Increasing Diversity in Clinical Trials: FDA Guidance and Industry Efforts

Medmarc Risk Management Webinar Series

October 2022

Topics

Context

Latest FDA Draft Guidance regarding submission of a Diversity Plan for Clinical Trials

Obstacles to diversity in clinical trials

Industry efforts

Recommendations to improve diversity

Why it matters

Why diversity in clinical trials matters

When some groups are underrepresented in clinical trials, there is a risk of collecting insufficient data to assess their effectiveness or safety in those populations.

Racial and/or ethnic background, in combination with other interdependent factors including social determinants and genetics, can contribute to differences in responses to diagnostics and/or treatment.

Clinical research contributes to scientific knowledge for treatment options that may potentially benefit patients, physicians, and the broader research community in the future. Equitable access to clinical trials is integral to achieving health equity.

Haque W, Ahmadzada M. Lack of diversity in clinical trials: the problem and potential solutions. Hopkins Biotech Network. Published November 20, 2020. Available at: https://hopkinsbio.org/academic/diversity-in-clinical-trials/; Ramamoorthy A, Pacanowski MA, Bull J, et al. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clinical Pharmacology & Therapeutics. 2015;97(3):263-73. doi:10.1002/cpt.61. Epub 2015 Jan 20. PMID: 25669658.

Example: Unrecognized Differences May Present Risks

Dec.17, 2020

The NEW ENGLAND JOURNAL of MEDICINE

Racial Bias in Pulse Oximetry Measurement

TO THE EDITOR: Oxygen is among the most frequently administered medical therapies, with a level that is commonly adjusted according to the reading on a pulse oximeter that measures patients' oxygen saturation. Questions about pulse oximeter technology have been raised, given its original development in populations that were not racially diverse.[1,2] The clinical significance of potential racial bias in pulse oximetry measurement is unknown.

Thus, in two large cohorts, Black patients had nearly three times the frequency of occult hypoxemia that was not detected by pulse oximetry as White patients. Given the widespread use of pulse oximetry for medical decision making, these findings have some major implications, especially during the current coronavirus disease 2019 (Covid-19) pandemic. **Our results suggest that reliance on pulse oximetry to triage patients and adjust supplemental oxygen levels may place Black patients at increased risk for hypoxemia.** It

FDA Reaction

Pulse Oximeter Safety Communication Updated with Advisory Committee Meeting Information

The U.S. Food and Drug Administration (FDA) is announcing a virtual meeting of the CDRH Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee on November 1, 2022, from 9 a.m. to 6 p.m. Eastern Time.

The committee will discuss ongoing concerns that pulse oximeters may be less accurate in individuals with darker skin pigmentations. The committee will also discuss factors that may affect pulse oximeter accuracy and performance, the available evidence about the accuracy of pulse oximeters, recommendations for patients and health care providers, and the amount and type of data that should be provided by manufacturers to assess pulse oximeter accuracy and to guide other regulatory actions as needed.

Example: Differences in drug effectiveness

Phase 3 trial of monotherapy ARB to lower blood pressure with intentional efforts to enroll more Black patients

Renin aids in controlling sodium

Black population more commonly have low renin

Black people in US have earlier disease onset, increased severity and comorbidities

Treatment was less effective in Black subjects – which was added to the label

Leads to trial of combination therapy specifically designed to address population-based differences

Diuretic that addressed low renin added

Treatment resulted in similar effect among Black and non-Black subjects

This information was added to the label

Case example: Azilsartan medoxomil (Edarbi®) & Azilsartan medoxomil/chlorthalidone (Edarbyclor®)

Azilsartan medoxomil (Edarbi®) is an angiotensin-II receptor blocker (ARB) used to treat hypertension in adults.[56] Designs of Azilsartan medoxomil phase 3 monotherapy trials were intentionally inclusive of Black patients, a population that more commonly exhibits low renin (the enzyme critical to helping control sodium balance) and reduced response to ARBs. The phase 3 trials of Azilsartan medoxomil did show a reduced effect in Black patients, a finding that is reflected in the prescription label, but was still safe and effective in reducing blood pressure regardless of age, sex, or race. Azilsartan medoxomil was approved by the FDA.

