care from their community provider
	  h. Mistrust of clinical research among certain populations

MDIC Selig W. *MDIC Report - Maximizing Patient Input in the Design and Development of Medical Device Clinical Trials (Revised Draft)*.; 2020. https://mdic.org/wp-content/uploads/2020/02/Maximizing-Patient-Input-Public-Comment-Draft.pdf	● Restrictive Eligibility Criteria (i.e., overly restrictive inclusion/ exclusion criteria ● Complex Informed Consent ● Burdensome Protocols (i.e., protocols place extensive demands on patients in terms of time, travel, physical demands, ability to communicate about their condition)

| **NMQF**

NMQF. Research Inclusion – Center for Sustainable Health Care Quality and Equity.

https://nmqf-shc.org/research-inclusion/ | "Although cancer clinical trials may provide a mechanism for patients to gain access to high-cost medication, the ancillary expenditures of cancer care such as transportation, lodging, and childcare and lower or lost wages due to gaps in work may be exacerbated for those participating in clinical trials and, therefore, continue to be barriers for patients and families." - Winkfield K, Cancer (October 2019). Improving Access to Cancer Clinical Trials by Reducing the Financial Burden. ACS Journals. Available: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.32523

There is uneven reporting of basic demographic information in clinical trials. "Suboptimal race reporting and representation (especially in blacks and Hispanics) occurs regularly in landmark oncology trials and increased efforts are needed to enhance minority representation and eliminate these disparities." **-** Loree, et al, Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals 2008 to 2018, JAMA Oncol. 2019;5(10):e191870. doi:10.1001/jamaoncol.2019.1870. |

3. Practical Strategies and Recommendations to Recruiting Underrepresented Subgroups

Source / Article / URL	Findings
RAPS FDA lays out 2021 regulatory science areas of focus . Published January 2021. https://www.raps.org/news-and-articles/news-articles/2021/1/harnessing-data-listening-to-patients-fdas-foci-in **U.S. Food and Drug Administration (FDA).** *2021: Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS).*; 2021. https://www.fda.gov/media/145001/download	To realize the promise of precision medicine and individualized therapeutics, FDA sees a critical need for more mechanistic understanding, improved manufacturing capabilities, and additional tools. FDA is exploring new technologies (omics) to advance major breakthroughs in thinking about diagnosis, prognosis, and treatment of disease. Key areas of focus for precisionFDA: ● More opportunities for information and data sharing ● More focus groups with patients from diverse backgrounds The FDA created precisionFDA, a cloud-based community research and development portal that engages users across the world to share data and tools to test, pilot, and validate existing and new bioinformatics approaches to NGS processing. Pharmacogenetics studies how individuals respond differently to drug therapies based on their genetic make-up or genes using technology such as NGS which allows sequencing of a human's entire genome in a short period of time (as short as one day). This technology combined with others enables researchers to identify precise genetic, mechanistic, or lifestyle reasons to understand why certain individuals or subpopulations respond positively or negatively when treated for the same disease with the same drug. Being able to more precisely classify the genetic basis of diseases and drug responses through diagnostic tests and devices enables the development of mechanistically targeted therapeutics. (**pg. 24**) FDA implements a variety of social and behavioral science research approaches: … Conducting extensive formative research, including more than 40 focus groups, representing the diverse backgrounds of consumers around the United States, to produce consumer-oriented educational materials for the Feed Your Mind Initiative. This agricultural biotechnology initiative provides consumers with science-based educational information informed by the latest science and research studies on the environmental, nutritional, food safety, economic, and humanitarian impacts of genetically engineered or bioengineered foods, commonly called genetically modified organisms. (**pg.46**)

FDA - Office of Minority Health FDA Insight: Minority Health and Health Equity. (12/2020) https://www.fda.gov/news-events/fda-insight/fda-insight-minority-health-and-health-equity	Transcript Excerpt: ***Anand Shah:*** *How does the office work with industry and other stakeholders to improve minority health?* ***RADM Araojo:*** *One way we work with industry and a broad group of stakeholders is through raising awareness on the need for diverse participation in clinical trials through our ongoing diversity in clinical trials campaign. Additionally, through our Research and Collaboration Program we work with FDA centers and external partners to support research studies about minority health and health disparities.* *These studies aim to: reduce health disparities by advancing minority health and health equity focused research, education, and scientific exchange. We aim to study medical conditions that disproportionately affect racial and ethnic populations as well as analyze data sets that address FDA concerns or questions. We also study human genetic variation in susceptibility and severity of medical conditions and conduct usability testing among diverse stakeholders and consumers to improve comprehension of FDA's communications.*
FDA - Office of Minority Health *Collection of Race and Ethnicity Data in Clinical Trials - Guidance for Industry and Food and Drug Administration Staff .; 2016.* https://www.fda.gov/media/75453/download	"This guidance recommends a format for collection of race and ethnicity clinical trial data that are submitted in standardized data sets per the Study Data Tabulation Model." "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required."

