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August 2022
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Clinical trial participant diversity has been a key topic in the pharmaceutical industry for decades. The subject first entered the literature following the National Institutes of Health’s (NIH’s) Revitalization Act of 1993 and was further propelled into the spotlight by the African American Heart Failure Trial in 2004.\(^1\) Research conducted following these landmark documents has shown that racial and ethnic diversity in clinical trial participant populations can help identify variations in treatment outcome, thereby increasing the accuracy and safety of results across populations. Despite mounting evidence of the importance of participant diversity in the drug development process and an increasing number of initiatives to promote it, low representation of Black, Indigenous, and People of Color (BIPOC) among the global clinical trial participant population persists.\(^2,3\)

As the issues surrounding participant diversity become better understood globally, driven in part by new guidance from the U.S. Food and Drug Administration (FDA)\(^4\) and publication requirements from peer-reviewed journals\(^5\), more eyes are turning to the next frontier in drug development diversity, equity, and inclusion (DEI): the clinical research workforce.\(^6–8\) Studies regarding the effect of diverse healthcare professional (HCP) staff in improving outcomes for BIPOC patient populations indicate that addressing established racial and ethnic disparities in the global clinical research workforce may be an important element in promoting participant diversity.\(^9,10\)
This study is an expansion and update of a study conducted by the Tufts Center for the Study of Drug Development (CSDD) at Tufts University in 2008 among 1,376 U.S.-based principal investigators, which found that significant racial and ethnic disparities exist among clinical investigators despite a comparable interest in clinical research involvement. The authors also proposed that physician race or ethnicity may influence the race or ethnicity of clinical trial volunteers—a conclusion supported by other recently published manuscripts. Although the 2008 study was limited to U.S. respondents, due to the increasingly global nature of the clinical research enterprise, as well as evidence of the need for both environmental and racial and ethnic diversity in the global clinical trial participant population, the research team felt that it was important to consider global perspectives in this follow-up initiative.

This updated study includes responses from nurses and other allied health professionals in addition to those of physicians. Individuals from this demographic, like physicians, interact with patients on a regular basis and are crucial to patient care in both clinical care and clinical trial settings. Additionally, non-physician allied health professionals have been shown to experience barriers in terms of racial and ethnic disparities, and their perspective is critical to promoting diversity among entire clinical trial teams.

Understanding how HCPs are motivated to get involved in clinical research, as well as perceived barriers to involvement, is an important step to providing opportunities for HCPs from all backgrounds to contribute their expertise to the clinical research workforce.

**Study Methodology**

Survey design and analysis planning were conducted and reviewed by a large working group of 24 organizations between December 2020 and March 2021. Following review and approval by the European General Data Protection Regulation (GDPR) committee and ethical review board at Tufts CSDD, the survey was distributed to a global audience between April and July 2021. Survey distribution was conducted through collaborations with a number of professional associations in addition to purchased lists.

Racial and ethnic identities were defined within the survey instrument and are provided in Table 1 as seen by respondents. These categories are consistent with those reported in a recent COVID-
19 study\cite{16} and informed by classifications recommended or used by United Nations and the U.S. Census Bureau, among others.\cite{17–21}

<table>
<thead>
<tr>
<th>Table 1: Race and Ethnicity Definitions as Seen by Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race and Ethnicity</strong></td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Black (or of African Descent)</td>
</tr>
<tr>
<td>LatinX (Spanish Origin, Hispanic, or Latino)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

*Racial and ethnic identities collapsed into the “Other” category were defined separately within the survey instrument.

Raw data were stored in Microsoft Excel and data cleaning and analysis were conducted in SAS version 9.4. Analyses performed included descriptive statistics, frequency comparisons, coefficients of variation (defined as the ratio of standard deviation to the mean), comparisons of mean overall and subgroup response values, significance testing, and correlations. Subgroups were created based on white or non-white racial and ethnic identities as well as highest degree earned by respondent, with MD/PhD compared as a subgroup to overall respondents. Analyses were conducted on nursing subgroups as well; however, certain questions were only shown to half of respondents. In these areas, the white/non-white subgroup sample of nursing respondents was insufficient for meaningful analyses.
Results

Respondents to the survey by region reflected the proportion of invitations sent to North American vs. Outside-North American HCPs. In addition to 34,552* purchased list e-mail addresses receiving the invitation, 10 professional associations distributed the survey to their members via e-mail or social media pages. Of these, 611 respondents consented to participate in the online survey, with 54% of respondents from North America (U.S. or Canada) and 46% from outside North America. Respondent characteristics are summarized in Table 2.

Table 2: Respondent Characteristics

<table>
<thead>
<tr>
<th>Highest Degree Earned</th>
<th>N</th>
<th>Percent of Total Overall</th>
<th>Percent of Total North America</th>
<th>Percent of Total Outside-North America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical or doctoral degree</td>
<td>295</td>
<td>62%</td>
<td>53%</td>
<td>72%</td>
</tr>
<tr>
<td>Nursing degree</td>
<td>115</td>
<td>24%</td>
<td>32%</td>
<td>16%</td>
</tr>
<tr>
<td>Other</td>
<td>66</td>
<td>14%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>207</td>
<td>56%</td>
<td>61%</td>
<td>50%</td>
</tr>
<tr>
<td>Male</td>
<td>162</td>
<td>44%</td>
<td>39%</td>
<td>50%</td>
</tr>
<tr>
<td>Race &amp; Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>253</td>
<td>68%</td>
<td>71%</td>
<td>64%</td>
</tr>
<tr>
<td>LatinX</td>
<td>16</td>
<td>4%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Asian</td>
<td>56</td>
<td>15%</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>Black</td>
<td>12</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Other (including mixed race)</td>
<td>37</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*The number of additional invitations sent by professional associations are not available, therefore, response rate can only be estimated (~2%).
This survey was open to both HCPs with and without clinical research experience, and the data show a fair balance between the two backgrounds, with 56% of respondents reporting having been on study staff (i.e., part of a clinical research team) in the past (see Table 3).

**Table 3: Clinical Research Experience by Subgroup**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total (N = 366)</th>
<th>Overall Non-White (44.2%)</th>
<th>Overall White (45.4%)</th>
<th>MD/PhD Non-White (45.1%)</th>
<th>MD/PhD White (35%)</th>
<th>Nurse Non-White (55%)</th>
<th>Nurse White (68.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Clinical Research Experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With Clinical Research Experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, white and non-white respondents reported similar levels of clinical research experience. Given the options of “extremely interested,” “somewhat interested,” and “not at all interested,” non-white respondents—both overall and within the MD/PhD subgroup—selected “extremely interested” in higher proportions. In North America, non-white MD/PhDs were significantly more likely (α = 0.001) to be “extremely interested” in clinical research work (see Table 4).

**Table 4: Percent of Respondents Without Clinical Research Experience Reporting “Extreme Interest” in Clinical Research by Subgroup**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total (N = 133)</th>
<th>Overall Non-White (27.9%)</th>
<th>Overall White (35.7%)</th>
<th>MD/PhD Non-White (24.7%)</th>
<th>MD/PhD White (50.0%)</th>
<th>Nurse Non-White (29.7%)</th>
<th>Nurse White (22.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

α = p-value < 0.05 in chi-square testing between white and non-white respondents in given subgroup.
Respondents with No Clinical Research Experience

Respondents with no work experience in clinical research were asked to rate a variety of barriers to clinical research involvement as “very important,” “somewhat important,” or “not at all important.” The percentages of total respondents in the given subgroup who chose “very important” for each barrier are reported in Table 5.