When investigating combination therapy for azilsartan medoxomil, developers specifically selected a diuretic that would accentuate the effect of the ARB in patients with low renin. Azilsartan medoxomil in combination with chlorthalidone (Edarbyclor®), was the most effective combination. In fact, wording in the drug product labeling states, "Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients; however, the blood pressure effect of Edarbyclor in blacks is similar to that in non-blacks."[57]

Bierer B.E., White S.A., Meloney L.G., Ahmed H.R., Strauss D.H., Clark L.T., (2021). Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document Version 1.2. Cambridge and Boston, MA: Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). Available at: https: https://mrctcenter.org/diversity-in-clinical-research/

2017 Guidance: Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies

While the U.S. population demographic is changing, diverse representation in clinical trials remains a challenge, and inconsistent analysis and reporting contributes to a persistent lack of publicly available data on device performance in diverse ethnic and racial groups. The 2013 FDASIA 907 Report showed a distinct lack of publicly reported race- and ethnicity-specific data for medical devices.[19] Only 27% of the studies reviewed contained a race- or ethnicity-specific subgroup analysis, and only 16% had public statements regarding a race- or ethnicity-specific analysis.

There are several devices where differences in effect were observed that were correlated with race and ethnicity. For example, differences in skin structure and physiology can affect response to dermatologic and topically applied products.[20] Mortality rates of patients on dialysis have been shown to differ across racial and ethnic groups.[21] FDA encourages sponsors to collect race- and ethnicity-specific data according to the recommendations in the FDA Guidance *Collection of Race and Ethnicity Guidance Document*.[22]

Prior FDA Actions

1997	FDA Modernization Act updated to include a clause around developing guidance, as appropriate, on the inclusion of women and minorities in clinical trials
2010	FDA established its Office of Minority Health with the goal of reducing health disparities among racial and ethnic minorities
2012	Food and Drug Administration Safety and Innovation Act (FDASIA) directed FDA to examine racial and ethnic subgroup data in new product applications and publish its findings
2014	FDA published its Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data, prioritizing the improvement of completeness and quality of demographic subgroup data, the identification of barriers to subgroup enrollment in clinical trials and development of strategies to encourage participation, and an increase in availability and transparency of subgroup data

FDA Drug Trial Snapshots and Summary Reports

2015	Initiation of FDA Drug Trial Snapshots: Database for each novel drug approved within a month of the official approval; provides statements on whether there were any observed differences in safety and efficacy by demographic subgroups at the time of approval.

Figure 2. Demographic Subgroups in 2015

DEMOGRAPHIC SUBGROUPS	WOMEN	AFRICAN AMERICAN	ASIAN	WHITE	OTHER*	AGE 65 and OLDER	AGE 75 and OLDER**	AGE 80 and OLDER**
PARTICIPANT AVERAGE	40%	5%	12%	79%	4%	37%	15%	6%

Table 1. Percent Participation in Clinical Trials by Subpopulation* for New Molecular Entities and Therapeutic Biologics Approved in 2020

	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 AND OLDER	UNITED STATES
AVERAGE	56%	75%	8%	6%	11%	30%	54%

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Prior FDA Actions

2016	FDA Guidance: Collection of Race and Ethnicity Data in Clinical Trials
2017	FDA Guidance: Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies
2020	2020, FDA Guidance: Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs

FDA Draft Guidance: April 2022

Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

What the Draft Guidance does

Draft Guidance provides recommendations to companies conducting clinical trials on how to create a Race and Ethnicity Diversity Plan to enroll representative numbers of participants from underrepresented racial and ethnic populations in the US, such as Black or African American, Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islanders, and other persons of color, in clinical trials.

Other Guidances address diversity of age, pregnancy, gender, etc.

