

Inclusive infrastructure for clinical trials

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The National Institutes of Health (NIH) operates with a two-part mission: to seek “fundamental knowledge” about living systems, and to apply this knowledge to enhance human health (NIH, 2022a). The agency’s success on the first dimension is striking: to take one example, recent estimates suggest that nearly all new medicines approved in the United States draw, in some form, on NIH-funded research (Cleary et al., 2018).² However, the persistent exclusion of racial and ethnic minority groups from medical research limits meaningful progress on the second dimension (NIH, 2022b; NASEM, 2022).

Although policymakers have faced pressure to address the informational inequality that results when certain groups are excluded from the evidence base, the intersecting causes of these disparities pose challenges for the design of reforms. Figure 1 illustrates one source of complexity: representation in clinical trials – relative to population share (Panel A) and disease burden (Panel B) – varies considerably across diseases. Consider cancer and HIV/AIDS, disease areas with large-scale impacts on morbidity and mortality and research environments supported by large federal institutes. In both cases, Black Americans experience excess mortality relative to their White counterparts, and investigators draw on resources provided by decades-old networks of federally funded research centers. Yet, Black Americans are well-represented in HIV/AIDS trials and poorly represented in cancer trials.³

This paper presents evidence on aspects of existing clinical research infrastructure – namely, trial site selection and patient recruitment protocols – that may explain these differences. I draw on historical case studies and clinical trial data to identify opportunities for reform. I conclude by highlighting forms of targeted NIH investment that are well-suited to this context.⁴

¹This paper draws heavily from Alsan et al. (2022). I am very grateful to Ezekiel Emanuel, Douglas Lowy, Lisa Larrimore Ouellette, Caleb Watney, Heidi Williams, and participants at the Brookings / Institute for Progress / Good Science Project meeting on “Building a Better NIH” for helpful comments and conversations.

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² Alternative approaches to measuring the contribution of public research to drug development yield different estimates. See Sampat and Lichtenberg (2011) and Cleary et al. (2018) for two distinct versions of this exercise.

³ Differences in representation persist when estimates are scaled to reflect disease incidence by race.

⁴ My examples focus on the inclusion of Black Americans, whose persistent underrepresentation in medical research should be interpreted in light of historical *overrepresentation* during episodes of medical exploitation. Trends are similar for other excluded groups, including Hispanic and Native American populations, and proposed policy levers remain applicable.

1. Trial Site Selection

The location of a clinical trial has real implications for its ability to produce representative evidence. Two aspects of trial location are of particular importance: whether a trial site is in the United States and whether a trial site is accessible – in terms of physical location and services offered – to patient populations.

1.1 International Site Selection

New drugs marketed in the U.S. are often approved on the basis of clinical tests conducted outside of the country. Between 2017 and 2020, the median clinical trial supporting a new drug application to the U.S. Food and Drug Administration (FDA) enrolled 64% of patients at foreign sites. Only 13% of these trials exclusively enrolled patients in the U.S. (FDA, 2022).

The rationale for this “offshoring” of clinical research is simple: trials outside of the U.S. are often substantially cheaper for sponsors. Qiao et al. (2019) estimate that trials conducted in Central Europe are 50% cheaper than trials in North America. Qualitative evidence suggests that cost savings stem from differences in the time required to complete trials. In particular, the existence of national health care systems in some countries allows firms to identify and recruit eligible patients more quickly (Petryna, 2009). Until recently, the FDA has approved drugs that recruited nearly all patients outside of the U.S. without objection. In February 2022, however, an FDA panel rejected an application from Eli Lilly for sintilimab, a cancer drug, on the grounds that trials had occurred only in China. The panel justified its decision by noting that regulators “clearly heard from all patient groups that they want faces like theirs” in trials (Kolata, 2022).

