Transcending Racial and Ethnic Analyses in Clinical Research: A Proposed Model for Institutional Review Boards

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Abstract

In 2005, the Food and Drug Administration’s approval of BiDil for use only in self-identified African Americans brought to the fore the longstanding debate about the use of race and ethnicity in medical research and practice. While this issue has received considerable attention in the science and social science literature, thus far there has been little consideration about the legal and regulatory implications of “race-based medicine.” This paper seeks to fill this gap by critiquing the requirements that clinical trials must satisfy in order to be approved by Institutional Review Boards (IRBs). The proposed model highlights a number of gaps in the regulatory framework’s response to research that uses racial or ethnic proxies. Compliance with such a model could significantly improve the process for developing any future race-based drugs.
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Introduction

The relative costs and benefits of undertaking racial and ethnic analyses in clinical trials has been the subject of passionate debate. Some commentators recommend, and even seek to mandate, the use of such analyses on the basis of the medical knowledge that they can bring to light and, as the argument goes, the potential for this knowledge to lessen health disparities.
Others counter that a focus on “medicalizing” race could divert attention from other, more important, areas of research, such as strategies for ameliorating social inequalities, or otherwise exacerbate inequalities by fuelling race discrimination. Surprisingly, however, little consideration has been given to the potential of drug regulatory frameworks to mediate these disputes. This paper seeks to fill this gap by critiquing the requirements that clinical trials must satisfy in order to be approved by Institutional Review Boards (IRBs). While consideration also is warranted with regard to other components of the drug regulatory framework—for example, approval from the Food and Drug Administration (FDA) for investigational new drugs—IRBs’ responsibilities are especially compelling given their responsibility for overseeing the ethical acceptability of research involving humans.

The paper is structured as follows. Part A sets out the history of the use of race and ethnicity in medical research, and discusses the reasons why race or ethnicity may be used in clinical trials and the scientific and social concerns that commentators have identified with such use. Part B considers relevant criteria for IRB approval of clinical trials, including scientific value and validity, and fair and equitable subject selection. Part C proposes a model for IRB approval of clinical trials based on the role of race or ethnicity in the study design. Factors considered are inclusion of racial and ethnic minorities: (1) with no specific analyses of racial or ethnic variability (race-inclusive research); (2) for the purpose of studying potential differences between racial or ethnic groups (race-targeted research); and (3) for the purpose of studying specific racial or ethnic groups (race-exclusive research). Finally, Part D counters some of the criticisms that may be raised against the proposed model.

The proposed model highlights a number of gaps in the regulatory framework’s response to research that uses racial or ethnic proxies. In particular, IRBs are not required to seek evidence from race-targeted studies before they approve a race-exclusive study. Information from such a study could have considerably ameliorated, for example, much of the controversy surrounding the race-specific registration of BiDil—the first, and thus far only, drug that has been registered in the United States or elsewhere for use only in a specific racial or ethnic group. Although the role of the FDA is beyond the scope of this paper, applying the model to drug labeling decisions suggests a need for the agency to require evidence from race-targeted studies before labeling a drug as having different effects among racial or ethnic groups.
Part A: Analysis of race and ethnicity in clinical trials

The resurgence of race in medicine

Hierarchical racial thinking is a longstanding and regrettable feature of western science. From at least the 17th century onwards, western science has been instrumental in inventing, justifying and disseminating ideas of racial hierarchies.¹ In the United States, many scientific research agendas fed into justifications for slavery, such as the diagnosis of a disease peculiar to slaves that caused them to run away (draphetomania).² In modern times, the dangers of racist and racialized medical research have become closely associated with the atrocities inflicted on Jews in Nazi Germany in pursuit of a wartime medical agenda, and the Tuskegee syphilis study, under which white government doctors systematically failed to treat and undertreated approximately 400 African American men presumed to have late-stage syphilis.

