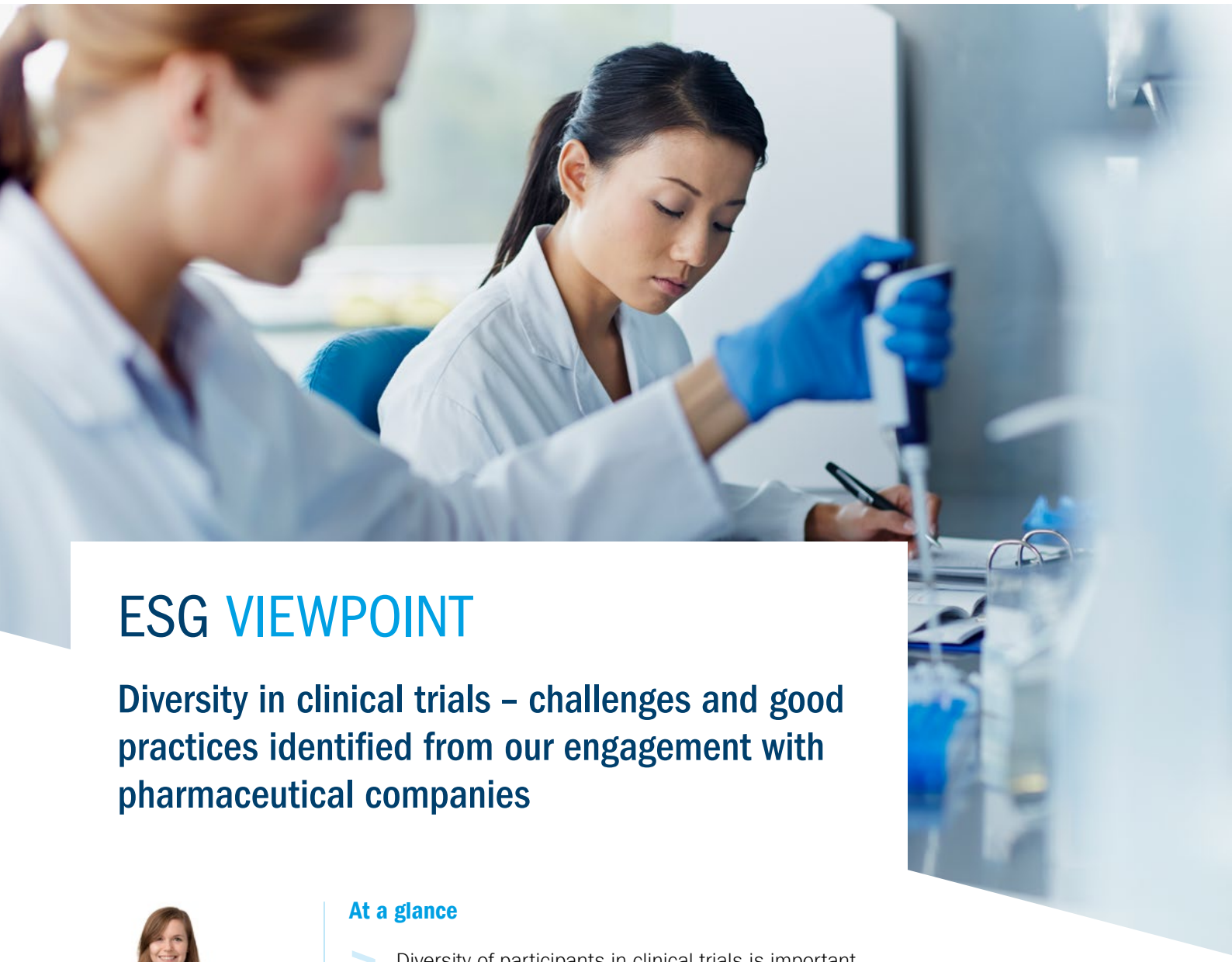
COLUMBIA THREADNEEDLE INVESTMENTS



ESG VIEWPOINT

Diversity in clinical trials – challenges and good practices identified from our engagement with pharmaceutical companies