Table 5: Percent of Respondents with No Clinical Research Experience Reporting “Very Important” Barriers to Involvement by Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Total N = 197</th>
<th>Overall Non-White</th>
<th>Overall White</th>
<th>MD/PhD Non-White</th>
<th>MD/PhD White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time constraints</td>
<td>48.6%</td>
<td>47.8%</td>
<td>48.9%</td>
<td>54.2%</td>
<td>50%</td>
</tr>
<tr>
<td>Lack of access to clinical trials</td>
<td>39.7%</td>
<td>55.6% α</td>
<td>30.9%</td>
<td>54.2%</td>
<td>42.1%</td>
</tr>
<tr>
<td>Personnel needs</td>
<td>32.6%</td>
<td>37.8%</td>
<td>29.7%</td>
<td>47.8%</td>
<td>32.4%</td>
</tr>
<tr>
<td>Infrastructural needs</td>
<td>29.5%</td>
<td>37.8% α</td>
<td>26.1%</td>
<td>52.2%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Lack of patient interest</td>
<td>21.2%</td>
<td>30.2% α</td>
<td>15.2%</td>
<td>23.8% α</td>
<td>8.1%</td>
</tr>
<tr>
<td>Complexity of the study</td>
<td>18%</td>
<td>18.2% α</td>
<td>16.1%</td>
<td>22.7%</td>
<td>16.2%</td>
</tr>
<tr>
<td>Lack of potential personal benefit</td>
<td>16.9%</td>
<td>31.8% α</td>
<td>10%</td>
<td>31.8% α</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

α = p-value < 0.05 in chi-square testing between white and non-white respondents in given subgroup.

A higher proportion of non-white MD/PhDs indicated that a variety of barriers were “very important” to their decision not to participate than did white MD/PhDs. Chi-square testing showed significant differences in white and non-white MD/PhDs in lack of patient interest (α = 0.04) and lack of potential personal benefit (α = 0.008). Overall, non-white respondents also reported most barriers as “very important” to their decision not to become involved in clinical research in higher proportion than white respondents, except for “time constraints,” which was the highest reported barrier overall. Statistically significant differences were seen between white and non-white respondents in “lack of access to clinical trials” (α = 0.01), “infrastructural needs” (α = 0.009), “lack of patient interest” (α = 0.006), “study complexity” (α = 0.0008), and “lack of potential personal benefit” (α = 0.004).
The North American subgroup saw similar results among overall respondents, with non-white North American respondents also reporting “lack of access to clinical trials” as a “very important” barrier to clinical research work in significantly higher proportion than white respondents from this region ($\alpha = 0.013$).

These data indicate that higher interest shown by non-white respondents, and particularly non-white doctors (Table 4) is accompanied by higher barriers to entry (Table 5).

When asked which trial sponsor would make the respondent “more likely,” “less likely,” or would not change their attitude (“neutral”) toward becoming a clinical researcher, government and academic institutions were chosen as “more likely” at the highest rate, with industry selected at the lowest rate. The percentage of total respondents in the given subgroup who chose “more likely” for each type of trial sponsor are reported in Table 6.

**Table 6: Percent of Respondents with No Clinical Research Experience Reporting Which Institutions Funding Clinical Trials Would Make Them “More Likely” to Become a Clinical Researcher**

<table>
<thead>
<tr>
<th></th>
<th>Total N = 101</th>
<th>Overall Non-White</th>
<th>Overall White</th>
<th>MD/PhD Non-White</th>
<th>MD/PhD White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>72.3%</td>
<td>58.1% $\alpha$</td>
<td>78.6%</td>
<td>66.7%</td>
<td>81.5%</td>
</tr>
<tr>
<td>Academic</td>
<td>67.3%</td>
<td>58.1%</td>
<td>71.6%</td>
<td>80%</td>
<td>84%</td>
</tr>
<tr>
<td>Non-profit</td>
<td>51%</td>
<td>53.3%</td>
<td>50%</td>
<td>57.1%</td>
<td>46.2%</td>
</tr>
<tr>
<td>Industry</td>
<td>22.4%</td>
<td>30%</td>
<td>19.1%</td>
<td>28.6%</td>
<td>26.9%</td>
</tr>
</tbody>
</table>

$\alpha = p$-value $< 0.05$ in chi-square testing between white and non-white respondents in given subgroup.

**Respondents with Clinical Research Experience**

The research team also surveyed those HCPs familiar with clinical research to deduce how they became involved and analyzed the differences in experience between subgroups. As seen in Table 7, the most reported catalysts to involvement in clinical research included applying for a job or grant and being asked by a mentor or peer to join the study. “Other” was selected by 17%
of respondents with clinical research experience, which warrants further investigation into other catalysts to clinical research involvement.

Table 7: Types of First Involvement (Overall) for Respondents with Clinical Research Experience Responding to Survey Question

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 197)</th>
<th>Overall Non-White</th>
<th>Overall White</th>
<th>MD/PhD Non-White</th>
<th>MD/PhD White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentor (included in Mentor or Peer)</td>
<td>23.4%</td>
<td>16.7%</td>
<td>26.8%</td>
<td>18.8%</td>
<td>29.6%</td>
</tr>
<tr>
<td>Mentor or Peer</td>
<td>38.6%</td>
<td>30%</td>
<td>41.7%</td>
<td>33.3%</td>
<td>44.9%</td>
</tr>
<tr>
<td>Applied for Job/Grant</td>
<td>24.4%</td>
<td>28.3%</td>
<td>23.6%</td>
<td>27.1%</td>
<td>20.4%</td>
</tr>
<tr>
<td>Proactive</td>
<td>8.1%</td>
<td>13.3%</td>
<td>6.3%</td>
<td>10.4%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Recruited/Referred*</td>
<td>11.7%</td>
<td>11.7%</td>
<td>11%</td>
<td>10.4%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Other</td>
<td>17.3%</td>
<td>16.7%</td>
<td>17.3%</td>
<td>18.8%</td>
<td>13.3%</td>
</tr>
</tbody>
</table>

*Includes recruitment by industry sponsor, academic institution, contract research organization, or site management organization, as well as referral via institutional office or site network.

This survey found that, out of those respondents with direct clinical trial experience, both overall white respondents and white MD/PhDs were more likely to have had a mentor or peer help them get involved in clinical research. Of those respondents with mentors, 93% agreed that mentors made them more comfortable with the clinical trial process, 91% agreed that mentors made them more comfortable with referring and screening patients for clinical trials, and 87% agreed that mentors helped them find greater access to clinical trials. Additionally, 100% of non-white mentored respondents agreed that mentors made them more likely to continue to get involved in clinical trials after their first trial, compared to 88% of white respondents.

In North America, non-white respondents were similarly less likely to have had a mentor get them involved in clinical research (see Table 8). North American results also revealed that non-white respondents were more likely to have acted proactively to get involved in clinical trials (contacting a pharma/biotech company, requesting a peer to include respondent in the study).
Although this was true for the overall dataset as well, the gap was larger among North American respondents. “Proactive” means of involvement in clinical research require expressed interest in the field and more effort from the individual, further highlighting the gap in access and opportunities readily available to this subgroup (Table 5).