The fall-out from these research scandals coincided with a widespread retreat from the concept of a biological meaning of race. Following on from the 1950 United Nations Educational, Scientific and Cultural Organization’s Statement by Experts on Race Problems, which concluded that race “is not so much a biological phenomenon as a social myth,”³ a growing number of medical anthropologists, biologists and psychologists argued that the race concept was scientifically invalid and should be discarded. While accepting that there are physical and genetic differences that exist among human populations, they stressed that these do not conform to “the discrete packages labeled race.”⁴ In 2000, Dr Craig Venter declared, during the press conference marking the completion of the draft map of the human genome that, from this point forward, “the concept of race has no genetic or scientific basis.”⁵ Many saw cause for celebration that the social construct of race and biological differences had been separated once and for all.

¹ Bernard Harris, Race, Science, and Medicine, 1700-1960 (1999). 5.
² This disorder is discussed in Troy Duster, Lessons from History: Why Race and Ethnicity Have Played a Major Role in Biomedical Research, 34 J Law Med Ethics 487-496 (2006).
However, a decade later, race and ethnicity remain closely tied to discussions of the safety and efficacy of medical interventions, both in the scientific literature and the popular press. Two trends have been influential in this regard:

1. A rise in political and academic interest in health disparities, which—at least in the United States—stratify principally along racial lines. One consequence of the focus on race disparities has been the introduction of legal and policy requirements to include minority groups in clinical research, and to analyze the trial results for each of these groups. This has resulted in the paradoxical situation whereby programs designed to correct historic discrimination against people of color risk reinforcing biological definitions of race that have historically legitimized racial inequalities.

2. An explosion in genetic research, including a change in focus among geneticists from investigating the human genome generally to investigating genomic differences between certain individuals and groups. Nowhere has this been more evident than in the development of large-scale genetic databases and mapping projects, almost all of which use samples collected on the basis of subjects’ race and/or geographic location.

Just how far modern medicine has shifted towards an acceptance of the biological significance of race was highlighted in 2005, when the FDA approved BiDil—a fixed dose of isosorbide dinitrate and hydralazine hydrochloride—for the treatment of heart failure in self-identified African Americans. While BiDil remains the only “race-based” drug to have been given (and, it would appear, to have sought) regulatory approval, claims have been made about the differential effects of many other drugs in persons of different races. In 2004, Sarah Tate and David Goldstein identified at least 29 medicines or combinations of medicines that had been claimed in peer reviewed scientific or medical journals, to have differences in safety or efficacy among racial or ethnic groups. A search by the author identified approximately 20 clinical trials...
currently listed as recruiting on the national clinical trials register that incorporated race- or ethnicity-specific inclusion criteria.\textsuperscript{10}

The costs and benefits of race-based medicine

The relative costs and benefits of race-based medicine have been highly contentious in the scientific and social science literature. On the one hand, a number of scientists have pressed the need to move beyond race-based classifications on the basis of insufficient scientific value and validity. Illustrative of this view was a 2001 editorial in the \textit{New England Journal of Medicine} claiming that race is “biologically meaningless” and warning that “instruction in medical genetics should emphasize the fallacy of race as a scientific concept and the dangers inherent in practicing race-based medicine.”\textsuperscript{11} Similarly, James Wilson and colleagues published an article in \textit{Nature Genetics} arguing that “commonly used ethnic labels are both insufficient and inaccurate representations of inferred genetic clusters.”\textsuperscript{12}

Contrasting with this scientific skepticism, however, is a growing body of literature documenting the advances in medical research and treatment that race-based groupings have made possible. Perhaps the most commonly cited example in this regard is evidence that African Americans respond less well than European Americans to certain cardiovascular disease therapies.\textsuperscript{13} Geneticists have hypothesized that the differences in gene variants probably contributes to some of these reported differences, with others likely attributed to confounded environmental factors.\textsuperscript{14} Either way, proponents of race-based medicine argue that ignoring racial and ethnic information in medical research and practice will work to further neglect already underserved populations.\textsuperscript{15}