FDA Draft Guidance: Submission of Diversity Plan

Recommends submitting a Diversity Plan for products requiring an IND or IDE and/or for which clinical trials are intended to support marketing submissions for a BLA, or for an NDA

Suggests submitting Diversity Plans early in development process

For drugs, no later than when a sponsor is seeking feedback for applicable pivotal trials (usually the End-of-Phase-II meeting)

For devices, as part of the investigational plan included in the IDE application

Diversity Plan should also be included in the marketing application, along with a description of the successes and challenges of implementing it

Elements of Diversity Plan

1. overview of the disease/condition;
2. scope of the medical product development program;
3. goals for enrollment of underrepresented racial and ethnic participants;
4. a specific plan of action to enroll and retain diverse participants; and
5. status of meeting enrollment goals (as applicable).

1. Overview of Disease/Condition

Describe available data on the pathophysiology of the disease/condition in underrepresented racial and ethnic populations. As appropriate, include any disparity in the application of currently available prevention, screening or diagnostic strategies or treatment strategies across racial and ethnic populations.

Discuss the current understanding of and available evidence supporting similarities and/or differences in the disease/condition associated with underrepresented racial and ethnic populations in the US.

2. Scope of Development Program

Describe the planned trials that will support the product's safety, effectiveness and, if a drug, dosage in a future marketing submission.

Outline:

study design, population (including eligibility criteria), endpoints, and expected geographic locations and how these aspects may specifically address inclusion of underrepresented populations.

any applicable differential findings from clinical pharmacology studies associated with certain racial and ethnic populations.

3. Goals for Enrollment

Define and justify the planned enrollment of participants from underrepresented racial and ethnic populations

Specify the underrepresented populations based on assessment in Category 1.

Specify goals for enrollment of the underrepresented population based on information that may impact outcomes, and whether greater than proportional enrollment of certain populations is necessary to identify important differences among populations.

4. Specific Plan of Action to Enroll & Retain

Describe the operational measures that will be implemented to enroll and retain underrepresented participants in the planned trials, and the planned use of data to characterize safety, efficacy, and dose, when applicable.

Describe specific enrollment and retention strategies, including:

site location and access,

sustained community engagement,

reducing burdens due to trial design (e.g., number of study-related procedures, the use of local labs and imaging, telehealth)

Describe metrics to ensure diverse participant enrollment goals are achieved and specify actions to be implemented during the trial if those goals are not met.

5. Status of Enrollment Goals

Discuss the current status of meeting the stated goals and a plan and justification for collecting data in post-marketing if the enrollment goals are not achieved.

Obstacles

Obstacles to diversity in clinical trials

Mistrust

Access

Trial availability

Costs of participation

Enrollment practices

Eligibility

Bias

Industry Efforts

AdvaMed Principles on Health Equity: 2020

Responding To Racial Disparities In Health initiative

AdvaMed issued four Principles on Health Equity to promote inclusion and equity in healthcare and research in the medtech industry

Principle 4: Promoting Research Equity in MedTech

4. PROMOTING RESEARCH EQUITY IN THE MEDTECH INDUSTRY

Principle: AdvaMed and its members promote innovation in medical technology development and design. Our methods for researching and developing these technologies should reflect the population of patients that will benefit from them. We will commit to the adoption of methods that promote improved recruitment of potential patients for clinical trials and medical device development.

Considerations: Policy should account for historic distrust on the part of some populations due to racially biased treatment in the past. Efforts will require engagement and partnership with other caregivers and groups to bridge the gap and promote the need for involvement in studies and research to include more diversity among investigators. This work may also involve alignment and partnership with groups specifically advancing the need for diversity among clinical investigators. Policy should be reflective of the need for innovative approaches to recruit and monitor subjects, including the use of primary care providers and the use of telehealth and digital medicine.