Ellen Brauers
Associate, Responsible Investment

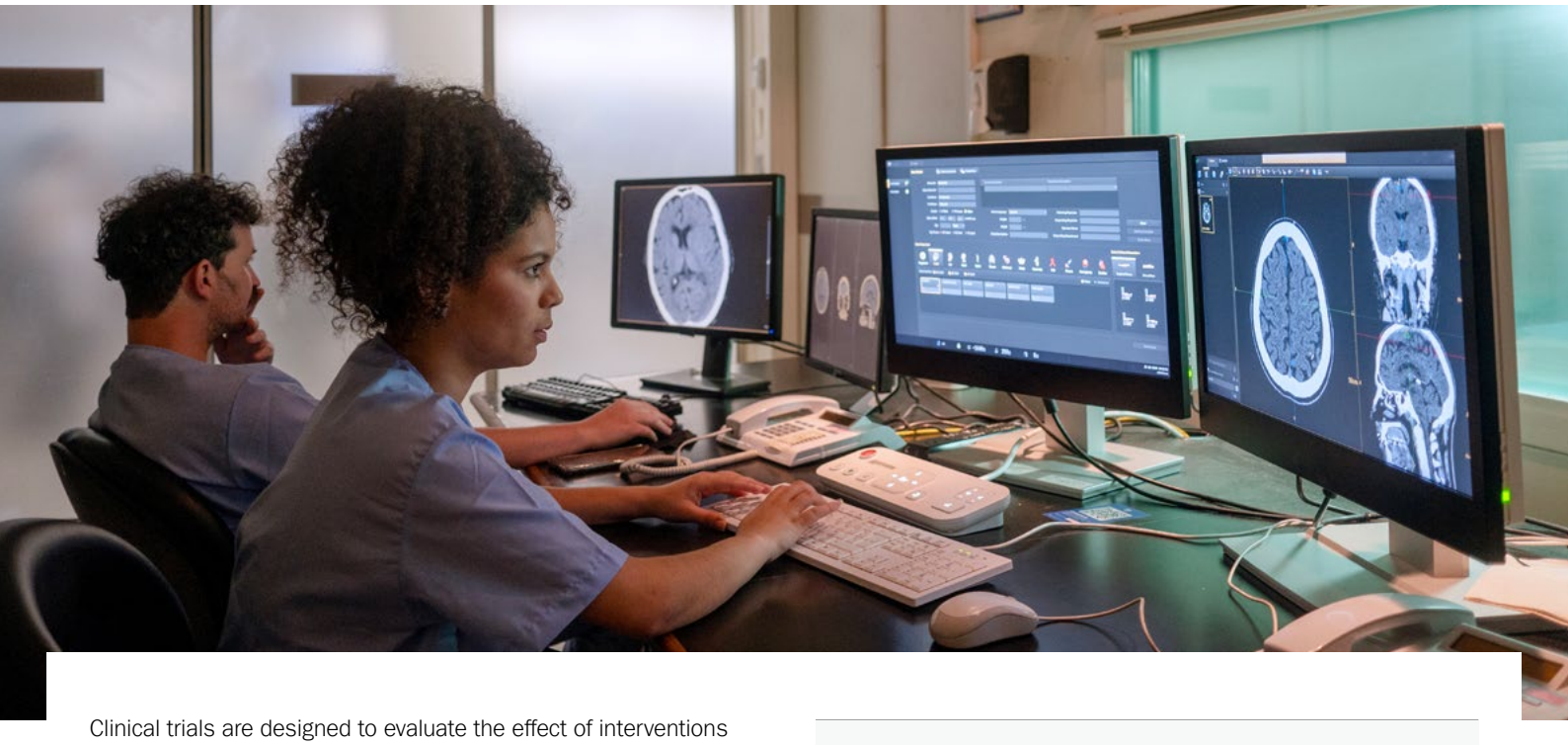
At a glance

- Diversity of participants in clinical trials is important to test for the quality and safety of drugs in different populations.
- Despite a clear scientific and commercial imperative, significant gaps between patient populations and trial populations persist. It is important to acknowledge the different challenges that patients, as well as companies, experience in order to narrow this gap.
- In this ESG Viewpoint, we discuss why this is material for investors and what different barriers exist to diversifying clinical trials. We also explain how we engage investee companies on this topic and which good practices we have identified from this.

The materiality of diversity in clinical trials for investors

Diversity in clinical trials is, first and foremost, a scientific imperative, but also increasingly a regulatory and commercial requirement. A trial population that represents the diversity of the target patient population is important for the full evaluation of safety and efficacy and building patient trust. However, for various operational and historical reasons, it is rarely straightforward to achieve. As investors, we are interested in assessing strategic thinking, action and progress on this topic across the sector, and encouraging improvements. Considerable groundwork is needed to enable greater trial diversity, and a failure to take timely steps risks delays and additional cost to drug development, which may impact commercial success.

Interested in learning more? Keep scrolling or click the quick links



Clinical trials are designed to evaluate the effect of interventions (such as drugs, devices, surgeries and diets) on health-related biomedical or behavioural outcomes.[1] To account for different genetic, (patho)physiological traits, as well as social determinants of health, it is important to include people that account for diverse traits and circumstances in clinical trials and reflect the epidemiology of the disease. As an example, women of colour are 41% more likely to die of breast cancer than white women, and they have a 39% higher recurrence rate.[2] However, for four new breast cancer treatments that were approved by the Food and Drug Administration (FDA) in 2020, black clinical trial participants only made up 2-9% of clinical trial participants.[3] Of the 53 novel drugs approved in 2020 by the FDA, 75% of trial participants were white, whereas 40% of the US population is comprised of minority racial and ethnic groups.[4 5]