Separate from these scientific strengths and weaknesses are the social critiques that have been voiced about the potential for the use of race or ethnicity in clinical research to “reinvok[e]

\begin{itemize}
  \item \textsuperscript{10} Appendix A.
  \item \textsuperscript{13} Tate and Goldstein, \textit{supra} note 9. S35.
  \item \textsuperscript{14} Id. S35.
\end{itemize}
the specter of earlier forms of racial science in some rather discomfiting ways.”¹⁶ One set of concerns has focused on its potential to “essentialize” race—that is, perpetuate a notion that each individual belongs to a category and can be diagnosed and treated accordingly.¹⁷ Beyond such identity politics, Dorothy Roberts suggests that race-based medicine helps to promote a biological explanation for racial inequities that obscures their sociopolitical causes and requires individualized and market-based solutions rather than social change: “By making black people’s subordinated status seem natural, this view provides a ready logic for the staggering disenfranchisement of black citizens, as well as the perfect complement to color-blind social policies.”¹⁸ In an article in the New England Journal of Medicine, Gregg Bloche raised similar concerns that, while different ancestry may play a role in racially disparate responses to treatment, focusing on race as a “genetic placeholder” risked discouraging attempts to elucidate other reasons for such disparities.¹⁹

Part B: Oversight of research by institutional review boards and institutions

All medical research involving humans conducted in public facilities or in facilities that receive funding from the National Institutes of Health (NIH) or certain other federal agencies must be reviewed by an IRB. Requirements for IRB review are set out in 45 CFR 46—“the Common Rule.” These requirements are largely derived from internationally accepted standards of research ethics, including those set out in the Nuremberg Code, the Belmont Report and the World Medical Association’s Declaration of Helsinki. Of particular relevance in the context of race-based research are the requirements for an IRB to determine that: (1) risks to subjects are reasonable in relation to any anticipated benefits to subjects and the importance of the knowledge that the research may generate;²⁰ and (2) selection of subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted.²¹

¹⁸ Roberts, supra note 7. 538.
²⁰ 45 CFR §46.111(a)(2).
²¹ Id. §46.111(a)(3).
Favorable risk/benefit ratio

Before approving a research proposal an IRB must be satisfied that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result from the research. The *Institutional Review Board Guidebook* (the Guidebook) issued by the Department of Health and Human Services advises that, in order to satisfy this requirement, IRBs must assess whether the research design will yield useful data. If, for example, a hypothesis is imprecisely formulated, subjects may be exposed to risk without sufficient justification: “While good research design may not itself reduce or eradicate risks to subjects, poor or faulty research design means that the risks are not likely to be reasonable in relation to the benefits.”

Implicit in such a risk/benefit analysis are the ethical requirements of *scientific value* and *validity*. Although these requirements are not articulated expressly in the federal regulations, the Guidebook explains that “if the underlying science is no good, then surely no important knowledge may reasonably be expected to result.” In their collation of the foundational principles of research ethics, Ezekiel Emanuel and colleagues have described *social or scientific value* as the potential for the research to improve health and well-being or increase knowledge. This requirement may be breached, for example, by clinical research that has non-generalizable results or a trifling hypothesis. In comparison, *scientific validity* depends on the rigor of the methodology with which the research is being conducted, including that the research has a clear scientific objective, and is designed using accepted principles, methods and reliable practices.

In applying these ethical requirements to race-based research, the insufficiencies and inaccuracies in definitions of “race” and “ethnicity” may limit the potential to replicate study results in future research, potentially breaching the requirement of scientific value. On the other hand, failing to consider the effects of race or ethnicity when, in fact, there are relevant differences—either because of genetic or confounded environmental differences—also could impinge on scientific value. So, a study could find that a therapy is safe and/or efficacious when in fact, this finding is true only for study participants of a certain background (in practice, this is

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22 Id. §46.111(a)(2).
24 Id. “Considerations of Research Design”.
most likely to be ‘whites’ who—at least for research conducted domestically—will almost always form the dominant study population). Research may fail to satisfy the requirement of scientific validity if it purports to analyze differences in the safety and efficacy of the study treatment on the basis of race or ethnicity without adequate statistical power. False positives that may arise from such underpowered analyses are particularly worrisome given the media attention that is likely to result from any reporting of racial or ethnic discrepancies.

A significant limitation to the application of the Common Rule requirement for a favorable risk/benefit ratio in the context of race-based research is the proscription on considering, as a part of the risk/benefit analysis, possible “long-range effects of applying knowledge gained in the research.”26 The Guidebook notes that this includes, for example, IRB concerns that “information gained about associative memory may enable advertising companies to develop new techniques for encouraging arguably harmful consumer behaviors,” or of the public policy implications of research that seeks to find associations between race or gender and intelligence.27 This would include, for example, the concerns raised by Zach and others about the potential implications of “racialized medicine.”