Of course, offshoring need not *mechanically* affect representation. In principle, trial sponsors could recruit patients across sites to perfectly mirror the eventual patient population. In practice, this is not the case. Figure 2 indicates that, for a given new drug approval, there is a strong negative relationship between the share of patients recruited outside of the U.S. and the share of Black patients.

Several aspects of the clinical trials ecosystem support the hypothesis that offshoring allows firms to reduce costs. Figure 3 displays differences in trial offshoring across sponsors. Trials that take longer to complete – and so are more expensive for private firms – are more likely to be conducted outside of the U.S. While government- and university/nonprofit-sponsored trials are less likely to recruit patients at foreign sites for longer trials, industry-sponsored trials are more likely to be offshored as they increase in duration. Similarly, drugs that require long clinical trials to establish effects – such as therapies for some cancers and neurological diseases, or vaccine candidates – may be more likely to be approved based on foreign data.

1.2 Accessible Site Selection

Although changes in the incentives to offshore clinical trials may be a necessary step toward improving representation, data on domestic trials suggest that this may not be sufficient. Differences in the demographic composition of cancer and HIV/AIDS trials, as described in the introduction, underscore the importance of selecting sites that are *accessible* to patient populations, in terms of both physical location and services offered.

There are institutional similarities across cancer and HIV/AIDS clinical trials. Drugs for both are, largely, approved in the U.S. based on domestic trial data. This reflects decades of federal investments into research networks across the country by two NIH centers: the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID). 71 dedicated research centers co-organize cancer trials (NCI, 2019), and 108 co-organize trials for HIV/AIDS (NIAID, 2017).

Investment in cancer research was driven by a series of policy changes in the 1970s, including the National Cancer Act of 1971, often considered the beginning of the “War on Cancer.” Various federal initiatives established new research centers, expanded the scope of NIH facilities across the country, and encouraged the development of public-private partnerships. Today, trial sites for cancer are typically located in these research centers at academic medical schools (Mukherjee, 2010).

In contrast to the top-down development of infrastructure for cancer, HIV/AIDS research has been defined by a series of campaigns that advocated for active community involvement. As one example, in the 1980s, following allegations of lack of transparency and insufficient scientific progress, the AIDS Clinical Trials Group (ACTG) invited community members to attend their meetings. Grassroots political organizations were instrumental in affecting funding priorities and regulatory reform in the 1990s, including changes in trial protocol design (Epstein, 1996). By 1990, ACTG had adopted the practice of seeking community involvement at each trial site when developing protocols; in parallel, since 1990, NIAID has required that all sponsored trials studying HIV/AIDS include explicit community engagement plans drafted in conjunction with community advisory boards (CABs) (Strauss et al., 2001). Of this phase in HIV/AIDS research, John Phair, M.D., director of ACTG sites in Chicago, notes:

I remember when one of the activists came up to me during the first ACTG meeting in Washington, D.C. that included community members. He said he was discouraged because he was convinced we had some treatment we were withholding. After attending our scientific sessions, he realized there was no such magic treatment and that this was just going to take a lot of hard work and time. Dr. [Anthony] Fauci had been correct: *including the community was necessary to diffusing [sic] these myths about research and to inform it.*⁵

As Royles (2020) details, community leaders pushed back against the narrative of HIV/AIDS as a “white gay disease” and worked to ensure that communities that many attempted to write off as too difficult to reach or engage with were adequately represented.

According to interviews with the HIV Vaccine Trial Network, described in Alsan et al. (2022), this process of community engagement has affected two features of trial site accessibility. First, site locations are more likely to be selected in conversation with community partners. Second, protocols are designed to identify, recruit, and support patients from many demographic groups.

These qualitative differences between cancer and HIV/AIDS translate into economically important demographic gaps in recruitment. Table 1 documents that, among 201,432 U.S.-based trial sites, sites that study drugs for HIV/AIDS are 25 percentage points more likely to be in a zip code with a safety net hospital than sites that recruit for cancer. This fact is consistent with the idea that cancer and HIV/AIDS trials recruit patients with different demographic characteristics and that HIV/AIDS trials may be more accessible to populations historically excluded from health care. These differences in location translate, in turn, into differences in patient composition. Figure 4 provides evidence of a large positive relationship between the share of Black residents in the zip code of a clinical trial site and the share of Black patients enrolled in the trial.