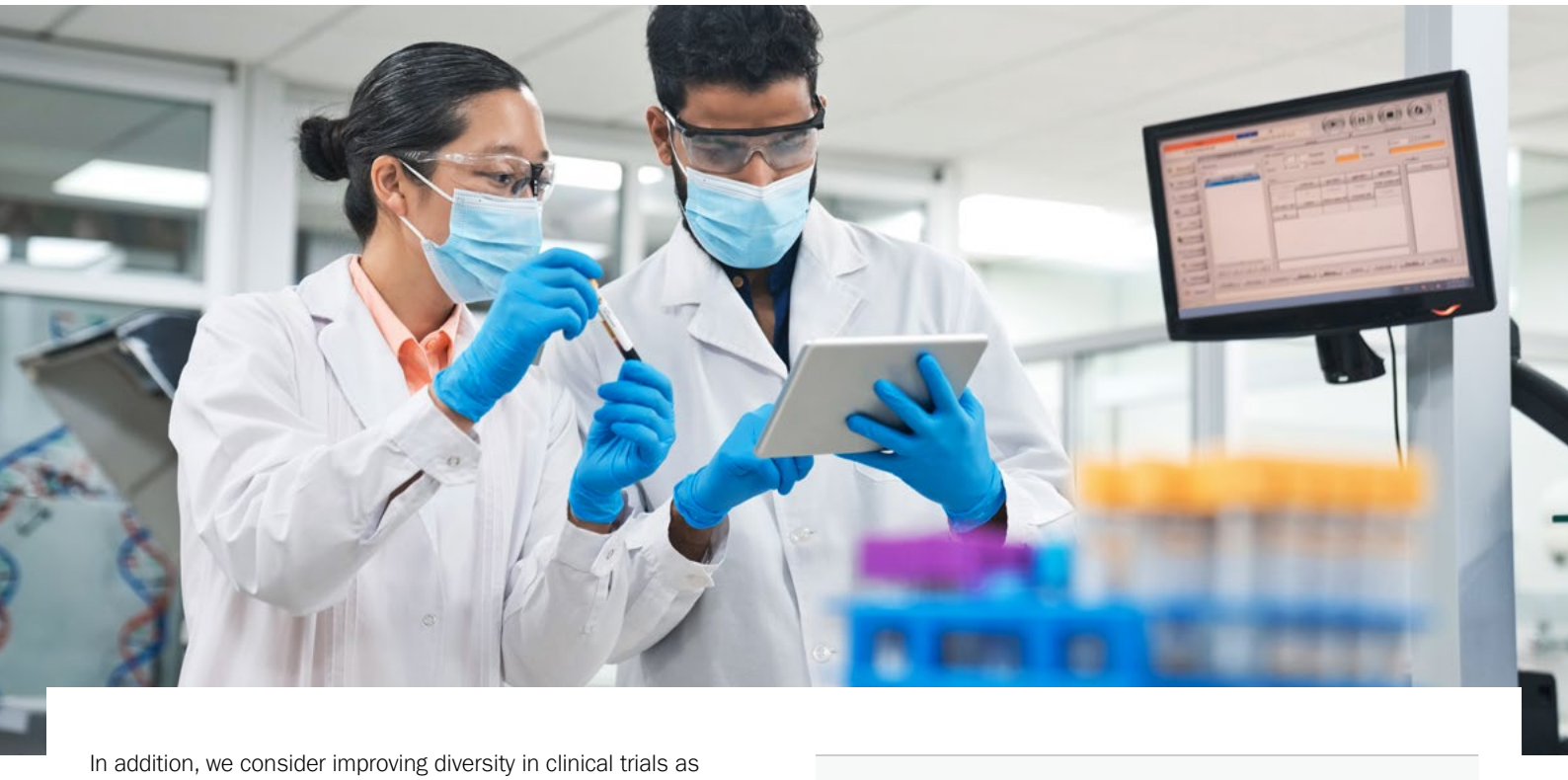
Gaining a full understanding of the safety and efficacy of novel therapies across all demographics can only be achieved when clinical trial enrolment is representative.[6] When companies are able to better identify safety issues for certain populations prior to market entry, this can limit financial and legal risks resulting from product recalls and patient litigation.[7] Upcoming regulatory requirements will push the industry to include diversity planning in their trial protocol or justify why this is not necessary. Being unprepared for this might result in novel drugs and therapies not being approved by the FDA, which poses a very material risk to drug manufacturers and Contract Research Organisations (CROs).

Moderna's COVE study
A success story about clinical trial diversity

During Moderna's Phase 3 COVE study for its ground-breaking mRNA COVID-19 vaccine, the company recognised underrepresentation of people of colour in its clinical trial. Knowing that commercial success could only be achieved by building trust in the vaccine when safety for all populations was proved, the company decided to slow down overall study enrolment to ensure more diverse representation. This was successful. In the end, 37% of the study population represented participants from communities of colour.

Slowing down a trial is not without risk. It costs time and money, and may even impact retention rates. Moderna has shown that, with its leadership and commitment, it successfully boosted trial diversity. This example also showcases the importance of real-world data and continuous monitoring of trial participants. The earlier a company incorporates diversity, the better.

1 https://www.nimhd.nih.gov/resources/understanding-health-disparities/diversity-and-inclusion-in-clinical-trials.html
2 https://touchbbca.org/blackdatamatters/
3 https://www.breastcancer.org/treatment/clinical-trials/diversity-in-trials
4 https://www.thelancet.com/journals/langas/article/PIIS2468-1253(21)00228-4/fulltext
5 https://www.fda.gov/media/145718/download
6 https://www.thelancet.com/journals/langas/article/PIIS2468-1253(21)00228-4/fulltext
7 https://www.sustainalytics.com/esg-research/resource/investors-esg-blog/esg-risk-clinical-trial-diversity



In addition, we consider improving diversity in clinical trials as an opportunity for the industry to enhance trust-building with current and future patients. As trust in the pharmaceutical sector is a persistent issue that also affects drug and vaccine uptake, trust-building has the potential to have a much wider effect on pharmaceutical companies. Studies find that higher levels of trust among disadvantaged communities can be expected to contribute to better health outcomes for their members, and can drive, in turn, a virtuous cycle – from higher-quality data to more expansive problem solving to better-targeted approaches, and to greater collaboration throughout the healthcare ecosystem.[8] This will ultimately be beneficial for the industry itself as higher trust will most likely also positively impact areas other than clinical trials – for instance, drug and vaccine