Fair and equitable subject selection

The Common Rule also requires that research use fair and equitable subject selection. That is, groups or individuals should not be excluded from the opportunity to participate in research without a good scientific reason or susceptibility to risk that justifies their exclusion. As explained by Emanuel and colleagues: “The essence of fairness in human subjects research is that scientific goals, considered in dynamic interaction with the potential for and distribution of risks and benefits, should guide the selection of subjects.”28

The ethical requirement of fair and equitable subject selection has its roots in the protection of vulnerable populations—including, for example, prisoners and wards of the state—from predatory research practices. The historical tendency to misuse vulnerable populations in research has been tragically illustrated in the recent revelations about a US Government study conducted between 1946 and 1948 that intentionally infected persons in Guatemala with

26 45 CFR §46.111(a)(2).
28 Emanuel, Wendler, and Grady, supra note 25. 2705.
sexually transmitted diseases. However, in more recent times, thinking about subject selection has shifted from clinical trials being a burden from which persons should be protected, to a benefit to which persons are entitled to seek access. To this end, the Guidebook warns against underrepresentation of minority groups and women in study populations to ensure that “the findings will be meaningful for those groups and they can, therefore, share in the benefits of the research.”

Supplementing this ethical principle of inclusion are specific statutory requirements introduced in the National Institutes of Health Revitalization Act of 1993. Congressional reports recommending that the Bill be passed emphasized the need to “ensure that advances in medicine and public health that result from NIH activities benefit all Americans, regardless of gender or race.” The Act requires the Director of the NIH to ensure that women and members of minority groups are included as subjects in clinical research conducted or supported by the NIH. In addition, the Act mandates that trials be conducted in a manner which allows a valid analysis of whether the intervention affects women or members of minority groups differently than other subjects in the trial. Exceptions to the inclusion requirements apply where it would be inappropriate with respect to the health of the subjects or the purpose of the research. Non-inclusion also may be permitted where there is “substantial scientific data” demonstrating that there is no significant difference in the effects of a clinical trial intervention on women or minority groups from those on study subjects.

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30 One indication of this shift is litigation claiming, presently unsuccessfully, that terminally ill patients have a constitutional right to access experimental drugs: Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach, 495 F.3d 695 (2007). See also: R J Levine, The impact of HIV infection on society’s perception of clinical trials, 4 KENNEDY INST ETHICS J 93-98 (1994).

31 OFFICE FOR HUMAN RESEARCH PROTECTIONS, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, supra note 23, ‘Selection of Subjects’.


33 National Institutes of Health Revitalization Act § 131, inserting § 492B(a) into Part G of Title IV of the Public Health Service Act.

34 Id, inserting § 492B(c).

35 Id, inserting § 492B(b).

36 Id, inserting § 492B(d)(2)(B).
Part C: Proposed model for IRB review

The preceding parts of this paper have shown the close relationship between scientific and social concerns raised by race-based medical research, and the obligations on IRBs to review research projects for consistency with research ethics requirements. However, the nature of these interactions differs considerably depending on the purpose for which racial or ethnic information is used in a clinical trial. The author is not aware of any comprehensive attempt to untangle these relationships.

This paper seeks to fill that gap by proposing three broad classes of clinical trials, based on the role of race or ethnicity in the study design—the inclusion of racial or ethnic minorities (1) with no specific analyses of racial or ethnic variability (race-inclusive research); (2) for the purpose of assessing potential differences in an intervention’s safety or efficacy between racial or ethnic groups (race-targeted research); and (3) for the purpose of assessing an intervention’s safety or efficacy in specific racial or ethnic groups (race-exclusive research). The paper identifies the dominant ethical requirements for each of these classes. Case studies are then used to clarify the manner in which an IRB review focused on such requirements may unfold.