In recent years, cancer research centers have implemented a variety of initiatives aimed at boosting recruitment from underrepresented communities – including the NCI Community Oncology Research Program.⁶ The diverging narratives presented about cancer and HIV/AIDS, however, highlight the

⁵ Reproduced from <https://actgnetwork.org/about-the-actg/#1571861045262-d77c068f-657a>, with emphasis added.

⁶ The National Cancer Institute Community Oncology Research Program is tasked with leading

extent to which large-scale investments in inclusive aspects of trial infrastructure as a whole – as opposed to more localized interventions – can be crucial in meeting policy goals. As in the case of trial offshoring, one takeaway from this section may be summarized in terms of costs: a large stock of existing investments has rendered it substantially easier (less costly) to recruit a representative sample for an HIV/AIDS trial than for a cancer trial.⁷

2. Connecting Patterns to Policies

2.1 Implementing Representation Requirements

The most straightforward option available to the NIH is to require all sponsored trials to meet minimum standards for appropriate representation. While specific benchmarks will vary across diseases and patient populations, the agency can require all funded researchers to submit plans outlining intended recruitment strategies – as the NIH Clinical Trial Diversity Act of 2022, introduced during the 117th Congress, proposed.⁸ Given the evidence presented on trial offshoring in Section 1.1, any such requirements should also restrict the extent of foreign data collection, although subsidies aimed at curbing specific instances of offshoring – such as in the collection of data for drugs intended to meet unmet medical needs in the U.S. – may also be effective.⁹

Both requirements will have the effect of shifting some studies conducted by federally funded researchers to domestic sites and, for this reason, are worth implementing. However, as nearly 40% of trials subject to regulation by U.S. agencies are sponsored by private firms, according to ClinicalTrials.gov, the effect of such a policy may be limited in scope (National Institutes of Health, n.d.). Moreover, if pursued in isolation, such a strategy would neglect the many health technologies with roots in NIH-funded research, which are “commercialized” by the private sector. The remainder of this paper focuses on opportunities for NIH investments that aim to improve features of the clinical trial ecosystem as a whole.

2.2 Investing in Patient Registries

Trial recruitment depends, in large part, on how potential patients are identified. In the United States, physicians typically identify candidates for active trials (George et al., 2014). If historically underrepresented populations have more limited access to academic medical centers where referrals are made, or if physician biases affect referral patterns, network-based recruitment can make it challenging for trial sponsors to identify diverse set of patients. As described in Section 1.1, qualitative evidence suggests that firms may prefer to conduct trials outside of the U.S. because centralized patient registries – a feature of national health care systems – facilitate rapid identification and recruitment of patients (Petryna, 2009).

trials in communities across the United States, with a particular focus on recruiting patients from under-represented groups. See <https://ncorp.cancer.gov/about/> for details. The NCI Center to Reduce Cancer Health Disparities is tasked with similar policy goals. See <https://www.cancer.gov/about-nci/organization/crchd>.

⁷ This intuition motivates our theoretical and experimental work in Alsan et al. (2022).

⁸ The full text is available here: <https://www.congress.gov/bill/117th-congress/house-bill/7845/actions?r=1&s=1>.

⁹ In the context of this proposal, the purpose of reducing offshoring is narrow: to improve representation of U.S. patient populations, who are nearly always excluded when trials are conducted in, for example, Central Europe or Asia. Data need not be wholly domestic to satisfy goals of adequate representation, and globalization of clinical trials has likely been important in making progress on global public health goals. It may be useful to note that the FDA is already empowered to impose rules around offshored data. The U.S. Code of Federal Regulations 21 CFR §314.106 permits the FDA to approve a drug on the basis of entirely foreign data *if* the resulting evidence is deemed “applicable to the U.S. population and U.S. medical practice.” Of course, this does not preclude independent action by the NIH.