AdvaMed Report on Increasing Diversity in Clinical Research: 2022

AdvaMed partnered with Meharry Medical College, an HBCU in Nashville, on a workshop series convened in April, May, and June of 2021 that focused on increasing diversity in clinical trials

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PhRMA Principles To Enhance Diversity In Clinical Trial Participation: 2020

At the core of these principles is the need for the industry to better serve historically underserved populations. By committing to enhancing diversity in clinical trial populations, we can better reflect the patients that will use the new therapy or medicine being studied and solve for improved health outcomes. For example, different populations may be at higher risk for certain diseases, such as sickle cell disease, diabetes or heart disease. Clinical trials for the development of new medicines for those diseases should aim to reflect the patient population they are aiming to help. Ultimately, diverse clinical trials support a better understanding of the medicine. This is one way the industry can improve the care for the patients we serve.

PhRMA

PRESS RELEASE July 19, 2022

PhRMA Joins Top Academic Leaders to Announce New Community-Based Initiative to Enhance Clinical Trial Diversity

First-of-its-kind initiative seeks to build trust and address systemic barriers to participation in the development of innovative medicines

Community-based trial sites will:

- Partner with trusted messengers and community leaders to raise education, awareness, and support for clinical trial participation
- Provide resources and technical support for local sites to be successful and sustainable long term
- Build training opportunities and mentorship for investigators and staff
- Create a comprehensive, collaborative network of sustainable, connected, community-based sites supporting clinical trial diversity in underserved communities

- PhRMA grant to support initiative: the ***Equitable Breakthrough in Medicine Development***

- Yale School of Medicine
- Morehouse School of Medicine
  - the Research Centers in Minority Institutions Coordinating Center at Morehouse School of Medicine, and
- Vanderbilt University Medical Center

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Recommendations to improve diversity in clinical trials

FDA Guidance mentions some steps companies can take

Reimbursement for expenses incurred by participation in a clinical trial or study (e.g., travel or lodging)

Providing language access to participants with limited English language proficiency

Partnering with community-based organizations to provide support to study or trial participants

AdvaMed Recommendations

Be aware of historical biases that exist in clinical research and potential mistrust of the healthcare system by underrepresented populations.

Have intentional conversations with company leadership and various stakeholders to highlight the potential impact of the lack of diversity in current trials. Develop goals to broaden evidence generation efforts to include a more diverse patient population in clinical research and measure your progress.

Use a variety of available tools to adequately define the targeted patient population, including leveraging RWD sources.

Create a sustainable community of researchers. Partner with more community-based clinicians. Coordinate with clinical investigators to inform other local clinicians of study opportunities to support diverse enrollment.

Be prepared to go to the patient by broadening the types and locations of the trial sites and diversity of investigators.

Understand the importance of building trust in recruiting diverse participants: between patients and clinicians, companies and clinical investigators/sites, and companies and communities.

AdvaMed Recommendations

- **Identify aspects of study design (e.g., inclusion/exclusion criteria, follow-up visits requirements) that may undermine efforts to increase diverse participation**
- **Offer more direct and clear communications about the importance of diversity for the study with the principal investigators (PIs)**
- **Support sites with development of cultural and linguistically appropriate outreach and study information/materials**
- **Consider additional/alternative sites, if current sites are not best suited to recruit and/or retain diverse participants**
  - Consider trial sites closer to minority patient communities
- **Address logistical challenges like limited office hours and locations may lead to loss of patients for follow-up**
  - Consider use of remote visits or visiting nurses where possible

PhRMA Recommendations

Establish policies or practices specifically focused on enhancing the diversity of clinical trial populations, and consider making them public

Enhance education and increase clinical trial awareness through community outreach

Identify sites where diverse patients with a particular disease or condition are located

Collaborate with investigators to address the goals of enrolling a diverse population

Involve patients, patient advocates, and caregivers from underrepresented groups in the trial design process

Consider recruitment challenges and enrollment barriers: planned visit schedules, location, financial implications, and how these factors might be addressed through flexible scheduling and utilizing digital technologies (e.g., mobile tools and wearable technologies to gather data from participants, decentralized or virtual trials)