**Table 8: Types of First Involvement (North America) for Respondents with Clinical Research Experience**

<table>
<thead>
<tr>
<th>Mentor (included in mentor or peer)</th>
<th>North America Total N = 102</th>
<th>North America Non-White</th>
<th>North America White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentor or Peer</td>
<td>16.8%</td>
<td>8.6%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Applied for job or grant</td>
<td>34.3%</td>
<td>25.7%</td>
<td>38.8%</td>
</tr>
<tr>
<td>Proactive</td>
<td>22.5%</td>
<td>22.9%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Recruited/Referred</td>
<td>10.8%</td>
<td>11.4%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Other</td>
<td>21.6%</td>
<td>20%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

These findings imply that white candidates have more access to mentorship opportunities both globally and within the North American region.

**Conclusions**

Tufts CSDD’s 2008 publication exposed the disparities that exist in the race and ethnicity of principal investigators in the U.S. by identifying a trend of non-white investigators conducting and initiating fewer trials annually despite similar levels of interest.\[11\] This study, 14 years later, shows that although the incidence of non-white MD/PhD respondents in clinical research is still lower than white MD/PhDs, “extreme interest” in participation as a clinical researcher is higher among non-white MD/PhD respondents, particularly in North America (Table 4).
By analyzing the root of these disparities at a global level and across allied health professions, the research team not only identified similar disparities in incidence of BIPOC healthcare professional involvement to the 2008 study, but also found that BIPOC healthcare professionals perceive higher barriers to clinical research involvement in access, infrastructural needs, lack of patient interest, complexity of the study, and lack of potential personal benefit. This report of higher barriers—particularly in access—among both global and North American non-white respondents was consistent with a lower proportion of this subgroup reporting having a mentor or peer ask them to join their first trial compared to white respondents.

This element is important to address, as mentorship has been found to be a more effective tool in diverse recruitment than other DEI initiatives such as mandatory diversity training, job tests, and grievance systems. This is supported by perspectives from respondents to this survey, who reported overwhelmingly that having a mentor had a positive impact on their clinical research experience, as well as increased their likelihood to refer patients and to continue working in clinical research after their first trial.

Emphasizing these barriers to access for BIPOC-allied health professionals and taking steps to mitigate their effect, such as instituting mentorship and educational programs among allied health students from diverse backgrounds, could contribute to decreasing disparities in the clinical research workforce. Although these programs do exist within the U.S., wider adoption of them—both outside the U.S. and across a larger proportion of U.S. sites— is an essential element in promoting diversity in the clinical research workforce, as is the availability of early intervention programs to promote clinical research education.

Existing programs are led by various organization types, including universities, government agencies, and professional associations. Some industry sponsors have mentorship programs focused on postdoctoral candidates, however these are not specifically dedicated to diversity and are limited in their target audience. Implementing more diversity-targeted programs within sponsor companies, as well as encouraging their development among sites and potentially sponsoring associated costs, are promising ways that industry can directly contribute to enabling more HCPs from a broader range of backgrounds to enter the clinical research workforce.
Study Limitations

The methodology in this study had several limitations. The original distribution plan was to reach out to professional organizations for collaboration, which was the strategy for Tufts CSDD’s comparable 2008 study. However, heavy burdens due to surges in COVID-19 infections and deaths during the distribution of this survey may have affected both the willingness of professional associations to distribute the survey as well as the willingness—or bandwidth—of HCPs to contribute time to fill out the survey. Additionally, the increased number of surveys from other sources targeting HCPs during this time exacerbated survey fatigue.\(^{27}\) Survey completion rates could have also been affected by these elements, as well as the length of the survey instrument. Bias may have been introduced with these recruitment methods, as the predominant demographics of members of professional associations collaborating in study distribution may have been more heavily represented than those of associations that did not respond to requests to collaborate.

Other limitations included the low awareness of DEI research from organizations outside the U.S. Some organizations, in addition to low awareness of the topic, did not perceive DEI as applicable to their region, further complicating this method of recruitment. Lack of familiarity and consideration for ethnic and racial diversity initiatives in clinical research outside the U.S. is a separate topic that requires further research and advocacy, as drug development is a global process that impacts patients worldwide. Due to these limitations, purchased e-mail lists were used.

Finally, a low number of non-white respondents made it difficult to avoid a white/non-white dichotomy. In a global study featuring a variety of geographic areas, each with varying racial and ethnic majorities, this subgroup approach may not fully account for the variations in experience among non-white respondents. Tufts CSDD is interested in following up on this study to expand the dataset and allow deeper subgroup analyses, particularly during a time when the COVID-19 pandemic does not restrict availability and enhance survey fatigue among HCPs.
Despite these limitations, these results can provide important insight into the barriers and experiences of the global clinical research workforce and introduce the subject of workforce diversity on a global scale.

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Government agencies, pharmaceutical companies, and patient advocacy groups increasingly involve patient and caregiver feedback at various checkpoints throughout the clinical trial process to develop research protocols with greater benefit and less burden to participants and their families.\(^1\) Involving patients and their support network in the protocol development process can take several forms, including patient advisory boards, surveys, and interviews. However, best practices and standardized processes for developing patient-centric trials have not yet been widely established.\(^1,2\)

In recent years, several organizations and initiatives have emerged with the intention of advancing patient engagement in drug development and/or research, including the Patient-Centered Outcomes Research Institute (PCORI),\(^3\) the Clinical Trials Transformation Initiative (CTTI),\(^4\) the U.S. Food and Drug Administration’s (FDA’s) Patient Engagement Collaborative with CTTI,\(^5\) the FDA’s Patient-Focused Drug Development (PFDD) program,\(^6\) and the not-for-profit Patient Focused Medicines Development (PFMD)\(^7\) organization. All seek to increase patient involvement across the lifecycle of medical product development, including through the phases of research, and to improve trials in terms of quality, efficiency, safety, and ethical conduct, as well as in engaging all stakeholders as equal partners. The current trajectory toward greater patient involvement represents an opportunity to develop and conduct more effective research via outcomes such as realistic inclusion and exclusion criteria, lower participant burden, and patient-relevant endpoints.\(^8\)
To create meaningful impacts, patient engagement strategies need to be put into place that result in substantive feedback and turn communication into actionable change.[9] Numerous types of patient engagement approaches exist, including community advisory boards, patient advisory boards, individual interviews, and surveys (see Table 1). Tools for implementing these models have been provided by the FDA, PFMD, the PARADIGM (Patients Active in Research And Dialogues for an Improved Generation of Medicines){10} initiative in Europe, and other organizations committed to furthering patient engagement across the lifecycle of medical product development.{11-14} For example, PFMD has published a series of toolkits, resources, and “how-to” guides for quality and effective patient engagement.{12,13}

**Table 1: Exemplar Models of Patient Engagement with Industry-Sponsored Research**

<table>
<thead>
<tr>
<th>Member Profile</th>
<th>Community Advisory Board</th>
<th>Traditional Patient Advisory Board</th>
<th>Patient Journey Workshops</th>
<th>Individual Interviews</th>
<th>Surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Member Profile</strong></td>
<td>n=8-10</td>
<td>n=8-10</td>
<td>n=8-10</td>
<td>n=4-15</td>
<td>n=30-100+</td>
</tr>
<tr>
<td>Variety of conditions within a therapeutic area (e.g., immunology)</td>
<td>Condition-specific</td>
<td>Condition-specific</td>
<td>Condition-specific</td>
<td>Condition-specific</td>
<td>Condition-specific</td>
</tr>
<tr>
<td>Experienced patients with advocacy experience and strong community ties</td>
<td>Both naive and experienced patients may mirror desired population for a proposed trial</td>
<td>Both naive and experienced patients may mirror desired population for a proposed trial</td>
<td>Both naive and experienced patients may mirror desired population for a proposed trial</td>
<td>Responses may be solicited among those who have and/or haven’t participated in a clinical trial</td>
<td>Global or region/country-specific</td>
</tr>
<tr>
<td>Global</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Engagement Frequency | | |
|----------------------|-------------------|
| Engaged routinely in a series of meetings and activities | Typically a one-time meeting |
| Ongoing resource | Typically a one-time meeting |
| | A one-time interview of 60-90 minutes |
| | One-time, online, 10-to-15-minute questionnaire |