The NIH should develop a set of resources that function similarly to a centralized patient registry. At present, the NIH maintains a list of patient registries that include individuals who have agreed to participate in clinical trials.¹⁰ As a first step, the agency should audit these existing lists to determine two facts: how often, and by whom, registries are used; and whether existing registries would enable trial sponsors to meet the “representation requirements” outlined in Section 2.1.

Based on the findings of this audit, the NIH should develop centralized, disease-specific registries of potential patients, which address any underrepresentation at this preliminary step.¹¹ By constructing a registry of patients who are likely to be eligible for trials, the agency will take on the responsibility of supporting patients as they make decisions about whether to participate in medical research in general. As patients from historically underrepresented groups may be more hesitant to participate, this preliminary recruitment to the registry itself shifts the burden from trial sponsors to agency staff (see, for example, George et al., 2014; Alsan et al., 2022).

An open-access registry would make it less costly to recruit representative patient samples on two margins. First, it will enable sponsors to identify a set of individuals who meet the eligibility criteria for a given trial quickly, thus eliminating the need to build networks of physicians and search for individual patients. Second, sponsors can focus on the “last-mile” of recruitment: convincing eligible and interested patients to enroll in a particular trial. In turn, the NIH can ensure – through the process of constructing patient registries and monitoring their usage – that agency goals for representation in research can affect a larger set of U.S.-based trials.

To pilot such a strategy, the NIH should leverage existing state registries – such as the California Cancer Registry – that record whether patients are willing to participate in clinical studies.¹² Registry data should be made available to all researchers who commit to using these records to meet minimum standards for representation in any associated studies. In tandem, the NIH should use this pilot as an opportunity to document evidence on the strengths and challenges of registry-based recruitment and, more broadly, on the barriers to clinical trial participation.

2.3 Expanding Community Advisory Board Programs

NIH-funded researchers who study HIV/AIDS are required to convene community advisory boards (CABs) as a condition of funding. CABs meet regularly with investigators and provide input into site selection, marketing, and recruitment strategies. In interviews with the HIV Vaccine Trial Network, detailed in Alsan et al. (2022), program leaders attributed the unique success of HIV/AIDS recruitment to this process. In particular, program leaders suggested that the influence of CABs can “spill over” to privately sponsored trials. Although sponsors without NIH funding are not required to engage with community groups, firms have often reached out to CABs to benefit from their local knowledge and recruitment networks.

The NIH should expand the CAB requirement to include trials funded by each of its centers. The Division of AIDS (DAIDS) maintains a suite of resources for investigators who convene CABs and community members who may join. These training and guidance documents provide a template for long-term relationships with community organizations and should also be provided to all NIH-funded

¹⁰ A list of registries maintained by the NIH is available here: <https://www.nih.gov/health-information/nih-clinical-research-trials-you/list-registries>.

¹¹ As an example of an existing NIH-sponsored registry, see, for example, the National Institute on Deafness and Other Communication Disorders’ National Temporal Bone, Hearing, and Balance Pathology Resource Registry, which is hosted by Mass General Brigham. <https://masseyeandear.org/tbregistry>

¹² Details on the California Cancer Registry are available here: <https://www.ccrca.org/learn-about-ccr/>.

investigators.¹³ As in the case of HIV/AIDS, public investments in community organizations that are enabled to engage with medical research can reduce the costs of recruiting representative patient samples for NIH-funded researchers and private firms.