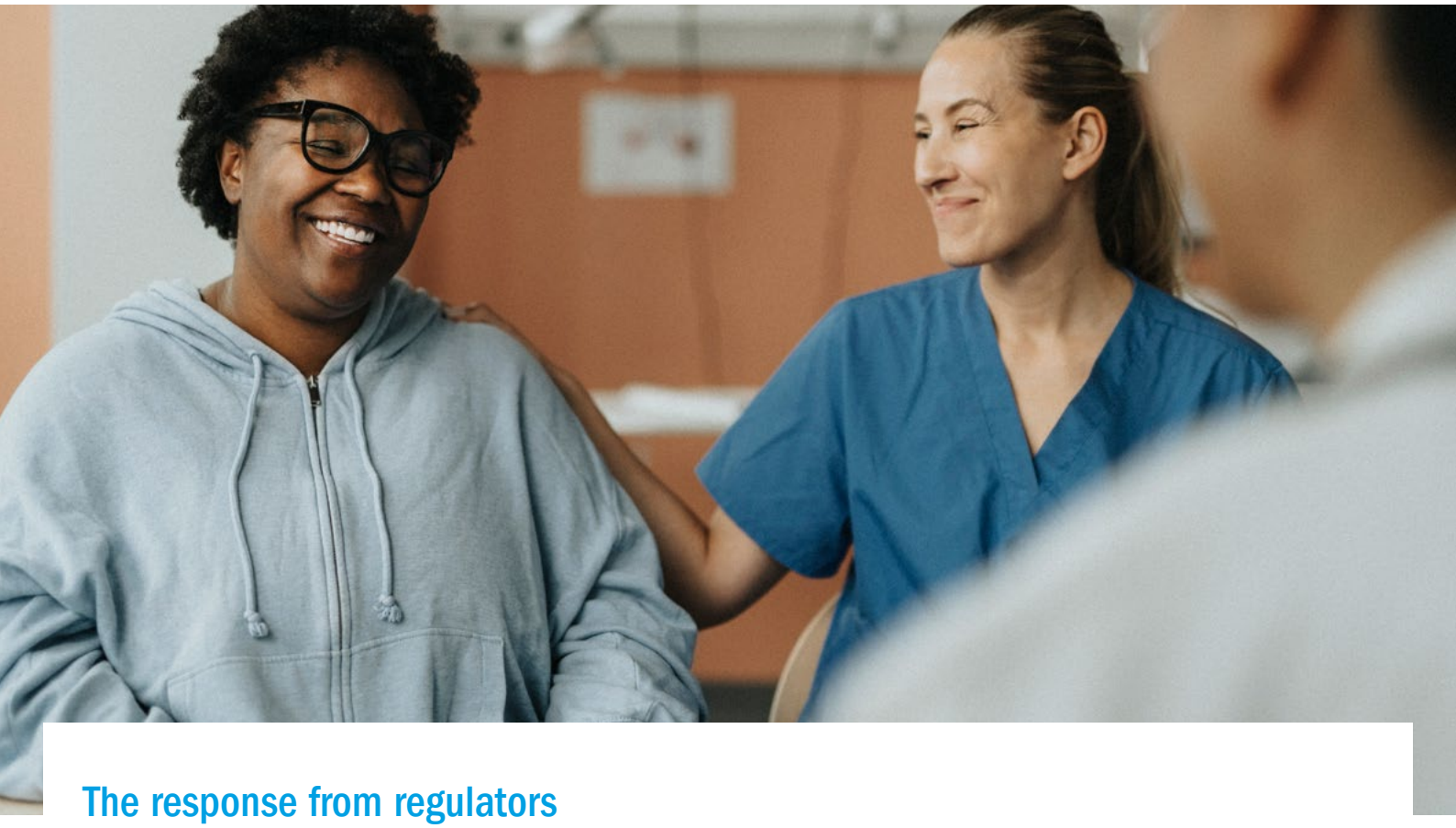
Improving diversity in clinical trials will have build up trust in the pharmaceutical sector and improve drug and vaccine uptake.

The Tuskegee Syphilis study
Historical foundation of distrust

Between 1932 and 1972, the US Public Health Service (USPHS) conducted a study to record the natural history of syphilis in black men. Six hundred black men – 399 with syphilis, 201 without – participated in the study. Their 'informed consent' was not collected, and they were told that they were treated for 'bad blood', a term that was used to describe several conditions, including anaemia and fatigue. In exchange for their participation, the men received free medical exams, free meals and burial insurance. In 1943, penicillin became widely available, and it was known that it could treat syphilis. However, participants in the study were not offered treatment, with fatal consequences.

Public health researchers have argued that this study has been a key source of distrust among African Americans of the medical industry. One study found that black men who were 10 years or older in 1972 (when the story about the syphilis study broke) are less likely to receive medical care and die at younger ages. ''The decrease in the life expectancy of black men attributable to the Tuskegee revelation represents 35% of the racial gap in male life expectancy in 1980 and 25% of the gender gap in black life expectancy."