<table>
<thead>
<tr>
<th>Member Tasks, Activities</th>
<th>Community Advisory Board</th>
<th>Traditional Patient Advisory Board</th>
<th>Patient Journey Workshops</th>
<th>Individual Interviews</th>
<th>Surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advise on universal protocol elements across treatment area portfolio</td>
<td>Share specific experiences from being diagnosed with and living with a specific condition</td>
<td>Provide thoughts on condition-specific treatments and specific protocol feedback</td>
<td>Use hands-on activities (e.g., collages, journey mapping) to explore patient experiences being diagnosed with and living with a condition</td>
<td>Share individual patient experiences in a 1-on-1 interview setting</td>
<td>Answer specific, focused questions about certain aspects of the patient experience</td>
</tr>
<tr>
<td>Provide insights on general patient-facing material</td>
<td>Brainstorm ideal participation experiences for clinical trials</td>
<td></td>
<td></td>
<td></td>
<td>Indicate receptivity to clinical trial participation and protocol design elements</td>
</tr>
<tr>
<td>Contribute input on new patient-centric initiatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Help develop patient engagement best</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
practices and principles

Key Outcomes

- Best practices for patient engagement across the therapeutic area
- Strong, established relationships with patients and extended patient communities
- New, patient-centric initiatives across the larger pharmaceutical organization

- Deeper understanding of the patient experience living with a particular condition and how that population perceives clinical trials
- Direct patient feedback on unique elements of a proposed clinical trial
- Deeper understanding of individual patient experiences
- Direct patient feedback on unique elements of a proposed clinical trial
- Visual representation of the patient experience and ideal clinical trial journey
- Deeper understanding of individual patient experiences
- Direct patient feedback on unique elements of a proposed clinical trial
- Surface-level understanding from a larger number of patients of the patient experience
- Feedback on perceptions, preferences, and receptivity from a larger group of respondents

Among the wide range of available tools and engagement strategies, one approach Janssen utilized was to implement a long-term, recurring global community advisory board. While one-time market research activities such as interviews and surveys can and do yield actionable insights, single touchpoint projects can also limit the amount and type of data obtained and usually solicit patient feedback only on a single protocol. In contrast, the community advisory board model’s long-term focus provides the opportunity to establish a long-term partnership with patients based on trust, knowledge-building, and the reciprocity of true dialogue.

Through the Patient Voice in clinical trials program, Janssen routinely obtains patient and caregiver feedback into clinical trial design across all therapeutic areas. Because many learnings apply to more than one clinical trial, and because of a desire to build on insights in an iterative manner, the Janssen Clinical Insights and Experience team collaborated with an independent third party—the nonprofit Center for Information and Study on Clinical Research Participation (CISCRP)\(^{15}\)—to create a standing Global Community Advisory Board (GCAB) for the immunology therapeutic area. The GCAB consisted of patient advocates with a variety of immunological conditions. The main objectives of the GCAB were to obtain feedback on strategies and solutions intended for patients, with a primary focus on clinical trial design; establish a strong working relationship between patients and Janssen; establish lines of communication with the broader community of patients with immunologic conditions that Janssen could connect with, both regularly and on an ad hoc basis; and ensure that patient-centric practices and principles are incorporated into clinical trials sponsored by Janssen.
This approach to engaging with patients aligns with industry recommendations and frameworks. It was formed to be a standing, long-term advisory panel consisting mainly of patients from around the world, and was facilitated by an independent third party (both CISCRP and Janssen personnel were active panel members). This model focused on the broader therapeutic area of immunology to promote a long-term, more impactful engagement. Thus, the GCAB provided the opportunity to explore a host of questions about Janssen’s clinical trials development and engagement strategies with a group of patient advocates in an atmosphere intended to build openness, trust, and mutual respect. The transparency and sense of trust built over time through this model were found to benefit both sides of the patient-sponsor equation.

Patients and Methods

Formation of the Immunology GCAB

Through relationships with patient advocacy groups and its own participant community, CISCRP identified a group of 11 individuals (eight women and three men) with various immunological conditions who expressed a willingness to serve on the GCAB. Some, but not all patients were familiar with the clinical trial process. Because of their experience in community and patient support groups, even GCAB members who were mostly unfamiliar with clinical trials had some knowledge about clinical research. The decision to convene an international advisory board resulted in a population of patient-advocates from seven countries across three global regions: North America (United States), Europe (Czechia, Denmark, Estonia, United Kingdom), and Asia-Pacific (India, Taiwan). Each patient advocate had a keen understanding of the specific challenges of his or her country of origin. CISCRP and Janssen intended for the GCAB to be a standing, long-term advisory panel with greater flexibility than the traditional, single touchpoint patient advisory board model. The Janssen team consisted of members in clinical research and operations roles, as well as members in patient engagement roles. Additional personnel from across the business also joined certain GCAB meetings as needed.

GCAB Activities

Over the course of one year, two in-person GCAB meetings were held: a kick-off meeting in February 2019 and a year-end review meeting in February 2020. In between, there were four
GCAB virtual meetings held via an online platform. GCAB members also engaged in *ad hoc* communications throughout the year, both to provide feedback on questions that arose between meetings and as they desired to support one another.

In addition to the six full-group meetings, a further six virtual condition/topic-specific meetings were held. Furthermore, one-on-one feedback was solicited from GCAB members during in-person meetings (see Figure 1).

**Figure 1: Immunology Global Community Advisory Board (GCAB) Meeting Schedule.**

GCAB members also completed surveys and reflection exercises for Janssen to address areas of interest. These included general questions, such as the perception of clinical trials among patient groups, and specific questions that assessed the effectiveness of trial information materials, receptivity to trial-related technologies, inclusion/exclusion criteria, and planned clinical trial assessments that could increase or decrease participation.
Results

Impact on Janssen Programs

For Janssen, the opportunity to seek patient feedback on various projects over time resulted in several operational and protocol changes to clinical trial study designs that fulfilled the original aim of the GCAB. The willingness of GCAB members to respond to study materials in conversation with staff and researchers has changed some of the baseline assumptions of the trial design process. This enabled a greater focus on patient-relevant outcomes, which procedures are truly necessary to achieve the desired results, and how to inform and empower patients using materials that respect their experience of living with a condition. The decision to involve patients with a broad range of immunologic conditions—rather than any specific one—presented the opportunity to gather feedback and discuss problems consistently, without the need to pause a trial or to complete work based on a specific protocol’s schedule. This efficiency enabled changes to be implemented as quickly as possible, which further built trust among GCAB members.