Underlying the development of this framework is a presumption of sameness of an intervention’s effect across racial and ethnic groups. This is consistent with Patricia King’s views that race-based medicine should have, as its starting point:

the defeasible presumption that blacks and whites are biologically the same with respect to disease and treatment. Presumptions can be overturned of course, and the strategy should recognize the possibility that biological differences in some contexts are possible. But the presumption of equality acknowledges that historically the greatest harm has come from the willingness to impute biological differences rather than the willingness to overlook them.37

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The proposed model could play a valuable role in promoting the transition of clinical research findings from the “flawed proxy” of race and ethnicity to the identification of more precise variations among individuals—a common goal among scientists, social scientists and others. However, like most policy developments, it is open to legal and policy questions. These are assessed in Part D.

The model differs in several respects from the requirements of the NIH Revitalization Act. Rather than formulating a model that fits with the legislation, the paper aims for consistency with broader principles of research ethics, based on those requirements set out in the Common Rule. Other commentators have commented on the need to address the manner in which the requirements of the NIH Revitalization Act should guide biomedical research policy, given the doubtful biological significance of race. Such guidance is a central aim of this paper. Should the model receive favor, consideration should be given to amending the NIH Revitalization Act for consistency with it.

Race-inclusive research

In the vast majority of clinical trials, there will be no indication of likely differences between racial and ethnic groups. The scientific value of these studies (and, flowing from this, the favorability of the risk/benefit ratio) will depend on the degree of generalizability of study results, indicating the need for a diverse study population. A similar need for diversity is raised under the requirement for fair and equitable subject selection, under which the benefits and burdens of a clinical trial should be justly distributed among populations including various racial

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and ethnic groups. Although researchers should recruit a diverse spectrum of participants, significant concerns about scientific validity are raised by attempts to use participants’ race or ethnicity as the basis of post-hoc analyses of safety and efficacy. Richard Peto and collaborators famously illustrated the fallacies that such analyses may generate by analyzing the sample for a large heart attack trial by the participants’ astrological sign to conclude that those born under Gemini or Libra were harmed by the aspirin therapy, while those born under all other astrological signs benefited. Troy Duster has published similar warnings, showing that the state in which a person lives can generate statistically significant differences in responses to an intervention.

Accordingly, when reviewing race-inclusive research projects, an IRB should ensure that the study is open to persons of all races and ethnicities—including through the use of appropriate recruitment strategies. The IRB also should be satisfied that the researchers do not intend to study race and ethnicity as discrete study variables. The potential application of such a framework for IRB review is illustrated by the below case study of the aborted development of AIDSVAX—a once promising AIDS vaccine.

**Case Study 1: AIDSVAX**

On 28 February 2003, VaxGen—the company developing the first prophylactic AIDS vaccine to enter phase 3 clinical trials—announced disappointing results. The vaccine had demonstrated only a 3.8% reduction in new HIV infections among study participants who received the vaccine as compared with the control group. However, there were hopes that the vaccine may work in certain subgroups: a subset analysis showed that Asians and blacks who received the vaccine had a 67% lower rate of infection than those in the placebo arm. Although the differences were entirely unexpected, VaxGen suggested that they could be explained by the fact that vaccinated blacks had higher levels of anti-HIV antibodies than their white counterparts. The numbers were based on very small sample sizes. Of the approximately 5,400 study participants, only 314 were classified as Black and 20 as Asian.

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Controversy immediately ensued. Four AIDS advocacy groups issued a joint statement calling VaxGen’s analysis “misleading and premature.” In comparison, USA Today quoted a leading vaccine expert and member of the FDA advisory committee saying: “I don’t think this is an occasion to scoff and walk away. I think it’s an opportunity to say this is fascinating, we can’t explain it, and we need to do some more research.” The same article quoted Phil Wilson, of the African American AIDS Policy and Training Center, stating that the results are a “clear call” for trials to reflect the demographic of the AIDS epidemic. Some months later, Dean Follman of the NIH reported that the results were “likely spurious.” The fallaciousness of the subgroup results were supported by the results of a phase 3 trial of AIDSVAX conducted in Thailand, which failed to show efficacy in the (Asian) study participants.

How would this study have fared under the proposed model for race-inclusive research? From all accounts, there was no suggestion at the study planning stage that the effects of the vaccine may differ between racial and ethnic groups. Consistently with the proposed requirements, participants were recruited from diverse racial and ethnic groups. However, none of the minority groups were represented in adequate numbers to justify subgroup analyses nor was there a clear scientific justification for undertaking such analyses. This was directly responsible for the incorrect findings about racial and ethnic differences in response, including the resources later spent on discrediting these findings. VaxGen’s attempt to analyze the results by an aggregated “minority group” subset, which appears to have absolutely no scientific basis, further compounded the fallacy. These subgroup analyses should not have occurred under the proposed model for race-inclusive research.