RAPS FDA lays out 2021 regulatory science areas of focus . Published January 2021. https://www.raps.org/news-and-articles/news-articles/2021/1/harnessing-data-listening-to-patients-fdas-foci-in	Three Strategic Initiatives: - The Power of Data - Innovation in the Service of Choice - Considering the View of the Patient - "Ongoing collaboration with patient groups, academia, and professional organizations seeks to broaden ways in which outcomes important to patients and their caregivers are included in regulatory decision-making."

PCORI/PCORNet
 	
Diversity and Inclusion in PCORnet: Need and Recommendations.
 	
https://www.pcori.org/sites/default/files/3928-PCORnet-Engagement-Committee-Diversity-Inclusion-Needs-Recommendations.pdf
	Diversity and Inclusion in PCORnet: Need and Recommendations
	
	HOW can we achieve diversity? Examples of strategies include:
	
	1. *Promote diversity among PCORnet governance and study populations, by assuring multiple group representatives serve on committees and influence decisions. All efforts are robust to avoid tokenism.*
	2. *Be intentional about diversity in PCORnet projects by assessing the composition and decision-making authority of leadership, teams, and participants.*
	3. *Form and nurture a workgroup(s) focused on diversity and underserved/special populations. 3*
	4. *Start with a comparable diversity and inclusion policy to other institutions 4,5 while leading and setting new standards for the field.*
	5. *Improve Front Door processes to expect and assess attention to diversity, identify deficiencies, and offer expertise.*
	6. *Develop methods to assess and improve cultural humility/competency of PCORnet and its member networks (internal staff, committee members, partners, funded project teams, and organizations).*
	   a. *Create organizational/project level cultural humility training requirements 6,7,8,9*
	   b. *Develop and use a diversity council10*
	   c. *Adopt policies with empathy, compassion, and transparency in mind11,12 (pg 1)*

PCORI	
Strengthening Diversity in Research Partnerships: Knowledge to Action. Published 2017. https://www.pcori.org/research-results/2017/strengthening-diversity-research-partnerships-knowledge-action	*A key output will be a Knowledge to Action Report—Strengthening Diversity in Research Partnerships and a set of related resources to provide guidance and best practices for supporting increased diversity among the patients and families who participate in research. IPFCC will conduct a literature search, interviews with experts, and site visits to exemplary programs that partner with patients and families from diverse and underserved communities in PCOR and CER. The innovative programs featured at the conference and these other major project activities will inform the Report and resources.* *IPFCC will establish an Expert Advisory Panel that will include national experts in health disparities research, PCOR and CER, and patient and family partners who have experience as members of research teams. Serving on this panel will be representatives from the Center for Community Health and Vitality – a part of the Urban Health Initiative at the University of Chicago Medicine, Smart from the Start in Boston, the UNC School of Medicine, the Center for Health Equity Research, the Florida Health Equity Research Institute, and others who will share their expertise and assist in Conference planning and developing and disseminating the Knowledge to Action Report and related resources.*
PCORI Gardiner P, Lestoquoy AS, Negash NL, et al. Lessons Learned and Strategies for Recruitment of Diverse, Low-income Patients into an Integrative Medical Group Visit Clinical Trial. *Explore*. 2019;15(3):215-221. doi:10.1016/j.explore.2019.01.003	Some authors suggest that social marketing approaches or partnerships with community organizations may be more effective than traditional approaches for reaching under-represented participants [10,18]. Other studies found engaging community groups to be no more effective than social marketing, use of letters and referral based recruitment [10,19]. Our Patient Advisory Group (PAG)reviewed all flyers, patient informational brochures, welcome materials or any other text targeted at patients in order to ensure materials were patient centered. The PAG was composed male and female chronic pain patients who participated in the pilot version of these groups and provided feedback and guidance on the running of the trial throughout the study. We discussed strategies for improving recruitment with our members and different ways to appeal to the target population. The PAG suggested for any men randomized to the IMGV groups the IMGV facilitators should make an effort to acknowledge their participation in the first session. Once a month we met with our SAG, including clini- cians, researchers, a statistician, and a patient representative in order revise recruitment strategies and demographics.