Seeking feedback from GCAB members on proposed trials resulted in several straightforward actions intended to increase enrollment and retention. For example, a proposed trial involved regular trial visits for bloodwork and medical photography, as well as required patients to wear an actigraphy device to monitor adherence and physical activity. GCAB members highlighted the time burden involved in short repeat visits to a study site would limit participation by those with unreliable transportation and/or a long travel distance. Numerous concerns also arose regarding the invasiveness of the actigraphy device, as well as regarding data security (the latter particularly from European members). Ultimately, investigators chose to remove these requirements from the study.

GCAB Feedback Additionally Supported and Informed Patient Engagement Strategies

In addition to gathering and acting on clinical trial design feedback, Janssen obtained insights from GCAB members to help shape MyTrialCommunity, a website for engaging with patients enrolled in Janssen clinical trials. Member feedback was integral to the development of this initiative. They recommended the site name and suggested changing logos and adding
testimonial videos from patients to explain the trial process in a non-threatening environment. In one example, a GCAB member shared personal experiences with the life-altering diagnosis of inflammatory bowel disease (IBD), as well as a video from a patient advocacy group about the day-to-day challenges of dealing with IBD. Janssen staff were moved by these patient stories and experiences and appreciated the opportunity for open dialogue about the impact of an IBD diagnosis, as well as the impact of living with the condition on people’s lives. The Research and Development team disseminated the video throughout the research group, to drive home the real-world impacts of their work.

*Trust, Awareness, and Advocacy Strengthened among GCAB Members*

This integration of GCAB feedback led GCAB members to feel empowered and enhanced their engagement in the advisory board process. GCAB members expressed surprise that their input affected the trial design, as some previous patient engagement experiences had not resulted in the same level of transparency and change. As a result, GCAB members reported a resulting sense of empowerment and engagement in the advisory board process, as they could observe the impact of their feedback and how it was genuinely valued.

Overall, GCAB members reported having a positive engagement experience and gaining a greater understanding of clinical trials as well as pharmaceutical companies in general. Before joining the GCAB, some believed clinical trials to be a last-resort option where patients were treated as “just a statistic.” Their perceptions evolved as members learned more about how clinical trials work, the level of effort and care pharmaceutical companies use to implement responsible trials, and the role of clinical trials in finding new treatments for their condition. Thus, GCAB members now understood that not only were clinical trials a viable treatment option for a wide range of patients, but they were an essential component in advancing the causes and objectives of their patient community.

These paradigm shifts among GCAB members highlight the success of the GCAB model in providing a collaborative, supportive environment where GCAB members could become more engaged in and educated about clinical trials. This enhanced the quality and actionability of
insights, as well as greater understanding of things that could not be changed in clinical trial design.

*Consistent Communication and Transparency are Important*

For many patients with chronic inflammatory conditions, barriers to research can be present from the onset of their condition journey, which can ultimately influence patients’ perception and willingness to participate or engage with clinical research. GCAB members reported difficulties obtaining a diagnosis, and once diagnosed, still dealt with feelings of shame and isolation brought on by their symptoms and the knowledge that they may never “get better.”

Outside the United States, patients reported greater difficulty obtaining information about clinical trials. This was particularly the case for smaller European countries without a robust patient organization network. Patients were frustrated by a lack of information about available trials on the part of their physicians and/or a perceived lack of interest from physicians who would not personally participate in the trial. Even when they searched online, barriers to information included a lack of clarity about where trials are available, limited country-specific public information about ongoing clinical trials, and engagement materials being available only in English.

Further barriers included an overuse of technical language by researchers. The era of molecular diagnostics (e.g., biomarkers) and treatment has added new layers of complexity to the research process, and this area of research remains too difficult for many patients to understand. GCAB members requested an in-depth, accessible explanation of what biomarkers are and how targeted therapy works.

A lack of transparency about what data will be collected from patients, how it will be used, and the risks and benefits of experimental interventions was also cited frequently. Long lists of potential adverse events can intimidate potential trial participants, especially when not accompanied by clear explanations of their true risk and prevalence. Further, patients consistently mentioned their discomfort with joining trials where they would never find out the results, whether their own or the overall trial outcomes, including not knowing whether they had been randomized to the active treatment or placebo arm of a study. The need for trial documents
Meaningful Communication is a Key Component of True Patient Engagement

Meaningful communication, as identified by the GCAB, was that which either resulted in actionable strategies (e.g., adjusting inclusion/exclusion criteria, changing ads to increase diversity/representation) or clarified the parts of a clinical trial that remain difficult for most patients to understand. One such opportunity is the regulatory and informed consent process—giving patients information about the importance and function of regulatory requirements in place to protect participant safety was repeatedly reported by the patients as increasing their sense of trust as well as their willingness to engage with a lengthy consent process. Additionally, many patients were unaware of the many “moving parts” of a clinical trial that are not patient-facing, so educating patients about the time constraints for things such as data analysis and regulatory approval can increase trust in the timeline of therapeutic development. Ensuring that patients will have access to results of a study—and thus an understanding of how their time and effort contributed to the study—is also advantageous to building trust.

One unexpected outcome of this engagement model was that, by educating and empowering patients, they become more comfortable with and supportive of the clinical trial process in general. Several GCAB members reported that their new understanding of safety measures for Phase I and II trials removed their fear of being “lab rats.”

On the sponsor side, in response to GCAB member feedback, Janssen took steps in several areas. For example, a patient brochure was substantially modified to provide more comprehensive data about the purpose and conduct of clinical trials. A patient testimonial video was also modified to increase a sense of inclusivity by starting with definitive statements instead of questions.

A meeting addressing topics of digital health brought up questions about data collection and security. There was a division between GCAB members on this topic, with European GCAB members expressing greater skepticism about providing digital information about themselves than Asian and U.S. members. In response, Janssen put in place measures to increase
transparency about what trial data would be collected and how the data would be stored and used. Discussion from yet another meeting spurred the development of patient educational materials to more clearly describe the benefits and purpose of early-stage clinical trials and the potential long-term benefits of these trials to patient health.

*Best Practices and Learnings for Future Engagement Models*

To ensure that meetings were structured, had pre-planned agendas and moderator guides, and were facilitated by an independent third party, Janssen partnered with CISCRP to implement the GCAB model. As a neutral party and liaison between patients and the pharmaceutical company, CISCRP helped establish a baseline of trust for both advisory board members and sponsor personnel. Because of its extensive experience in patient engagement initiatives such as community advisory boards, CISCRP was also able to manage the logistical coordination of GCAB meetings, ensure that the project progressed according to determined timelines, and accommodate GCAB member needs and questions in a timely manner.

Despite favorable responses about the GCAB and the approach taken, there were some limitations reported by GCAB members across several broad categories. These included: respect for patients’ time, organization of activities, information overload, burdens to patients caused by holding several meetings, a focus on English language, and a general U.S.-centric focus on materials. Although non-U.S. GCAB members had excellent English-language skills, several non-native speakers expressed discomfort with the speed of presentations, calling for a greater level of comfort with written communication to ensure that non-English native speakers are not excluded or discriminated against. Non-U.S. patients remarked that, especially in smaller countries, pathways to information about clinical trials are lacking. This presents an opportunity to explore enrollment opportunities via non-U.S. patient advocacy and physician networks.

Regardless of language of origin, patients reiterated the need for materials and presentations to be given in plain language and in easily digestible amounts. Adequate discussion was a key factor leading to patient engagement and trust in the process. Patients frequently noted the need to keep meetings—both online and in-person—organized and on a schedule that respected patients’ time constraints.
Discussion

A growing focus on patient-centered outcomes by sponsors and regulatory agencies is an opportunity to establish practices that mutually benefit patients and pharmaceutical companies and other stakeholders. The year-long experience with the GCAB provided rich, actionable insights that could not have been obtained from other stakeholders, and demonstrated that a key component tying the GCAB’s feedback together was the sense of trust built by consistent, two-way dialogue.