Consider the incidence, prevalence, and severity of the condition or disease in various populations, as well as other prognostic factors that might influence the response to any intervention or outcome variable

Use information on the populations at risk for a particular disease to enhance understanding of the heterogeneity of treatment effect, or lack thereof, for selected subgroups, to broaden the inclusion and exclusion criteria

Continue to gather data about how a treatment or preventative measure works in certain diverse populations after a medical product is approved

MRCT Suggestions

Utilize diverse traditional & social media outlet; incorporate community engagement

Prior to finalizing protocol assess screening & eligibility criteria to ensure not unduly restrictive

Consider multi-lingual translations

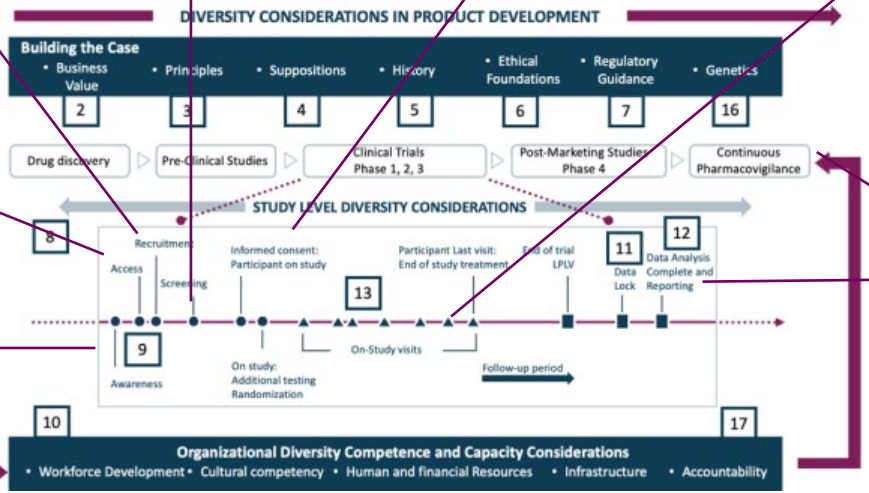
Incorporate decentralized or hybrid trial options to reduce study travel burden

Ensure sites reside in diverse locations

Incorporate diverse patient imagery into trial awareness materials

Analyze safety, efficacy data along sub-populations most impacted by disease

Figure A: Layout of the Framework



Bierer B.E., White S.A., Meloney L.G., Ahmed H.R., Strauss D.H., Clark L.T., (2021). Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document Version 1.2. Cambridge and Boston, MA: Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). Available at: https: https://mrctcenter.org/diversity-in-clinical-research/