The Data Safety Monitoring Board also reviewed recruitment data. The DSMB provided additional guidance to increase male recruitment, such as reviewing the sex of the participants referred by providers or self- referred in order to determine if there was a provider or participant bias as to whom would be interested in participating in this study.

Recommendations for Future Studies with a Low-Income Diverse Population

- Hire research staff that reflects the study population.
- Allocate a significant amount of time for recruitment and data collection efforts.
- Have multiple and flexible methods of recruiting patients such as being able to collect data by phone or in person, as well as during non-working hours.
- Be aware of substance use and other common co-morbidities in a low-income patient population.
- Include a patient advisory group in being part of the research design and implementation.
- Design patient materials to be at the correct literacy level both in terms of reading comprehension and health literacy.

Provider Letter: Provider letters informed patients about the trial, endorsed and signed by their PCP. We identified potential participants by generating lists of patients over 18, using ICD-9/ICD-10 diagnosis codes for chronic pain, depression, and other co-morbidities (e.g. rheumatoid arthritis, fibromyalgia, joint/hip/back pain, and neuropathy) in the electronic medical records (EMR) of study sites. We sent the resulting lists to assigned providers to determineappropriateness of patients for the trial. The study team then sent approved patients the recruitment letter by mail.

Adaptation of Recruitment Methods: Research assistants were trained to interview low literacy, low income racially diverse patients and to answer common questions that participants had during the interventions.They were also encouraged to bring any concerns that arose during the course of the recruitment or data collection process to weekly team meetings in order to ensure that the study team had protocols for any sensitive situations (e.g., suicidality, sub- stance abuse, mania, intimate partner violence), and that all concerns were handled in a uniform manner. As a result of this process, we developed protocols for intimate partnerviolence (IPV) or suicidality and mental health concerns.

PCORI *Community-Campus Partnerships for Health - Final Report.* https://www.pcori.org/sites/default/files/Final-Report-Table.pdf	Excerpt: *Words of Caution: To effectively engage in culturally responsive research, a participant in the Hmong community forum cautioned that the community need to be supported in deconstructing their own biases about research and to construct a positive relationship with CBPR. This ties into the recommendation identified in the Latino/a/x community forum regarding the importance of educating the community about what research is and how it can be relevant and beneficial to the community. Tying into the words of caution regarding partnership building, a participant in the Hmong community forum also posed the following question for researches to consider as part of their self-reflection process: "Are you ready to be changed? Derailed? By what you have learned, engaged in, and uncovered? And then, how are you going to be accountable to the community?" The importance of accountability was addressed across all community forums and is a critical piece of being culturally responsive. (**pg. 3**)*
PCORI Strengthening Diversity in Research Partnerships: Knowledge to Action. Published 2017. https://www.pcori.org/research-results/2017/strengthening-diversity-research-partnerships-knowledge-action	**Community partnerships strategies (researchers)** - Gain knowledge and awareness of the community in general, and community's desire and concerns for specific projects - resist notion of community heterogeneity - Be aware of heterogeneity and work to reach diverse people - Be critically aware - Raise own awareness and consciousness of self, biases, and assumptions - Be part of the community - Act according to community's desires - Listen to community to understand their desired level of engagement, and what respectful engagement means to them - Listen to what the community wants - Be present in the community - Value people and their experiences - Use clear and accessible language - Act with cultural humility