The opportunities for trust-building among stakeholders occur across the spectrum of clinical research. Education is a foundation of this process—issues surrounding control groups, informed consent, and the potential that results will never be published are sources of potential opacity that can be overcome by presenting clear, patient-focused information.[16,17] GCAB members consistently reported that as their knowledge increased over the course of the initiative, so did their sense of engagement, ability to provide relevant feedback, and determination to help their patient and community networks come to a greater understanding of the importance of trial participation.

Two overall themes became clear during the data review of the GCAB’s first year in operation. First, patients want more information and transparency. Throughout meeting sessions, patients wanted to know more about the purpose of clinical trials, the thinking behind different trial procedures, data collected, and inclusion/exclusion criteria. They wanted to know that results would be communicated to trial participants, and how their personal information would be used for the purposes of the clinical trial. To this end, Janssen has taken steps, such as creating educational materials about drug-development trials, with the aim of lessening the stigma of these studies as a “last resort.”

GCAB feedback highlights the importance of engaging patients in the clinical trial design process. Effective communication about how patients are centered in the conduct of a study can increase retention through trust and transparency. Patient engagement can allow researchers and sponsors to ask questions such as:
• Are there opportunities to reduce the number of procedures, especially those which are 
highly burdensome for patients (for example, invasive and painful procedures like 
biopsies, endoscopies, and blood draws)?
• How can visits and data collection be grouped to minimize travel and time burdens on 
participants and their support networks?
• Which interventions, either additive (such as patient comfort kits for procedure days) or 
subtractive (for example, requiring fewer blood draws), have the greatest impact on the 
participant’s trial experience?

These types of practical questions can help researchers design protocols focused on greater 
efficiency, minimized invasiveness, and respect for the people taking part, while still enabling 
the collection of necessary evidence. The actions Janssen took in response to GCAB feedback 
resulted in increased engagement by both research teams and GCAB members.

It is beyond the scope of this article to delve into the financial metrics of this type of partnership, 
but involving patients as partners is a pragmatic strategy to increase transparency of the research 
process and overcome disparities in health research.\{18\} Other groups have assessed the 
financial benefit to sponsors and found significant potential for savings in terms of efficiency and 
retention.\{19\} One such potential is to troubleshoot trials before they even start. Not only does 
this potentially increase enrollment and retention, but it can prevent costly protocol amendments. 
The investment in time and educational materials in this new type of engagement model was 
well worth the outcomes in terms of engagement and trust.

**Conclusions**

A meaningful partnership among the various stakeholders in any clinical trial depends on 
defining goals, choosing the right partners, and investing the time to ensure that all voices are 
heard.\{20\} By engaging an advisory board consisting of knowledgeable patient advocates, we 
were able to present and receive valuable feedback on numerous projects and scenarios, 
including educational materials, inclusion/exclusion criteria and other protocol elements, and 
regulatory and consent documents. In doing so, the sponsor received actionable takeaways, 
which resulted in changes to different elements of several protocols. Engaging a neutral third
party to serve as primary contact for patients, ensure well-planned meeting objectives and agendas, and collate feedback helped achieve quality engagements and effectively summarize feedback.

Further, the opportunity to make changes and demonstrate them to the GCAB was a powerful motivator for Janssen staff and researchers, as was the increased understanding of the real-world, daily experiences of patients living with immunological conditions. Because the GCAB was convened as a long-term advisory body, we were able to demonstrate to GCAB members the actions Janssen took in response to their recommendations. This investment in time and evidence proved to be key in the trust-building process and was cited by all GCAB members as a major factor in their overall positive reaction to this initiative and their views on clinical research in general.

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Drug development success is driven by a deep understanding of the disease of interest—its etiology, epidemiology, presentation, manifestations, and progression. For rare diseases, where patient populations are small and historical data collection is inconsistent and dispersed across treating physicians in diverse geographies, much of this information may be unknown. Therefore, sponsors seeking to design reliable clinical trials with relevant, clinically meaningful outcome measures may rely on patient registries and natural history studies as valuable sources of rare disease information.

In this column, we explore the distinctions between registries and natural history studies, highlighting the potential value of each in informing and shaping clinical development in rare diseases.

**Challenges of Rare Disease Development**

In rare diseases, developing a comprehensive understanding of the disease of interest is hampered by:

1. Inherently small populations
2. Frequent lack of timely diagnosis
3. Scarce, incomplete, or inconsistent data
• Disease heterogeneity, which complicates diagnosis, categorization, and data collection
• Lack of precedents
• Scarcity of validated methods for assessing disease-specific conditions
• Need for more careful, more extensive planning

Observational studies play a critical role in addressing these challenges and filling in knowledge gaps, creating a solid foundation of disease knowledge to support product development.

Types of Observational Studies

Unlike clinical trials, where patients receive interventions according to a well-defined protocol, observational studies do not assign participants to specific interventions and do not attempt to affect the outcome.

Observational studies are divided into two categories:

1. **Registry studies**, which may include a broad collection of defined data
2. **Natural history studies**, which are used for controlled, detailed collection of data that may be subject to review by a regulatory agency

While the terms registry study and natural history study are often used interchangeably, they differ in definition and application.

The Role of Patient Registries

A patient registry is an organized system for collecting, storing, retrieving, analyzing, and distributing information on individuals who have one of the following:

• A disease of interest
• A condition or risk factor that predisposes them to a health-related event
• Prior exposure to substances that are known or suspected to cause adverse health effects

A subset of patient registries is designed for a specific purpose—for example, collecting particular demographic, epidemiological, efficacy, cost-effectiveness, quality of life, or care
pattern data. However, most registries are less restrictive and less structured and can be set up to collect data, including patient communications and post-marketing data.

Since registries are typically broad in scope, registry studies may be useful throughout drug development. Common applications of patient registries include:

- Collection of disease information
- Study of the standard of care or best practices
- Recruitment for clinical trials
- Observation or identification of population behavior patterns
- Monitoring of long-term outcomes

If a drug product is included in a registry study, that product must be approved, commercially available, and used in accordance with the approved labeling.

**The Role of Natural History Studies**

A disease’s natural history refers to how a disease process progresses over time without any treatment. The objective of a natural history study is to document the course of a disease, starting just before it begins and progressing through its different clinical stages until the patient is cured, chronically disabled, or deceased.

Unlike registries, natural history studies are designed with a specific purpose, such as tracking the evolution of a disease over time, identifying factors that correlate with the disease and outcomes in the absence of treatment, or informing clinical trial design. These studies may also be used for:

- Obtaining more accurate estimates of disease prevalence
- Identifying and differentiating among disease subtypes
- Identifying demographic, genetic, environmental, or other factors that affect disease prognosis
- Identifying and assessing potential serological, tissues, and imaging biomarkers
- Evaluating and validating potential clinical outcome assessments
• Assessing the background risks associated with rare untreated diseases, providing context for assessment of potential risks associated with future therapeutic interventions
• Refining protocol design, including study duration, inclusion and exclusion criteria, and appropriate endpoints

Data collected from natural history studies may also be useful for understanding the dynamics of laboratory and clinical changes that can help identify the optimal time for therapeutic intervention. Natural history studies may be especially valuable in rare disease research where it is not possible to include a placebo control clinical trial arm for logistical or ethical reasons. In certain situations, a natural history study can even serve as a surrogate for the control population, provided the study has been designed to meet the requirements for regulatory submission.