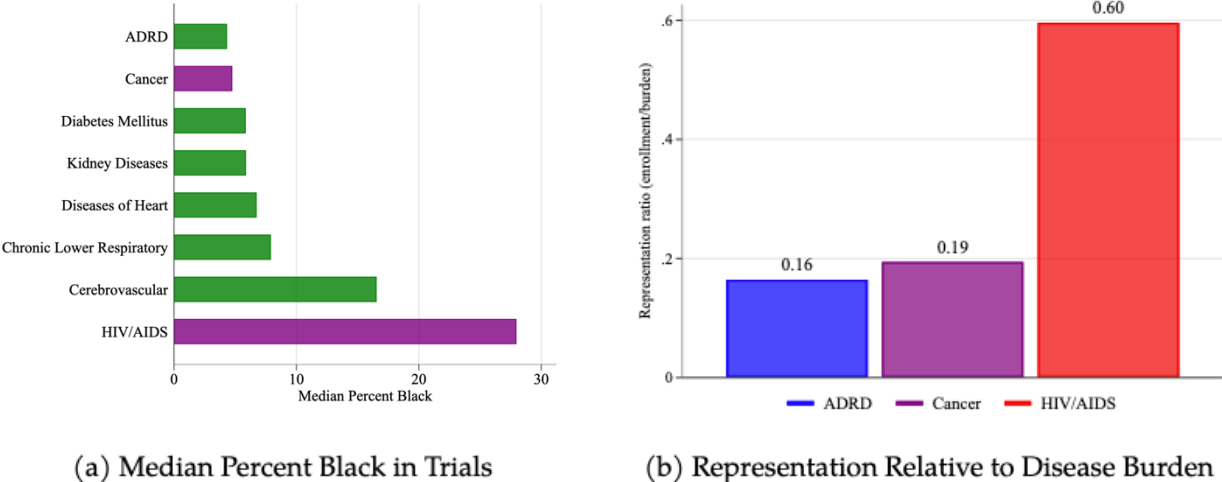
3. Conclusion

Exclusion from medical research has become the norm in the U.S. As long as large differences in recruitment costs across geographies and population groups persist, goals of appropriate representation in clinical trials will be out of reach.

Case studies of cancer and HIV/AIDS – disease areas that benefit from decades of public sector investment, with very different histories of inclusion in medical research – suggest opportunities for reform. The case of HIV/AIDS makes clear that generating representative data is, in fact, feasible. The NIH is ideally situated to make a series of targeted investments that, together, can close these gaps in representation. In doing so, the agency will deliver better data, cheaper trials, and more effective therapies for *all* patients in the U.S.

Figures and Tables

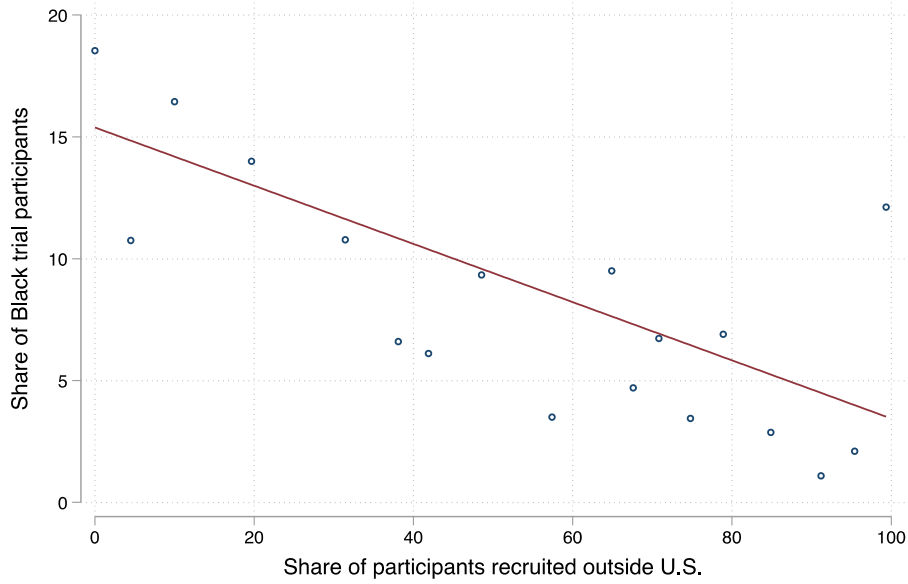
Figure 1: Trial Representation by Condition