[8] Health equity: A framework for the epidemiology of care | McKinsey



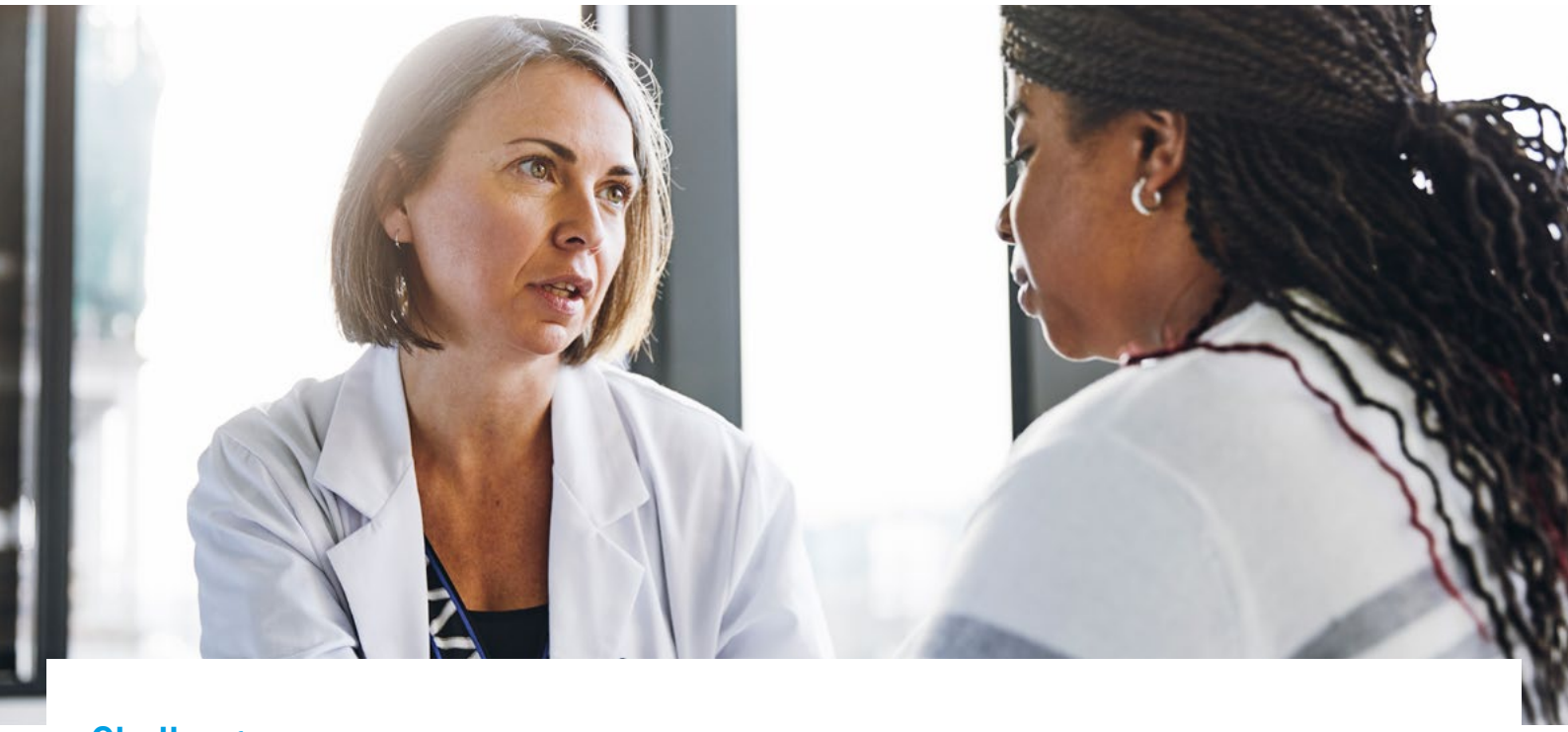
The response from regulators

Diversity in clinical trials is, by no means, a new topic and has been on the (policy) agenda for decades. The FDA has promoted diversity in clinical trials since the 1980s[9] and, in 1993, the National Institutes of Health (NIH) Revitalisation Act directed the NIH to establish guidelines for the inclusion of women and minorities in clinical research.[10] It is only more recently that regulatory bodies have issued guidance and mandatory requirements. In January 2022, the European Medicine Agency (EMA) updated its Clinical Trials Regulation to ensure sponsors justify any non-representative procedures.[11] In April 2022, the FDA published a draft guidance on developing "Race and Ethnicity Diversity Plans" and setting enrolment goals based on the affected patient population.[12] [13]

The 2023 Omnibus spending bill requires diversity action plans for clinical trials that are used by the FDA in order to decide whether drugs are safe and effective. From 2024 onwards, the FDA will have to publish an aggregate report of diversity action plans, including an explanation for trials that did not include diversity action plans.[14] These developments have put renewed pressure on sponsors and CROs to improve representation in clinical trials and, despite the FDA still finalising its guidance and aligning this with stakeholder feedback and the Omnibus law, it is highly recommended that sponsors and CROs start now.[15]

Diversity in clinical trials has been on the policy agenda for decades. It's only recently however, that regulatory bodies have issued guidance and mandatory requirements.

[9] Diversity in Clinical Trials at FDA Gets a Boost From New Law (bloomberglaw.com)
[10] NIH Revitalization Act of 1993 Public Law 103-43 - Women and Health Research - NCBI Bookshelf
[11] https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation
[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations
[13] In August 2023, the FDA also released guidance on post-marketing approaches to obtain data on populations underrepresented in clinical trials, to acknowledge that despite the sponsor's best efforts, some populations may not be adequately represented in premarket clinical trials. Therefore, it can be appropriate to collect such data in the post-marketing setting. https://www.fda.gov/media/170899/download
[14] Diversity in Clinical Trials at FDA Gets a Boost From New Law (bloomberglaw.com)
[15] Diversity in Clinical Trials at FDA Gets a Boost From New Law (bloomberglaw.com



Challenges

But how easy is it really to increase diversity in clinical trials? Despite the most recent regulatory developments and the sector's long-standing expertise on designing and conducting clinical trials and patient engagement, it is likely that many drug companies and CROs will struggle to narrow the gaps between patient populations and trial populations. Below, we explain some key challenges that persist in attracting and retaining trial participants.

1. Trust – One of the most important factors that impedes people to participate in clinical trials is a lack of trust in the pharmaceutical sector. This is also known to be a critical factor in people's willingness to use drugs or receive vaccinations – for instance, the COVID-19 and the Human Papillomavirus (HPV) vaccines.[16] [17] [18] Black communities often reference particular historic events as a reason for distrusting the sector, such as the Tuskegee Syphilis study (see text box).[19] [20] [21]

Mistrust or distrust in the medical establishment can be exacerbated by the experience of racism, inequality and bias. When people have experienced this in previous encounters with healthcare practitioners, they can fear a similar experience in clinical trials, making them less likely to participate. Many underrepresented and underserved communities also point to an overall lack of representation in the medical sector. When patients interact with medical professionals from, for instance, their own communities or the same gender, they are more likely to trust them.