Race-targeted research

Some clinical trials are conducted in the context of prior knowledge or suspicions of racial or ethnic disparities. In the absence of a better proxy, this may warrant a structured analysis of racial or ethnic categories (‘race-targeted research’). This may be the case, for example, where there is a high degree of inter-subject variability in clinical trial safety or efficacy, or where there

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44 EPSTEIN, supra note 41.
are known racial or ethnic health disparities that cannot adequately be explained by other environmental factors. However, for such an analysis to be scientifically and ethically robust, certain requirements must be met.

First, the principles of scientific validity and value require clarity about the manner in which racial and ethnic groups have been selected and defined. This may involve moving beyond the standard categories set by the Office of Management and Budget (and, on this basis, required under the NIH Revitalization Act) to more specific geographic ancestral groups. For example, where the researchers hypothesize that differences result from as-yet-unknown genetic variation, they may classify subjects on the basis of ancestral information markers. In comparison, to capture differences relating to the experience of discrimination, researchers may classify subjects on the basis of color.45 Despite a number of scientific journals having issued publication guidelines that require researchers to justify racial or ethnic classifications,46 recent evidence suggests that the terms race and ethnicity often are not accompanied by a definition of the concepts. Instead, these rely on an “a priori assumption that readers would simply recognize or understand what the terms meant.”47

Secondly, the requirement of scientific validity demands that a race-targeted study have adequate statistical power to assess potential differences between targeted racial and ethnic groups. Usually, this will necessitate considerably larger studies than race-inclusive models. The study also should have the potential to clarify whether some other variable can better explain any purported racial or ethnic differences including, for example, socio-economic status. Untangling these variables will require careful attention to study design.48

Finally, in accordance with the requirement of fair and equitable subject selection, researchers must study the broadest feasible selection of racial and ethnic groups. For example,

without further justification, limiting a study to “Whites” and “Blacks” excludes others (such as participants who identify as Asian or Native American) from the benefits of study enrolment and any future research on, and use of, the intervention. Notably, however, broadening out the study in this way may detract from the study’s validity by lessening the homogeneity of the comparator arm. IRBs should consider this trade-off between the inclusiveness and minimization of background noise on a study-by-study basis.

There are limited examples of race-targeted studies that can be drawn upon to discuss issues that may arise with the proposed model. However, one example is a trial sponsored by the Henry Ford Health System that is currently recruiting participants—Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE).

**Case Study 2: Asthma Treatment**

Inhaled corticosteroids are first-line therapy for managing and controlling patients with persistent asthma; however, studies show considerable inter-subject variability in response. African-American patients, in particular, appear less likely to respond to corticosteroid therapy when compared with White patients. It is not currently known whether this difference results from genetic or environmental factors, or whether differences exist in the recommended route of therapy. The SAPPHIRE study aims to assess differences in inhaled corticosteroid responsiveness between self-identified African-American and White patients with asthma following six weeks of treatment. It also seeks to identify genetic variations associated with responsiveness to treatment.

Relatively strong justifications exist for undertaking race-targeted research in this area, given the high levels of inter-subject variability and anecdotal racial differences. Indeed, given the unexplained racial differences in response to corticosteroids, *failing* to consider racial disparities arguably could breach ethical requirements. However, a researcher would need to provide further information in order to satisfy the requirements of scientific value and validity. First, he or she should justify clearly why self-identified race has been selected as the basis of

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49 Commentators have identified a lack of clinical research that seeks to compare the influences of genetic and sociocultural factors, or interactions between them: Gravelle, Non, and Mulligan, *supra* note 45.; Kaufman and Cooper, *supra* note 48.

50 Information in this case study has been drawn from National Clinical Trials Register, *Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity*, http://clinicaltrials.gov/ct2/show/NCT01142947 (last visited Dec 6, 2010).
classification. Given the hypothesized genetic basis for differences, geographic ancestry may be a more accurate proxy. In addition, the study should consider a broad spectrum of environmental factors, including socio-economic status and proximity to environmental pollutants. It is unclear from the information available which of these factors the researchers will assess.