Academy Health Edmunds M, Bezold C, Johnson B, et al. *The Future of Diversity and Inclusion in the Health Services and Policy Research: A Report on the Acadmey Health Workforce Diversity 2025 Roundtable.*; 2015. https://academyhealth.org/sites/default/files/AH_230DiversityReport2015_09.15.pdf *Making Health and Health Care Better for Everybody: A Progress Report (2015-2017)*.; 2018. https://academyhealth.org/sites/default/files/Progress_Report_Feb2018.pdf	Increasing diversity and inclusion on an organizational level can help promote diversity in health services and policy research (HSR). Organizations can do this by: 1. Formally developing a plan and making a public commitment to promoting diversity and inclusion in HSR; 2. Communicating clearly about goals for increasing diversity and inclusion; 3. Publicly report on progress toward meeting diversity goals; 4. Promoting best practices for diversity and inclusion in HSR workforce; 5. Creating a more diverse pipeline for HSR by helping expand training opportunities and recruitment strategies with communities of color
NHC *The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric The Patient Voice in Value: The NHC Patient-Centered Value Model Rubric*.; 2016.	● Caution against relying too heavily upon current peer-reviewed, clinical literature when developing qualitative interview guides ● Attend patient group annual meetings or regional meetings to hear from diverse groups of patients ------------------

http://www.nationalhealthcouncil.org/wp-content/uploads/2019/12/Value-Rubric.pdf NHC Commitment to Ensure Representativeness in all Policy Work - National Health Council. https://nationalhealthcouncil.org/blog/nhc-commitment-to-ensure-representativeness-in-all-policy-work/	● Clinical trial sponsors should engage patient organizations in the design of the trials ● Representativeness in patient engagement is key ● Clinical-trial sponsor efforts to enroll a diverse set of participants should be condition specific ● Reduce the burden of clinical-trial participation ● Consider clinical-trial design for rare-disease products ------------------------ ● Provide clinical-trial sites in geographic locations with higher concentration of racial and ethnic minority patients ● Incorporate diversity considerations when selecting health care providers to assist with clinical-trial recruitment ● Incorporate strategies for public outreach and education ● Facilitate collaboration among industry, patient advocacy groups, medical associations, and other stakeholders to educate participants about clinical-trial participation
MRCT *Achieving Diversity, Inclusion, and Equity in Clinical Research*.; 2020. https://mrctcenter.org/diversity-in-clinical-trials/	Use of plain language Images relating to specific population Multi-format explanations of numeric information Application of clear design principles Translations and additional cultural considerations that contribute to the creation of materials that are designed specifically for a heterogeneous population.
LUNGevity Regnante JM, Richie NA, Fashoyin-Aje L, et al. US Cancer Centers of Excellence Strategies for Increased Inclusion of Racial and Ethnic	● Have deliberate operational standards to support access to healthcare innovations and sustainable and productive inclusion standards in research (i.e., having the right people, processes, and technological capabilities to ensure inclusion of racially, ethnically, and otherwise diverse populations in clinical trials) ● Link to service providers in the community, provide charity care, support needs such as transportation

Minorities in Clinical Trials. *J Oncol Pract*. 2019;15(7):E289-E299. doi:10.1200/jop.18.00638
 	
Regnante JM, Richie N, Fashoyin-Aje L, et al. Operational strategies in US cancer centers of excellence that support the successful accrual of racial and ethnic minorities in clinical trials. *Contemp Clin Trials Commun*. 2020;17:100532. doi:10.1016/j.conctc.2020.100532
	● Minimize patient burden (e.g., by careful selection of trails that better match needs of the patient population; engagement of patients and community representatives in designing trials from the start; effective communication with racial and ethnic minority group communities; providing education about the research process; building trust and engagement in research broadly)
	● Mitigate strategies to decrease recruitment time (i.e., plan ahead and have appropriate communication tools and approaches in place to address factors such as: limited healthcare access; receiving services from providers uninvolved in the research and without resources to recruit for trials; language barriers requiring translated materials; patient-level barriers such as transportation and child care costs)
	● Build a comprehensive understanding of patient barriers and provide support mechanisms to mitigate known obstacles, and proactively communicating these solutions
	● In plain language - ensuring the patients fully understand what to expect during the clinical trial process, as well as the potential benefit/risks associated with the study
	● Research sponsors should carefully evaluate the clinical relevance of exclusion criteria with insights from investigators, patients and care partners
	● Low-resource strategies
	   ○ Launch awareness campaigns
	   ○ Share recruitment materials with patients and care partners that are in plain language or translated into the languages desired by the targeted population
	   ○ Ask patients and community leaders for input on questions to be answered during trials and feasibility of trial implementation
	   ○ Advocate for consolidation of tests required for screening for a trial into a one-day process
	   ○ Engage family members or caregivers in addition to the patient
	   ○ Be cognizant of timing of research offering - trial is best offered by the provider at the time of treatment discussion
	