2. Health literacy – A crucial factor in attracting and retaining trial participants is health literacy. Health literacy is defined as the capacity to obtain, process and understand basic health information and services needed to make informed and appropriate health decisions. Lower health literacy is associated with lower income-levels and education, and appears to be more prevalent in minority groups, elderly and non-native speakers. The National Assessment of Adult Literacy Survey found that over a third of US adults has basic or below-basic health literacy.[22]

When people have a limited understanding of medical concepts, this can increase stress, confusion and anxiety. Together, these challenge the patient's ability to make informed decisions about a possible treatment and participation in a clinical trial.[23] Health literacy is also known to be an important factor in retaining patients during the trial. One reason why participants drop out of a study mid-way is that they did not sufficiently understand the purpose of the trial, the commitments and the outcomes prior to participating. Ensuring that patients fully understand what

[16] https://www.frontiersin.org/articles/10.3389/fpubh.2021.598625/full
[17] https://noelbrewer.web.unc.edu/wp-content/uploads/sites/16987/2022/03/2021_Calo.pdf
[18] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9033046/
[19] The legacy of the Tuskegee study - Harvard Global Health Institute
[20] https://www.cdc.gov/tuskegee/timeline.htm
[21] The legacy of the Tuskegee study - Harvard Global Health Institute
[22] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7889072/#:~:text=The%20National%20Assessment%20of%20Adult,%2C%202015%3B%20Berkman%20et%20al.
[23] https://journalforclinicalstudies.com/wp-content/uploads/2022/10/Improving-Health-Literacy-to-Transform-Clinical-Trials.pdf

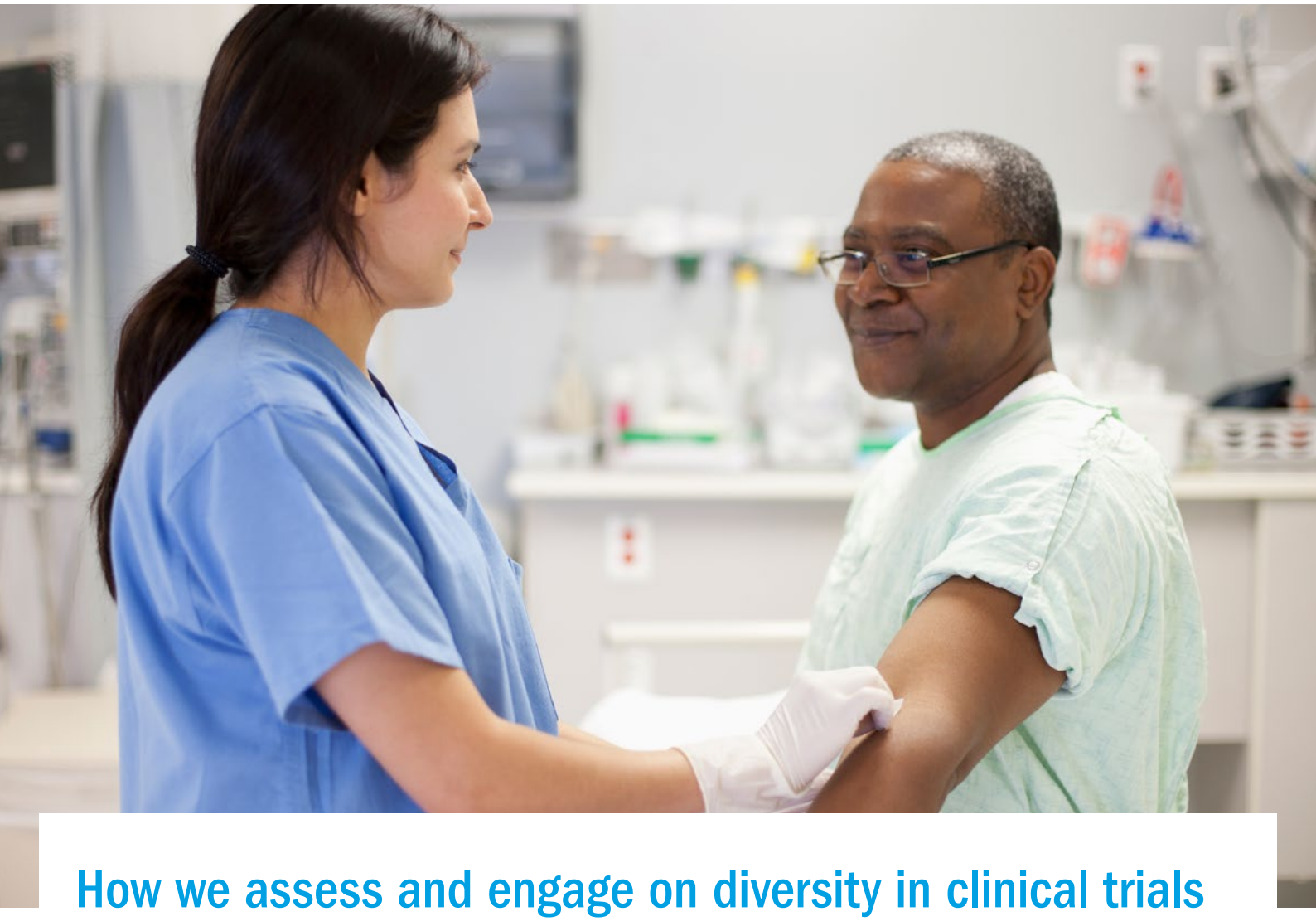
they sign up to requires a dedicated approach from sponsors and CROs but should have a positive impact on attraction and retention rates, patient engagement and patient experience, as well as reducing the risk of poor patient compliance with clinical trial instructions.

3. The complexity of trial design and execution – Pausing trials is a costly decision that directly impacts company's chances of developing successful drugs and therapies earlier than competitors. With increasing regulatory requirements, the case for early adoption and integration of diversity planning is clear. However, clinical trial protocols are not short of complexity, and including diversity plans might not always be straightforward. Taking into consideration that the industry experiences a shortage of investigators and trial locations,[24] increasing diversity in clinical trials will not happen overnight.