As regards the requirement for fair and equitable subject selection, the researchers would need to give some justification for comprising the control group solely of “Whites”. If the relevant difference is between self-identified Blacks and the rest of the American public, then it may be preferable for the control group to include all eligible participants other than self-identified Blacks. In particular, this would enable individual participants who are neither “Black” nor “White” to access the study and benefit from its results.

Race-exclusive research

In rare circumstances, restricting enrolment in a clinical trial to persons of a certain race or ethnicity (race-exclusive research) may be justifiable. This could be the case, for example, where insurmountable safety or efficacy issues have been reported in the general population and there is strong evidence to suggest that the concern does not arise in specific racial or ethnic populations—whether defined on the basis of ancestral information markers, color or through self-identification. However, given the scientific and ethical concerns that such restrictions raise, IRBs should give close attention to any such study design.

First, an IRB will need to assess the risk-benefit ratio of a race-exclusive study. Charles Weijer has noted that the results of a clinical trial with a very narrowly defined study population are likely only to have clinical implications for a small number of patients. Conversely, the results of a widely inclusive trial may have implications for the entire clinical population. This makes it much more likely that any dedicated research risk in the narrowly defined study will be warranted in light of the potential gains in scientific knowledge (the "risk-knowledge" calculus). Further, to satisfy the requirements of scientific value and validity, researchers must provide a scientifically meaningful rationale for the manner in which they are classifying participants into racial or ethnic groups. Often, this will be based on as-yet-unknown genetic

variation between ancestral groups, with classification based on ancestral information markers. However, situations can be envisaged where unknown environmental factors or gene-environment interactions are responsible, which may warrant classification on the basis of self-identification. Evidence from prior race-targeted research will be essential to demonstrate that the classification researchers have selected is a suitable proxy to account for differences in the intervention’s safety or efficacy.

An IRB also must determine that the race-exclusive research satisfies the requirement for fair and equitable subject selection. This requirement appears to be especially perilous. Adverse outcomes from participation in the research will fall exclusively on the identified racial or ethnic group—a particularly worrisome situation if an investigational treatment is found to be detrimental and the study has been performed only on a historically vulnerable group such as African Americans. Equally, the potential future benefits of the research also will be limited to the racial group under investigation. Considering that some people in other racial and ethnic groups are likely to respond to the treatment, albeit in smaller numbers and/or to a lesser degree, their exclusion from the study may be unfairly discriminatory. Once again, the fairness or otherwise of restricting enrollment to a racial or ethnic group will depend on the researcher providing sufficiently compelling results from a race-targeted research program.

It is instructive to consider how the much-discussed story of the registration of BiDil for self-identified African Americans would fare under this proposed model.

**Case Study 3: BiDil**

The FDA’s registration of the first racially specific treatment started with studies demonstrating the efficacy of BiDil’s two constituent drugs—hydralazine and isosorbide dinitrate (H/I)—in treating hypertension: the Vasodilator Heart Failure Trials (V-HeFT). V-HeFT I showed H/I to be an effective treatment for heart failure; however, in V-HeFT II, ACE inhibitors were found to be a superior treatment. The investigators later decided to re-analyze the data with a particular focus on racial disparities. On the basis of the 49 African American men enrolled in the V-HeFT I trial, they became convinced of BiDil’s race-specific action. The investigators acquired a new race-specific patent on BiDil (the lead investigator, Jay Cohn, had

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52 The path of BiDil development described in this case study has been drawn largely from Gregory Michael Dorr & David S Jones, *Introduction: Facts and fictions: BiDil and the resurgence of racial medicine*, 36 J LAW MED ETHICS 443-448 (2008).
previously been granted a race-neutral patent, which had been due to expire shortly) and licensed the rights to the company NitroMed.

In 2001, NitroMed began a placebo-controlled study to investigate BiDil’s action in self-identified African Americans—the African American Heart Failure Trial (A-HeFT). The researchers halted A-HeFT early when analysis of the initial data revealed a 43% decreased mortality rate among patients on BiDil as compared with those on placebo. On 23 June 2005, the FDA approved BiDil for use in self-identified African Americans. A storm of controversy immediately resulted.