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	● Themes for strategies for increased participation
	   ○ Commitment and center leadership (e.g., establishing leadership roles dedicated to diversity and minority faculty recruitment; inclusive patient engagement and outreach to increase visibility of trials)
	   ○ Investigator training and mentoring (e.g., hiring research staff that is reflective of the community and organizational commitment to quality and diversity in hiring practices,

	development, and cultural training) ○ Community engagement - must also extend beyond individual research project (e.g., institutional presence in the community; learn about the community, its needs and potential facilitators and barriers to participation) ○ Patient engagement - work closely with providers as their recommendations are the most important factor that influence a patient's willingness to participate (e.g., engage the patient in trial participation decision-making; ensuring the availability of culturally appropriate, ethnicity-specific materials to earn the trust of the patient) ○ Operational practices ● Notable practices ○ Increased engagement of healthcare professionals ○ Presence of formal processes for obtaining patient/caregiver input on research projects ○ Engagement of community groups ○ Increase in allocation of resources to improving health disparities ○ Increased dedication of research staff to racial and ethnic minority group participation ● Other strategies ○ Strategic engagement with providers ○ Community leader engagement ○ Seeking dedicated input into research programs ○ Establishing clear, leadership commitment to quality and hiring practices to ensure the composition of research staff represents the population served
MDIC Selig W. *MDIC Report - Maximizing Patient Input in the Design and Development of Medical Device Clinical Trials (Revised Draft).*; 2020. https://mdic.org/wp-content/uploads/2020/02/Maximizin	● Sponsors should take the time and make the effort to build relationships with patient groups and individual patients that are based on shared commitment to the effort, clear expectations, regular communications and a common language about the project ● Engage and implement patient feedback on the design of clinical studies can help maximize opportunities for successful trial recruitment ● Aim to understand patient barriers and their impact on patients and be willing to consider refinements to their trial plans

g-Patient-Input-Public-Comment-Draft.pdf	- Engage patients to review informed consent materials and approaches for conducting the consent process (e.g. using plain language, translated material, e-consent tools, multimedia platforms) - Ask patients to review draft study documents, including the protocol - this can highlight areas where adjustments can be made to ease burdens on the patients - Patient engagement - Engage early and engage often' - Engage with patient advocacy groups early in the process - Clearly define the patient's role
CTTI *CTTI Recommendations: Advancing the Use of Mobile Technologies for Data Capture & Improved Clinical Trials.*; 2020. https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/mobile-devices-recommendations.pdf#Pg2Ln13	Recommendations Mobile Technology Selection - Know what you want to measure before selecting the mobile technology - Mobile technology selection should be specification-driven and collaborative - CTTI recommends that a technology's regulatory status not be the sole driver in sponsors' decisions about which mobile technology to use - The appropriateness of the selected mobile technology should be justified through verification and validation processes - Feasibility studies conducted before full implementation in a large study reduce risk Data Collection, Analysis, and Interpretation - Biostatisticians and data scientists, as appropriate, should be involved in all decisions regarding protocol design, data collection, analysis, and interpretation. - Collect the minimum data set necessary to address the study endpoints - Include appropriate strategies for monitoring and optimizing data quality - Address data attribution proactively with patient input - Identify acceptable ranges and mitigate variability in endpoint values collected via mobile technologies - Minimize missing data - Plan appropriately for the statistical analysis of data captured using mobile technologies

	- Establish industry-wide standards to drive the successful scaling and more rapid acceptance of clinical trials using mobile technologies for data capture Data Management - Ensure the authenticity, integrity and confidentiality of data over its entire lifecycle - Optimize data accessibility while preventing data access from unauthorized users. - Ensure that access to data meets your needs prior to contracting an electronic service vendor - Apply an end-to-end, risk-based approach to data security - Monitor the quality of data captured by mobile technologies centrally through automated processes - Ensure that site investigators have access to data generated by their participants. Protocol Design and Execution - Data sharing decisions should be driven by safety and trial integrity - Communication and transparency with participants regarding safety monitoring is critical - Define and test processes for the implementation, operation, and maintenance of mobile technologies in the field prior to launching the trial Page 3 of 3 - Have a plan in place for mobile technology failure - The considerations that inform adaptive designs in a trial using mobile technologies are the same as for traditional studies. FDA Submission and Inspection - Ensure that trials conducted using mobile technologies for data capture may be readily reconstructed (i.e., end-to-end traceability) - Source data should be the primary data resource provided to FDA during inspection - Be prepared to provide supporting material for mobile technology-based claims to FDA as part of any marketing application
MRCT *Return of Results Guidance Document*.; 2015. https://mrctcenter.org/wp-	Create clear, explicit and understandable research results summaries Implement a process to disseminate them in a manner that: • Adheres to health literacy principles • Includes information for all populations included in the trial • Offer participant support and address questions when study results are delivered