Furthermore, trial criteria are often very stringent and not susceptible to modification. Comorbidities, such as high blood pressure and diabetes, are often exclusion criteria, yet research shows that such criteria can contribute to enrolment disparities for racial and ethnic subgroups.[25] [26] Inclusion and exclusion criteria are strict for a very good reason, which is to protect and safeguard the patient's safety. However, sponsors and CROs are increasingly looking to challenge existing criteria to see whether some can be loosened or modified, without compromising patient safety.

Lastly, it may not always be as straightforward for patients to participate in clinical trials, even when they are fully aware and understanding of the benefits or when a trial might offer the last opportunity for a cure. Clinical trials are, more often than not, a time and cost-intensive process. Participating often requires people to travel to a site location, take time off work, arrange for childcare and pay for gas, etc. Lack of compensation or alternatives (such as decentralised trials or trial visits outside office hours) will prevent many eligible patients from participating. Reimbursement is sometimes legislated. Under the DIVERSE Trials Act, drug and device manufacturers are allowed to provide free digital health technologies and other remuneration to enable underrepresented communities to participate, regardless of socio-economic status.[27] [28] With the upcoming regulatory requirement, it remains vital for sponsors, CROs, patient advocacy groups and governments to work together to address these barriers for patients.

[24] Recruitment and retention of participants in clinical studies: Critical issues and challenges - PMC (nih.gov)
[25] https://ashpublications.org/blood/article/142/3/235/495571/Eligibility-criteria-and-enrollment-of-a-diverse
[26] https://ascopubs.org/doi/full/10.1200/JCO.22.00537
[27] S.2706 - 117th Congress (2021-2022): DIVERSE Trials Act | Congress.gov | Library of Congress
[28] Addressing ESG Risk in a Shifting Landscape for Clinical Trial Diversity (sustainalytics.com)



How we assess and engage on diversity in clinical trials

We invest in pharmaceutical companies and CROs worldwide. Since the beginning of 2023, we have engaged 12 investee companies to understand their approach to diversity in clinical trials, how they prepare for stricter regulation and how they address barriers to diversity in clinical trials.

Drawing on our conversations with these companies, as well as the available literature, we have developed the below overview of findings and evolving good practices. We are also pointing out a number of companies we believe show real leadership in some of these areas. As the industry is moving forward, we expect to refine this overview over time.

1. **Policy commitment and strategy** – Leading companies recognise the importance of matching trial participants with patient populations from both a commercial and scientific perspective. They publicly commit to improving diversity in clinical trials. (See, for instance, Eisai and Novartis, Roche and Sanofi.) The strongest policy commitments lay out how the company aims to achieve diversity in clinical trials and how to overcome challenges to attract and retain trial participants. See, for example, Moderna.

The Second Diversity in Clinical Trials Summit

In May 2023, we attended a two-day Summit on Diversity in Clinical Trials in Philadelphia. The Summit brought together companies, patient advocacy groups and professionals working in DEI, clinical trial research, site management and regulatory affairs. It was aimed to provide in-depth analysis and conversation about the necessity of diverse clinical trials; the role of partnerships with patient advocacy groups; the role of real-world data; and best practices and challenges. Speakers included Pfizer, Moderna, BioMarin, Bristol-Myers Squibb, Merck & Co., Abbott, GSK, AbbVie and Gilead. Outcomes and learnings from this Summit were used to further inform our conversation with companies and understand the complexity of the issue.

2. Governance of diversity in clinical trials – Leading companies that have committed to diversity in clinical trials have senior level involvement and dedicated resources to ensure successful execution of diversity in clinical trials commitments and targets. An example is Johnson & Johnson, who have a dedicated DEI in Clinical Trials team.

A number of companies with whom we spoke shared how diversity in clinical trials was started as a stand-alone project, which, over time, was integrated into the wider company strategy. We consider this a best practice. Diversity in clinical trials is a complicated effort involving cross-departmental collaboration and knowledge to effectively address all barriers and complexities in trial design and ensure compliance with (future) regulatory requirements.

3. Setting targets and tracking progress – The most robust diversity in clinical trial commitments are backed up by targets to ensure immediate action and a clear direction of travel. We encourage companies to set targets to prepare for upcoming regulation, and to be cognisant that targets are highly dependent on the diverse product portfolio of a company and directly influenced by the company's operational capacity and resourcing, as well as the above-mentioned challenges.

We have identified a number of companies that have set targets to achieve better representation in clinical trials. The nature of these targets can vary significantly, as showcased by the examples below:

- AbbVie set a goal to use a diversity plan template to create 16 indication-level diversity plans. It exceeded its goal and developed 19 plans.
- Bristol-Myers Squibb set a target to locate more than 25% of clinical trials in highly diverse regions in the US by 2025. In 2022, it exceeded its goal and had already located 58% of its trials in diverse regions.
- GSK aimed to ensure that over 75% of interventional clinical trials had a clear demographic plan aligned with disease epidemiology. It achieved the target, with 100% of phase III trials initiated in 2022 having proactive demographic plans in place.