Notes: Panel (a) plots the median share of Black patients in trials across HIV/AIDS and the ten leading causes of death (excluding unintentional injuries and suicide) in the United States (Heron 2021). Data on trial composition are drawn from ClinicalTrials.gov. Panel (b) plots “representation ratios” for three disease categories: Alzheimer’s and Related Dementias (ADRD), cancer, and HIV/AIDS. Representation ratios are defined as the enrollment ratio for a disease category divided by the disease burden ratio. See Alsan et al. (2022) for details on data construction.

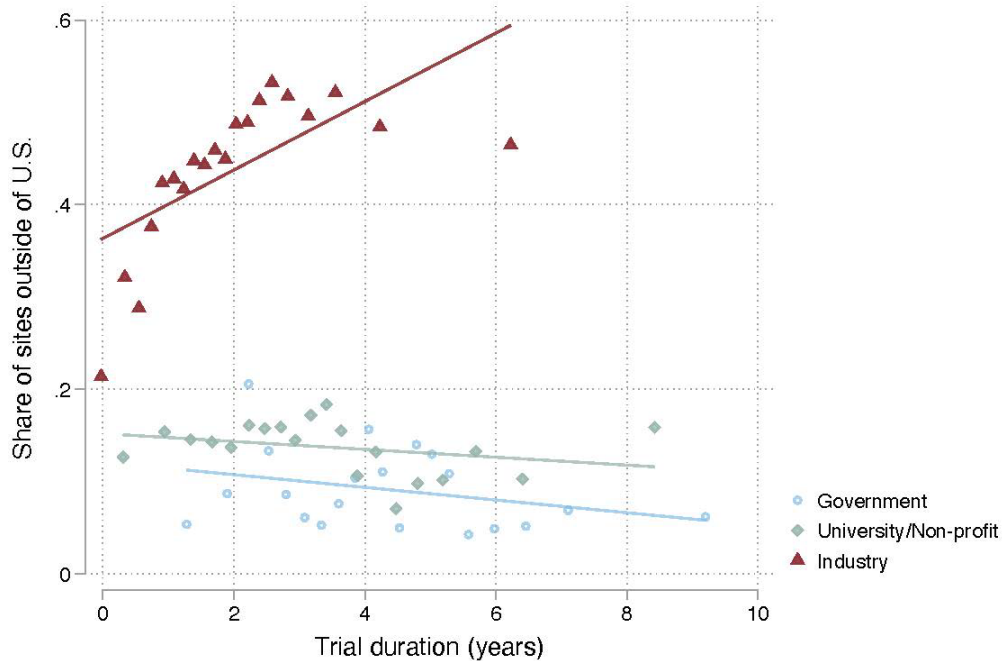
¹³ For additional information on resources available to DAIDS investigators and community partners, see details here: <https://www.niaid.nih.gov/daids-ctu/community-engagement-NEW>.