content/uploads/2015/11/2015-03-19_mrct_ror_guidance_1.0.pdf#:~:text=The Harvard Multi-Regional Clinical Trials Center (MRCT Center),from industry, academia, patient advocacy and non-profit centers.	Ensure that the process for returning results reflects cultural literacy principles, including: • Translation of research results summaries into language used by all trial locations and participants • Review of research summaries by a medical professional with knowledge of the culture to ensure that descriptions reflect cultural norms • Ensure that delivery of results follows cultural norms Health literacy principles: • Organization of information should make key messages clear (given first) and with an explanation of what the information means to the individual • Incorporate design elements to improve readability, including bullets, white space, limited use of complex tables, and contrast between font and background color • Information should be written in simple prose that avoids complex sentences, avoids jargon or technical language, explains complex concepts, and avoids ambiguous phrases • Test the readability of text with a tool (such as the Flesch-Kincaid Grade Level Test) to assess grade reading level

Appendix 3 - Survey

IVI Patient Questionnaire - Improving Patient Representativeness in Research and Practice

The purpose of this questionnaire is to secure your feedback on strategies IVI should implement to improve representativeness of patient participants in our research.

1. Please share with us your name, organization, and email address.

2. Please rank the key challenges (from most important to least) that should be addressed so that patient-centered, health-related research reflects representative populations consistent with the epidemiology of the disease in the real-world context?

- o   Defining characteristics of a representative patient sample
- o   Partnering with patient and patient advocacy organizations to define the representative patient populations, particularly in underrepresented patient subgroups
- o   Partnering with organizations that have expertise and reach for recruitment of underrepresented patient subgroups
- o   Addressing technology barriers (e.g., access, use)
- o   Lack of trust in scientific enterprise and research programs in certain patient subgroups
- o   Others (please provide a brief description in Q3, if any)

3.   If any, please describe other issues that were not included in the options for Question 2.

4.   Please rank (from highest importance to lowest) which strategies IVI should adopt to ensure representative patient samples are recruited in patient-centered research initiatives.

- o   Partnership with patient organizations in the medical condition of interest
- o   Partnership with community-based organizations and advocacy organizations representing minority and underserved populations
- o   Ensure health literacy at appropriate level for all materials (recruitment and research)
- o   Work with organizations (focus group organizers, academic centers) with expertise in engagement with underrepresented populations (e.g. stipulate requirement in such agreements for research partners)
- o   Simplify the enrollment process and requirements when signing up to participate in a research study
- o   Simplify the data collection process in research studies

5. **If any, please add additional suggested strategies and approaches not listed in Question 4 here.**

6. **As IVI plans current and future research projects, what would be helpful to you and your organization to support our common goal to improve the inclusion of patients from more diverse backgrounds in value assessment and patient-centered research?**

7. **May we contact you with any additional questions?**

Appendix 4 - Survey Results

1. **Respondents were from the following organizations:**

   - The Assistance Fund
   - National Minority Quality Forum
   - National MS Society
   - Partnership to Improve Patient Care
   - Institute for Patient Access
   - Depression and Bipolar Support Alliance
   - National Patient Advocate Foundation
   - LUNGevity Foundation
   - National Health Council
   - EveryLife Foundation
   - Mental Health America

2. **Ranking of the challenges (from most important to least):**

   1) Partnering with patient and patient advocacy organizations to define the representative patient populations, particularly in underrepresented patient subgroups
   2) Defining characteristics of a representative patient sample
   3) Partnering with organizations that have expertise and reach for recruitment of underrepresented patient subgroups
   4) Lack of trust in scientific enterprise and research programs in certain patient subgroups
   5) Addressing technology barriers (e.g., access, use)
   6) Others