**Timing of Natural History Studies**

In its draft guidance document, *Rare Diseases: Natural History Studies for Drug Development,* the U.S. Food and Drug Administration urges sponsors to carefully consider the timing of natural history studies in the development process. The guidance includes a discussion of the pros and cons associated with implementing natural history studies at various stages of clinical development. Generally, these studies are likely to be most useful if completed before initiating interventional studies, but they can also be performed in parallel with clinical trials.

**Types of Natural History Studies**

There are several natural history study designs, each with advantages and disadvantages. The designs may be retrospective, focused on the present, or prospective.

Medical literature reviews are the easiest, least expensive way to begin elucidating the natural history of a disease. Still, data may be difficult to standardize, and these studies may not meet natural history study objectives. Retrospective chart reviews are also relatively inexpensive, though missing and non-standardized data may present hurdles to the research.
Prospective natural history study designs include cross-sectional and prospective longitudinal studies (see Figure 1). Cross-sectional studies collect data from a variety of patients at a single point in time. While these studies may provide insight into disease generalities, they do not provide any insight into the progression or patient experience. Meanwhile, longitudinal studies collect data over a prospectively defined period. These studies can be lengthy and costly, but may provide valuable information on how the disease progresses over time.

Figure 1: Comparison of Prospective Natural History Study Designs

<table>
<thead>
<tr>
<th>Description</th>
<th>Pros</th>
<th>Cons</th>
</tr>
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<tbody>
<tr>
<td>Collection of data from a variety of patients at one point in time</td>
<td>Limited duration of study</td>
<td>Doesn't collect patient experience in time; data is a 'snapshot'</td>
</tr>
<tr>
<td></td>
<td>Predefined data elements</td>
<td>Doesn't provide robust data on the pace of progression of a disease state</td>
</tr>
<tr>
<td></td>
<td>May provide insight into generalities about disease</td>
<td>Difficult to extrapolate from 'snapshot' to make assumptions about disease progression on a per patient basis</td>
</tr>
<tr>
<td>Collection of data from a variety of patients over a defined period of time</td>
<td>Predefined data elements</td>
<td>Can be lengthy to complete, especially in diseases that progress slowly</td>
</tr>
<tr>
<td></td>
<td>Able to assess disease progression over time</td>
<td>Can be expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need to plan for changes in measurements and SOC over time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May require amendments to adjust for additional assessments or biomarkers over time</td>
</tr>
</tbody>
</table>

Natural History Study Design Considerations

Though natural history studies may collect information on therapeutic interventions, it is essential to ensure that data gathering also includes measures that assess all facets of the disease of interest. When considering what data to collect, sponsors should anticipate any questions that might arise over the course of drug development. This includes disease presentation, manifestations, morbidity, and progression. Often, natural history studies include evolving protocols that incorporate plans to refine data collection as new disease knowledge emerges. (1) Ideally, the data collected should be sufficiently robust to support the development of multiple therapeutic options.

Data collection requirements, assessment type, and frequency must align with the standard of care, which may differ among providers or institutions and may even change over time. Standard
of care may help inform the selection of meaningful endpoints and appropriate assessments for measuring or monitoring disease progression. It is also critical to understand how the standard of care may impact site feasibility, study duration, and inclusion/exclusion criteria.

Due to regulatory scrutiny, data quality and monitoring are essential for any study subject. Even if the planned natural history study will not be included in regulatory submissions, it is critical to ensure high-quality data. While 100% source data verification is not mandatory, some level of monitoring is recommended.

**Collecting and Ensuring High-Quality Data in Natural History Studies**

As with interventional clinical trials, data collection in natural history studies can be performed through either local sites or one or more central sites. With local sites, data are collected by a patient’s existing provider and submitted to central data collection. While this approach limits the burden on the patient, it may introduce variability. With central sites, all study assessments are performed at a limited number of experienced sites. This approach to data collection increases consistency and helps minimize the risk of missing data or protocol deviations, but may increase the study burden if patients need to travel long distances to those central sites.

Combination models offer a hybrid approach where complex or specialized assessments are performed at central sites and routine assessments are completed at local sites. Sponsors may also opt for a patient-reported model where all assessments and data collection are performed in the patient’s home. Although this approach is the most convenient for the patient, it may introduce variability and requires significant training of in-home providers. Ultimately, the most appropriate data collection model for a natural history study will depend on the overall objectives.

**Conclusion**

Both registries and natural history studies play important but different roles in the clinical development of therapeutics for rare diseases. Therefore, understanding how—and when—each of these observational studies should be used is essential for guiding the design of successful clinical trials.
References


2. Centers for Disease Control and Prevention. Lesson 1: Introduction to Epidemiology, Section 9: Natural History and Spectrum of Disease. 


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ACRP HOME STUDY
CLINICAL RESEARCHER—AUGUST 2022 (VOLUME 36, ISSUE 4)
We’re All in This Boat Together: Patients, Professionals, and Promising Solutions for Keeping Study Sites Afloat

Article #1: Racial and Ethnic Disparities Among the Clinical Research Workforce: Insights and Opportunities

LEARNING OBJECTIVES
After reading this article, the participant should be able to highlight top concerns regarding diversity in the clinical research workforce, characterize the importance of workforce diversity in regard to patient recruitment and retention, and summarize the most relevant findings of a Tufts Center for the Study of Drug Development examination of factors influencing diversity in the workforce.

DISCLOSURES
Emily Botto, BA; Maria Florez, MA; Adrelia Allen, PharmD; Ruma Bhagat, MD, MPH; Ellyn Getz, MPH; Kenneth Getz, MBA: Nothing to disclose

1. How do the authors characterize the state of representation of Black, Indigenous, and People of Color (BIPOC) among the global clinical trial participation population?
   a. Healthy
   b. Acceptable
   c. Low
   d. Undetectable

2. Which of the following is a factor that studies suggest should be addressed to promote participant diversity in clinical trials?
   a. Assurances that only other participants of the same race will be in a study.
   b. Racial and ethnic disparities in the global clinical research workforce.
   c. Release of study results to participants’ hometown newspapers and stations.
   d. Spreading each study’s active sites evenly across the United States and Canada.

3. Who were the respondents to the study described in this article?
   a. Only healthcare professionals who had helped conduct multiple studies.
   b. Newer study coordinators who had previously been trial participants.
   c. Principal investigators who had responded to the earlier survey by Tufts CSDD.
   d. Healthcare professionals with and without clinical research experience.

4. Who among the survey respondents were significantly more likely to be “extremely interested” in clinical research?
   a. Non-white MDs and PhDs in North America.
   b. Whites overall from all regions.
   c. Non-whites overall from all regions.
   d. White MDs and PhDs from outside North America.
5. Which of the following were listed as the two highest “very important” barriers to involvement in trials by respondents with no clinical research experience?
   1. Personnel needs
   2. Lack of access to trials
   3. Time constraints
   4. Lack of patient interest
   
   a. 1 and 2 only
   b. 1 and 4 only
   c. 2 and 3 only
   d. 3 and 4 only

6. Which two kinds of trial sponsors were rated highest as “more likely” to make survey respondents interested in becoming a clinical researcher?
   a. Industry and non-profit
   b. Government and academic
   c. Non-profit and government
   d. Academic and industry

7. Among all experienced respondents to the survey, what was the top factor for first becoming involved in clinical research?
   a. Joining an established clinical study team proactively.
   b. Applying for a job or grant involving clinical trial work.
   c. Having been recruited or referred into a trial position.
   d. Being asked by a mentor or peer to work on a study.