Figure 2: Trial Offshoring and Representation



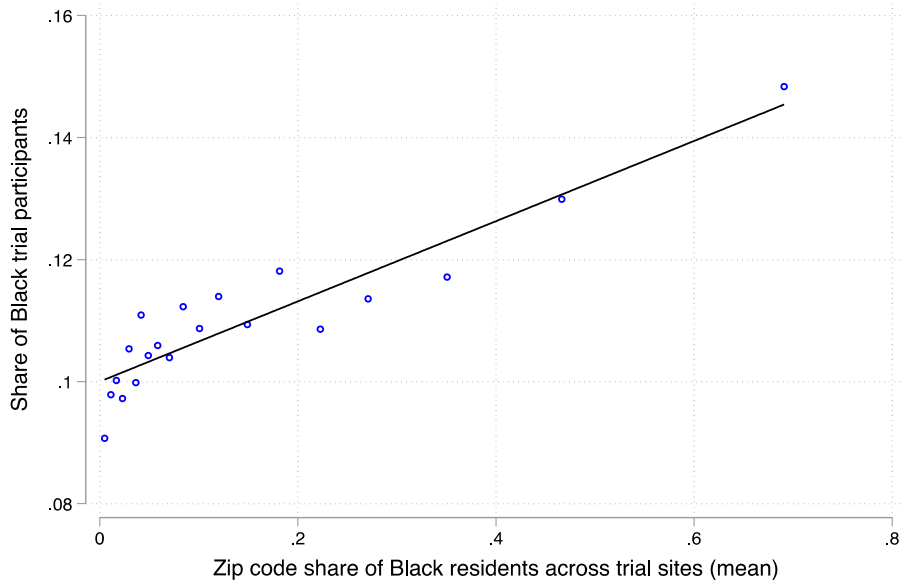
Notes: Figure plots the share of Black participants in pivotal trials supporting a new drug application to the FDA against the share of participants recruited outside of the U.S. Observations are at the new drug application level. Each observation may correspond to more than one pivotal trial if sponsors submitted data from multiple studies. Data are drawn from the FDA Drug Trials Snapshots data. See Alsan et al. (2022) for details on data construction.

Figure 3: Trial Duration and Offshoring by Sponsor



Notes: Figure plots the share of a trial's sites that are located outside of the U.S. against its duration, measured as the time between its reported start date and primary completion date. Observations are at the trial level. Sponsors are listed "primary sponsors." Data are drawn from ClinicalTrials.gov. See "Sample Construction" below for details on data construction.

Figure 4: Racial Composition of Clinical Trials and Trial Sites



Notes: Figure plots the share of Black participants in a clinical trial against the average share of Black residents across trial sites. Observations are at the trial level. Data are drawn from ClinicalTrials.gov and the American Community Survey (2019). See “Sample Construction” below for details on data construction.

Table 1: Trial Sites at Safety Net Hospitals

	Safety Net Hospital in Trial Site Zip Code
HIV/AIDS (vs. Cancer)	0.251*** (0.007)
Constant	0.393*** (0.001)
Observations	201,432

Notes: Table reports OLS estimates from a regression of an indicator variable that captures whether a trial site is located at a safety net hospital on indicators for trial disease area. We define “safety net hospital” following the definition in Popescu et al. (2019). HIV/AIDS (vs. Cancer) is an indicator equal to one if a trial studies HIV/AIDS and zero if a trial studies cancer. See “Sample Construction” below for details on data construction. *, **, and *** refer to statistical significance at the 10, 5, and 1 percent levels, respectively.

Sample Construction

We draw on two publicly available sources of clinical trials data: ClinicalTrials.gov and the FDA's Drug Trials Snapshots database. See Alsan et al. (2022) for a discussion of the FDA's Drug Trials Snapshots database. Below, we describe the ClinicalTrials.gov sample.

We construct a sample of records from ClinicalTrials.gov that: (i) study products that are eventually approved for sale in the U.S., (ii) are regulated by U.S. agencies, and (iii) that are completed more than one year before the end of our dataset and, thus, are subject to reporting requirements. To do so, we collect clinical trials records from the Aggregate Analysis of ClinicalTrials.gov (AACT) data, a publicly available relational database that contains information on all studies registered on ClinicalTrials.gov (Tasneem et al. 2012).¹⁴ We follow Anderson et al. (2015) to develop a procedure for identifying "highly likely applicable clinical trials," which are subject to registry reporting requirements.

¹⁴ We downloaded a version of this database on 21 December 2021. Dataset versions are released frequently and changes in compliance rules for ClinicalTrials.gov reporting mean that historical records *may* change between versions.

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