3. **Other considerations included (open-text input):**

There is a legitimate concern that there is insufficient data and evidence to support value assessment. There is also a concern regarding the degree to which value assessment puts different patient or population cohorts at risk for poor health outcomes by creating barriers to access to therapies that may be effective. Further, these constraints on access further compromise the availability of data and evidence to inform the development of research questions that would improve the ability of the system to support the biology and health of populations that are historically under-represented in research, and historically and continually underserved by a health services financing and delivery system that uses econometric rationales and assessments of their financial risk to justify rationing or marginalization of these populations. Would that the same effort and commitment were made to finding ways to reverse this culture of inequity.
What constitutes innovation for medical treatments

A successful strategy that I use with my clients when possible is to conduct a claims database search to find all treating MDs and # of patients as indicated by the ICD10 code/custom algorithm for said condition. This provides a rich source of data including all episodes of careand drugs taken (and tests if added to the search). Can chat with you about this if you'd like
Access is not just a technology issue. There are other issues related to access: restrictive eligibility criteria (such as comorbidities that are more common in underrepresented patient subgroups) and logistical issues such as travel and accommodation.
Culture - acceptance of stakeholders that patients need o be engaged.
Others include analyzing the description of subgroups to come up with something more workable

4. **Ranking of the strategies (from highest importance to lowest)**

   1) Partnership with patient organizations in the medical condition of interest
   2) Partnership with community-based organizations and advocacy organizations representing minority and underserved populations
   3) Work with organizations (focus group organizers, academic centers) with expertise in engagement with underrepresented populations (e.g. stipulate requirement in such agreements for research partners)
   4) Ensure health literacy at appropriate level for all materials (recruitment and research)
   5) Simplify the enrollment process and requirements when signing up to participate in a research study
   6) Simplify the data collection process in research studies

5. **Other strategies recommended (open-text input):**

Ensure that language when discussing the research and the goals of the research is culturally competent, and also explains why this is important to individual patients and caregivers and why they should participate.
The size of the representative samples must be statistically significant, and the methodologies employed must not perpetuate statistical and algorithmic biases jor enable inequity by default.
Work with patients from underrepresented communities who can serve as ambassadors for clinical research
Influence the thinking / culture of thought leaders in researcher sector (academia/professional associations) to help influence culture.

6. Suggested action steps for IVI (open-text input)

It would be helpful to learn about methods successfully used in the past to recruit and engage underrepresented groups in the past. It would also be helpful to better understand how IVI has recruited and enrolled patients in their research in the past. What is the forum? What is the language used? How is the language changed based on the patient population or targeted group?
In addition to the answer to question 3, please revisit your organizational thinking and resulting communications which perpetuate stereotyping regarding the education and/or intelligence of the historically disenfranchised. It is almost intolerably patronizing and insulting. Please also give some front-end consideration to those organizations with whom you contract. I recommend that you also give some consideration to what you are really trying to accomplish, why and for whose benefit.
It would be great to see some tangible examples of assessments that are conducted using a representative patient population. It would be nice to have "right way" to point to here.
We would be very interested in partnering with you on future research efforts.
We are doing similar work in defining a clinical outcome assessment for clinical trials and are following a similar path. We just concluded a similar survey to all of the stakeholders (peers, family members, clinicians/researchers and pharmaceutical staff. We have identified our largest challenge is identifying the target population. We are evaluating a strategy that allows us to narrow in on a concept of interest by exploring identifying a target population with the most reach, and a concept that has the highest potential to bleed into other target populations with similar clinical benefit. Not an easy task as I am sure you know :)
We would love to learn about what other patient groups are doing (so as to not recreate the wheel) and also have a platform to share the work we are doing - in this area.
We have a Diversity Inclusion Fellow on our team whose participation in this effort would be beneficial; creation of a working group/sub group of the PAC might be an idea?
Sharing back with patient communities what is learned from study participants, even if it's anecdotal data.

Appendix 5 - Research Projects Summary

Patient Preference Study

The purpose of the patient preference study is to test a novel approach to elicit patient-prioritized value elements in evaluating treatment options for MDD and estimate the preference weights associated with these value elements using a discrete choice experiment design. The study is developed based on a set of patient-centered value elements, developed by Dr. Susan dosReis and colleagues at the University of Maryland[e].