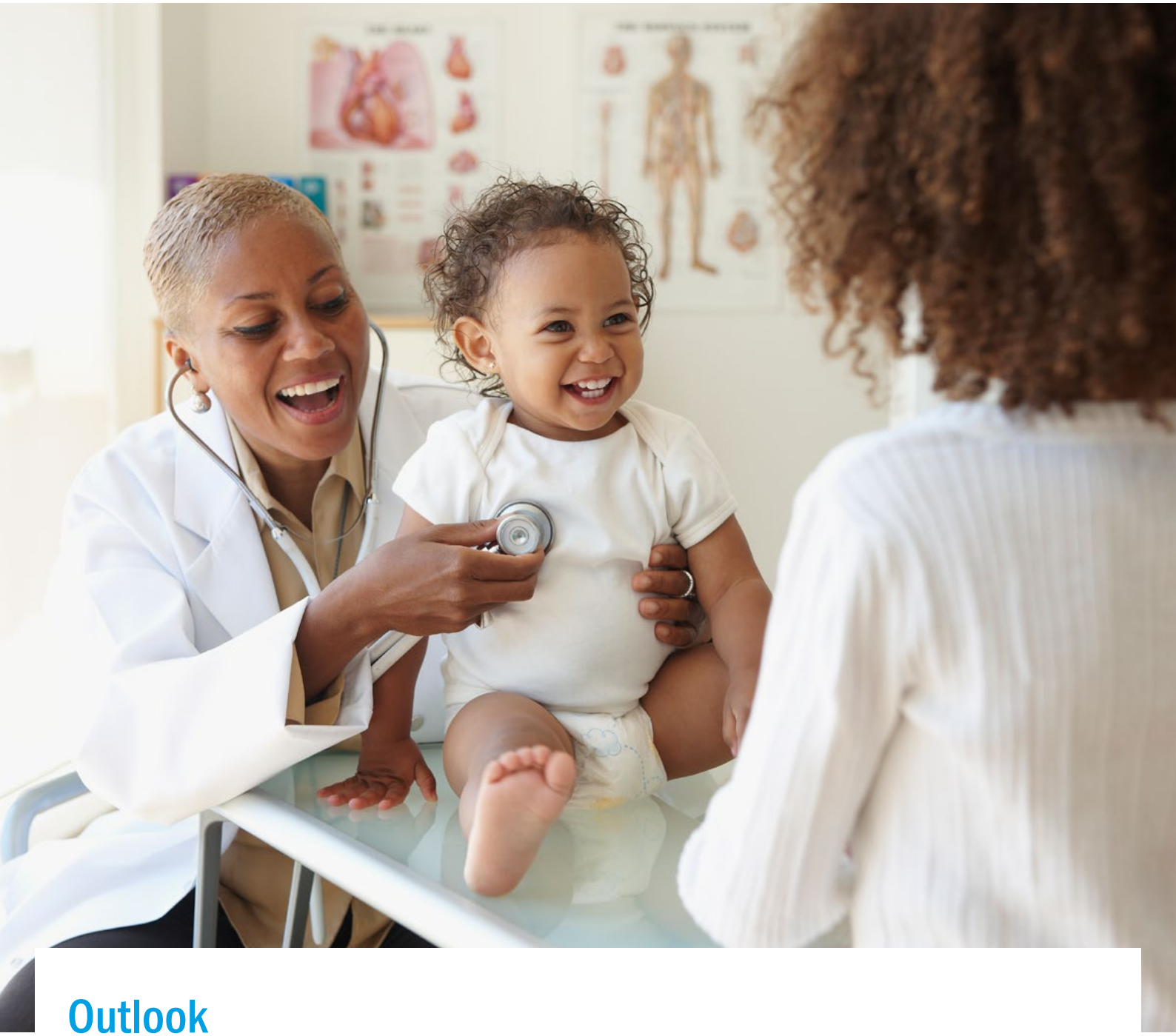
4. Stakeholder and community engagement – A crucial component of a diversity in clinical trials strategy is the close collaboration with patients, patient advocacy groups and trusted leaders. This has proved to be vital in building and gaining trust as well as further understanding patient needs and the specific barriers they face. In addition, there is an increasing body of academic literature that suggests community engagement is a key lever to address structural barriers such as trust and health literacy. For an example, see this article published in the Lancet Gastroenterology & Hepatology.

Working with patient advocacy groups is very common in the industry. What has proved to be key is to collaborate and communicate on an ongoing basis. Reaching out to the communities you aim to address close to the starting date of the trial is considered too late.

In our conversations with companies, it has become clear how indispensable these collaborations are for companies. We have been presented with great case studies of companies' engagement with patient groups and trusted community leaders. For an example, see Biogen.

5. Address systemic challenges – Sponsors and CROs can only increase diversity in clinical trials when they systematically address the underlying roadblocks to attracting and retaining (diverse) trial participants. In our conversations with companies, we have learned about great examples of health literacy programs, training programs for investigators from minority communities, bias training and the use of decentralised clinical trials to overcome time and resource constraints. An example that stands out is the Beacon of Hope Program – a collaboration between Sanofi, Novartis, Merck, Amgen, 26 Historically Black Colleges and Universities (HBCUs) and other stakeholders to address the root causes of disparities in health and education and to empower a next generation of clinical trial investigators.

Since the beginning of 2023 we've engaged with 12 companies to understand their approach to diversity in clinical trials.



Outlook

To stay ahead of evolving regulation and increasing commercial risk, we encourage companies to make full use of industry best practices and collaborations to assess and improve diversity in clinical trials. With FDA guidance still being finalised, some companies might take a 'wait and see' approach. However, as highlighted in this viewpoint, diversifying clinical trials is a marathon, not a sprint. It takes time to build trust and address the systemic barriers to attraction and retention of participants. Our findings and identified good practices are shared with our investee companies and we will continue this insightful dialogue.

We encourage companies to make full use of industry best practices.

Meet the authors

Ellen Brauers, Associate, Responsible Investment

Ellen is an ESG analyst in the Responsible Investment team and covers engagement with healthcare, pharmaceutical and life sciences companies. She also leads the team's work on public health. Ellen started her career as a researcher at Wageningen University (NL), researching and teaching on corporate accountability, human rights and modern slavery. After, she worked for two Dutch financial institutions as a human rights advisor. She holds a Bachelor's and Master's degree in International Development from Wageningen University and is fluent in Dutch, English and French.

Contact us

columbiathreadneedle.com

Follow us on LinkedIn

To find out more visit **columbiathreadneedle.com**

COLUMBIA THREADNEEDLE INVESTMENTS