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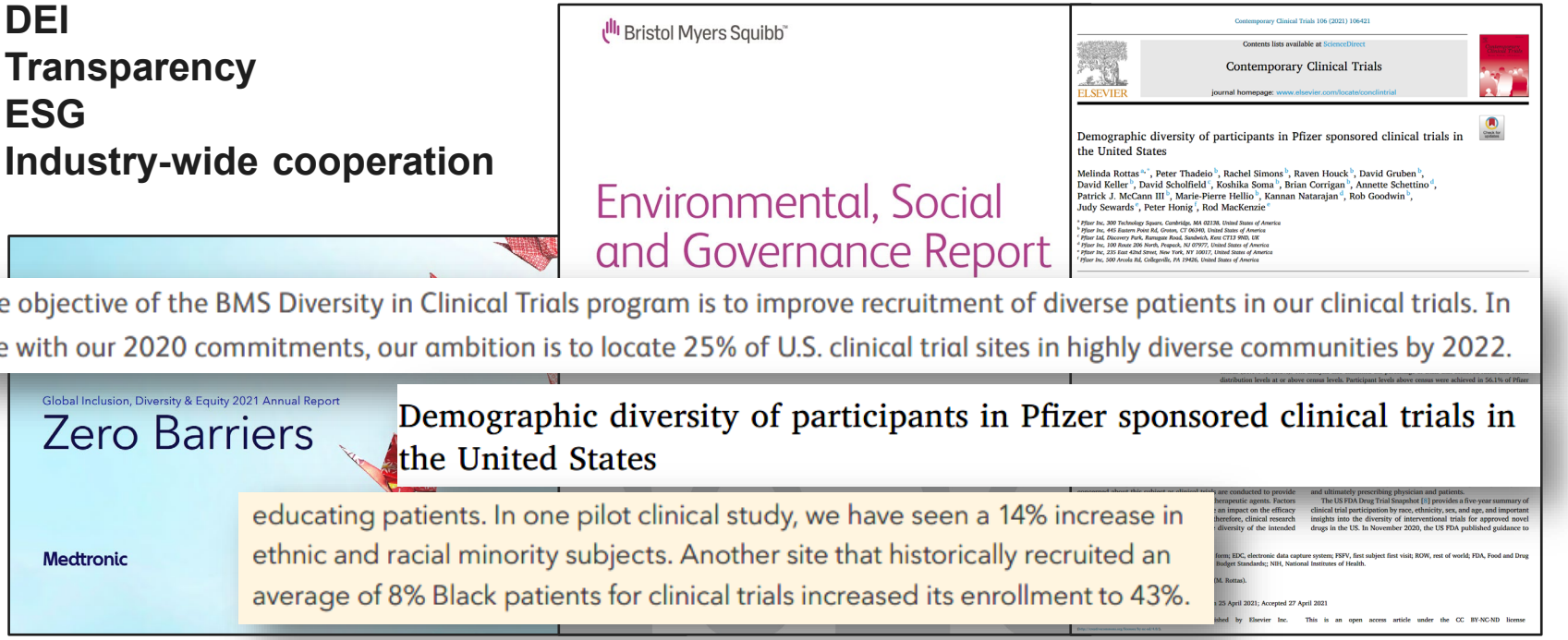
Additional Issues

Relationship to Other Corporate Goals

- DEI
- Transparency
- ESG
- Industry-wide cooperation



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What about paying for more than travel?

FDA does not consider reimbursement for reasonable travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence.*

But what about lost work time? Child care? Elder care?

FDA recognizes that payment for participation may raise difficult questions that should be addressed by the IRB, such as how much money participants should receive for participation, what they should receive payment for (e.g., time, inconvenience, discomfort, or some other consideration)*

Payment to research subjects for participation in studies is not considered a benefit that would be part of the weighing of benefits or risks; it is a recruitment incentive. IRBs should be sensitive to whether other aspects of proposed payment for participation could present an undue influence, thus interfering with the potential subjects' ability to give voluntary informed consent.*

* Draft Guidance: Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry (April 2022), pg. 4, footnote 12. FDA website. https://www. https://www.fda.gov/media/157635/download. See Information Sheet "Payment and Reimbursement to Research Subjects" (January 2018) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects.

What about waiving cost-sharing?

Remuneration paid to subjects in clinical trials, whether direct (compensation) or through the waiver of cost-sharing responsibilities under private or government insurance, may be viewed as an inducement

We typically worry about the Office of Inspector General (OIG) considering waiver of insurance cost-sharing for clinical research participants as potential inducement:

"[M]any clinical trials . . . will study items and services for which there are effective, well-established treatments already available. In such cases, enrollees could well be induced to forgo equally effective or more appropriate care. . . . Payments to providers and participating patients potentially present a risk of fraud and abuse." See OIG Advisory Opinion No. 04-01.

OIG issued 2 advisory opinions in the last year stating it would not impose administrative sanctions against entities subsidizing participants' out-of-pocket expenses, including Medicare cost-sharing obligations, specifically citing the sponsor's goal of increasing diversity among study populations to support its conclusion. See OIG Advisory Opinion No. 21-13 and No. 22-05.

Questions?

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