The study is being conducted in two phases: a phase 1 value element elicitation and a phase 2 value element prioritization. In the recently completed phase 1 work, the goal was to identify a diversity sample of individuals (N=20) living with MDD in order to elicit the attributes of treatment that are most important to them when selecting among treatments. The inclusion/exclusion criteria were specified as follows:

- Inclusion Criteria
    - Age 18 or older
    - Diagnosed with MDD
    - Speak/Read English
- Exclusion Criteria
    - Bipolar or psychotic depression
    - Living in a residential or institutional setting
    - Post-partum depression

Recruitment occurred over two months to identify and enroll 20 participants in phase 1. The outreach strategy engaged champions at each organization to engage potential participants along with a targeted approach to ensure inclusion of patient diversity.

The phase 1 patient preference study revealed several important considerations when aiming to build diversity and representativeness in research. First, we must be flexible in how we connect and engage participants. Acknowledging that even though someone has an email account this does not mean that they are comfortable conducting an interview via a web-based platform. Adapting to different methods of engagement in research will aid in reaching a more diverse group. Second, national advocacy groups may not sufficiently represent the spectrum of individuals living with the targeted medical condition, and so we must consider alternate and complementary modes of recruitment. We learned that recruitment through local community organizations or clinics can lead to inclusion of subgroups less often represented in research. Third, the timeline for recruiting a diverse patient sample will take considerable time. There must be sufficient time to build a relationship and trust with the community and organization as well as with the individuals one seeks to recruit. This often takes much longer than many study timelines can accommodate. That said, inclusion of diverse patient groups must be secured even before the study starts.

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[e] dosReis S, Butler B, Caicedo J, et al. Stakeholder-Engaged Derivation of Patient-Informed Value Elements. *Patient*. 2020;13(5):611-621. doi:10.1007/s40271-020-00433-8

Appendix 6 - Action Plan

Patient Preferences for Major Depressive Disorder:

Action Plan to Ensure Patient Representativeness in Quantitative Phase

In Phase One (*completed)*, researchers interviewed 20 individuals to learn about their experiences living with major depressive disorder (e.g., treatment history, impact on life) and identify key value elements from the PAVE value element set considered in evaluating potential treatment options for depression.

In Phase Two, a discrete choice experiment will be developed and administered to a targeted patient sample of at least 300 participants. With a larger sample size, researchers are seeking strategies to improve the representativeness of patients participating as survey respondents.

Priority Areas/Themes	Next Steps	Target timeline *(tentative)*
Review Stakeholder Recommendations	● Use findings from this paper (**Table 1)** and engagement with the MDD Advisory Group to identify additional recommendations to refine criteria of representativeness and ensure the recruitment of underrepresented subgroups	Ongoing, quarterly basis
Partnership Development and Stakeholder Engagement	● Follow-up on outreach to Federally Qualified Health Centers, Medicaid organizations, National Alliance for Hispanic Health, Asian Health Foundation, and others to build relationships ● Formal outreach to partner organizations (e.g., National Minority Quality Forum) for insight and connections ● Conduct additional outreach to local community organizations and partners	Q1, 2021

Define Representativeness	● Use FDA guidance and Advisory Group recommendations to establish explicit criteria to measure representativeness for the patient preference study, including:
	  ○ Key patient characteristics for subgroups
	  ○ Minimum sample sizes
		Q1, 2021

Technology and Accessibility	● Review draft survey instruments to ensure documents are written at a 5th grade reading level ● Ensure materials are accessible across multiple survey formats (including online, paper-based, and phone-based)	Q1, 2021
Cross-Validation	● Conduct internal review of during the fielding period to ensure that recruited patient patients satisfy specific criteria for representativeness ● Recalibrate recruitment strategies as necessary	Biweekly during the recruitment period (approximately Q2, 2021)
Activation and Recognition	● Share study results with participants and communities ● Ensure payment of honoraria ● Explore co-authorship with patients	Q3, 2021

Abbreviations: FDA, Food and Drug Administration; MDD, major depressive disorder.

Appendix 7 - Glossary

CTTI	Clinical Trials and Transformation Initiative
FDA	Food Drug Administration
I/E	Inclusion and exclusion
IVI	Innovation and Value Initiative
IVI-MDD	IVI Major Depressive Disorder value model
MDD	Major Depressive Disorder
MDIC	Medical Device Innovation Consortium
MRCT	Multi-Regional Clinical Trials Center of Harvard
NHC	National Health Council
NIH	National Institutes of Health
NMQF	National Minority Quality Forum
PCORI	Patient-Centered Outcomes Research Institute
POC	Proof of Concept
SES	Socio-economic status
VA	Value Assessment