8. How many non-white mentored vs. white mentored respondents agreed that mentors made them more likely to continue to get involved in clinical trials after their first trial?
   a. 100% vs. 88%
   b. 75% vs. 63%
   c. 50% vs. 38%
   d. 25% vs. 13%

9. How many North American respondents overall said their first involvement in clinical research came by way of applying for a job or grant?
   a. 10.8%
   b. 21.6%
   c. 22.5%
   d. 34.3%

10. In addition to instituting mentorship and educational programs among allied health students from diverse backgrounds, the authors recommend which of the following as an essential element to promoting diversity in the clinical research workforce?
    a. Mandates from industry sponsors that clinical trial teams consist of diverse members.
    b. The availability of early intervention programs to promote clinical research education.
    c. Pressure from patient advocacy organizations for more representative clinical researchers.
    d. Favored publication status from medical journals for trial results from highly diverse teams.
Article #2: **Findings from a Long-Term Patient Engagement Model**

**LEARNING OBJECTIVES**
After reading this article, the participant should be able to list multiple examples of major patient engagement initiatives in medical research and their sources, summarize the opportunities represented by greater patient involvement in studies, and explain the functioning and accomplishments to date of Janssen’s Global Community Advisory Board.

**DISCLOSURE**
Annick de Bruin, MBA; Shalome Sine, MPH; Lieven Van Vijnckt, PharmD; Alyson Gregg, MBA; Catherine Cole: *Nothing to disclose*

11. Which of the following is characterized by the authors as an opportunity to develop and conduct more effective research?
   a. U.S. Food and Drug Administration support of breakthrough therapies.
   b. Greater involvement by patients in medical product development.
   c. Increased competition for clinical trials among developing nations.
   d. Improved standardization of patient consent and recruitment practices.

12. Which of the following is cited as an advantage provided through Janssen's implementation of a long-term global community advisory board (GCAB)?
   a. A partnership based on trust, knowledge-building, and dialogue.
   b. A reliable pool of engaged participants for upcoming studies.
   c. A source of actionable intelligence on what competitors are doing.
   d. A legal backstop in the event of participant lawsuits or accusations.

13. Which of the following is noted as a primary focus for feedback obtained from members of the GCAB?
   a. Hiring study coordinators
   b. Compensating study participants
   c. Designing clinical trials
   d. Repurposing existing drugs

14. How much awareness of clinical trials did the GCAB members have at first?
   a. All of them had participated in multiple clinical trials in their lives.
   b. Half of them had completed at least one clinical trial in recent years.
   c. Some, but not all of them were familiar with the clinical trial process.
   d. None of them had ever been exposed to clinical trials or research.

15. GCAB members helped shape which of the following website resources for patients?
   a. CISCRP.org
   b. Antidote.me
   c. PatientsLikeMe
   d. MyTrialCommunity
16. The authors cite which of the following as an attitude GCAB members had toward clinical trials before joining the board?
   a. They are too expensive.
   b. They are last-resort options.
   c. They are highly unethical.
   d. They are prone to be biased.

17. Which of the following was experienced by GCAB members outside the United States?
   a. More stringent inclusion/exclusion criteria for enrolling in trials.
   b. Near-zero availability of trials for advanced medical conditions.
   c. Greater difficulty obtaining information about clinical trials.
   d. Easier access to long-term observational clinical trials.

18. Which of the following is cited as an area of research that remains too difficult for many patients to understand?
   a. Billing and reimbursement policies
   b. Recruitment and retention practices
   c. Regulatory compliance and oversight
   d. Molecular diagnostics and treatment

19. Patients consistently mentioned their discomfort with joining trials under which of the following conditions?
   a. Never knowing the results of the study.
   b. Being told they would all receive placebos.
   c. Having to keep a patient diary up to date.
   d. Knowing they were sponsored by industry.

20. Which of the following steps was taken by Janssen in response to GCAB member feedback?
   a. Trial enrollments were opened to more terminally ill patients.
   b. A patient brochure was modified with more useful data.
   c. Several trials involving randomization were scrapped.
   d. Patient reimbursements were substantially increased.

[Test continues on next page...]
LEARNING OBJECTIVES
After reading this article, the participant should be able to describe the function of patient registries, compare and contrast the elements of different types of observational studies, and outline the applications of these concepts to rare disease research situations.

DISCLOSURE
Kris O’Brien: Nothing to disclose

21. In rare disease research, developing a comprehensive understanding of the disease of interest is hampered by which of the following?
   1. Scarce, incomplete, or inconsistent data
   2. Discouragement from regulators
   3. Lack of precedents
   4. Inherently small populations

   a. 1, 2, and 3 only
   b. 1, 2, and 4 only
   c. 1, 3, and 4 only
   d. 2, 3, and 4 only

22. Observational studies differ from clinical trials in which of the following manners?
   a. They may only be conducted in academic medical center settings.
   b. They are not allowed to be run on a multinational basis.
   c. They must reimburse patients at twice the normal rate.
   d. They do not attempt to affect the outcome of a health situation.

23. Observational studies include which of the following categories?
   a. Randomized and intent-to-treat
   b. Natural history and registry
   c. Interventional and retrospective
   d. Decentralized and hybrid

24. An individual whose information is included in a patient registry will have which of the following?
   a. A condition or risk factor that predisposes them to a health-related event.
   b. A willingness to participate in multiple long-term clinical trials when asked.
   c. A disease which has never before been identified in a living person.
   d. An ailment that is known to strike less than one in 1 million persons.
25. Common applications of patient registries include which of the following?
   1. Targets for holistic treatments
   2. Monitoring of long-term conditions
   3. Recruitment for clinical trials
   4. Proposals for organ donors

   a. 1 and 2 only
   b. 1 and 4 only
   c. 2 and 3 only
   d. 3 and 4 only

26. What is the objective of a natural history study?
   a. To follow individuals who are not aware they are ill.
   b. To document the course of a disease.
   c. To identify and hospitalize disease-prone persons.
   d. To discover new diseases in animals.

27. Natural history studies may also be used for which of the following?
   1. Reconstructing clinical trials for validation of reported results
   2. Evaluating and validating potential clinical outcome assessments
   3. Identifying and differentiating among disease subtypes
   4. Obtaining more accurate estimates of disease prevalence

   a. 1, 2, and 3 only
   b. 1, 2, and 4 only
   c. 1, 3, and 4 only
   d. 2, 3, and 4 only

28. Natural history studies may be especially valuable in rare disease research in which of the following situations?
   a. When lack of funding precludes treating all participants.
   b. When many patients refuse to admit they have the disease.
   c. When a placebo control arm cannot be included.
   d. When too many participants drop out early in the study.

29. Which of the following is characteristic of a prospective cross-sectional natural history study?
   a. It collects data from a variety of patients at a single point in time.
   b. It is capable of assessing the progression of a disease over time.
   c. It requires planning for changes in standard of care over time.
   d. It helps researchers pre-select participants from electronic health records.

30. Submission of data on a patient to central data collection by the patient’s local provider can introduce which of the following in an interventional clinical trial?
   a. Variability
   b. Consistency
   c. Legality
   d. Clarity