Many commentators raised concerns that the decision to limit enrollment in the study to self-identified African Americans relied solely on the post-hoc analysis of the earlier V-HeFT data. Ellison and colleagues noted, for example, that post hoc subgroup analyses result in a loss of statistical power and the potential for covariate imbalances. They also expressed concerns that disaggregated data on the baseline characteristics of the “Black” and “White” participants in the V-HeFT studies was not provided, which made it impossible to assess whether the apparent racial differences were actually the result of confounding factors.53 Interestingly, one of the investigators on the A-HeFT study has remarked that, in retrospect, the labeling of BiDil may have been clearer if it simply noted the drug’s benefit in patients with symptomatic systolic heart failure, noting that this benefit was largely based on a study of 1,000 self-identified Blacks in the United States.54 Other concerns related to the social implications of approving any race-based drug, including the potential to falsely imply that social categories of race have meaning on a biological or genetic level.

Examining the BiDil narrative in the context of the proposed model for approving the use of race or ethnicity in clinical research clarifies several matters. The reported differences in underlying etiology of heart failure and increased prevalence of heart failure overall in African Americans would justify the development of a race-targeted research program. However, immediate progression to a race-exclusive study raises scientific and ethical concerns. Without

the benefit of race-targeted studies, it is impossible to know whether race is a valid proxy for variations in participants’ response to the treatment. This limits the study’s scientific value and validity. Additionally, the gaps in information about whether variables other than race may better predict a BiDil’s safety and efficacy mean that the A-HeFT study is likely to breach the requirement for fair and equitable subject selection.

The Common Rule expressly proscribes IRBs from considering possible long-term effects of applying the knowledge gained from clinical trials. As such, an IRB could not consider concerns about the potential for race-based drugs to heighten racism or divert attention from arguably more important environmental causes of health disparity.

Part D: Potential critiques of the proposed model

Balancing acts, such as the model proposed in this paper, often remain open to criticism from both directions. On the one hand, detractors may claim that the model imposes illegal or unjustifiable restraints on medical research; on the other, that it condones illegal or ethically flawed research. Below, I consider the likely strengths and weaknesses of these critiques. For the sake of clarity, I first deal with the legal arguments that may be raised against the model before discussing policy critiques.

Legal critiques

Freedom of speech

First Amendment “freedom of speech” protections are relevant to the constitutionality of certain regulations on scientific research. Restrictions on components of the research program that fit within the concept of “expressive” activity—for example, receiving ideas or information from another or publishing in scientific journals—will warrant First Amendment scrutiny. The characterization of a restriction as “content-based” or “content-neutral” will determine whether a strict or intermediate level of scrutiny applies. Under strict scrutiny, a law is upheld if it is proven necessary to achieve a compelling governmental purpose. Strict scrutiny usually is fatal
to a challenged law. In comparison, under intermediate scrutiny a law is upheld if it is substantially related to an important government purpose.\textsuperscript{55}

Restrictions on nonexpressive activity—for example, the conduct of scientific experiments\textsuperscript{56}—may be struck down on First Amendment principles when “speech” and “nonspeech” elements are combined in the same course of conduct and the speech elements are constitutionally significant.\textsuperscript{57} Barry McDonald has suggested that the incidental burdens doctrine may extend First Amendment scrutiny to restrictions on biomedical research that are designed to halt the discovery, use and potential spread of new scientific information. Moreover, since the government’s justification for these restrictions would be “content-based”, a strict level of scrutiny may be warranted in preference to the intermediate scrutiny usually applied in incidental burden cases.\textsuperscript{58}

Some commentators have gone further by suggesting that—given the parallels between conduct designed to express or communicate ideas and conduct designed to develop ideas or information—all regulation of scientific research should be treated as regulation of speech for First Amendment purposes.\textsuperscript{59} However, such an approach has been criticized as confusing the First Amendment’s protection for speech with one of its underlying objectives of the discovery of truth and knowledge—what has been termed the “marketplace of ideas.”\textsuperscript{60} The marketplace of ideas rationale itself also has been strong criticized. As explained by Harry Wellington: “In the long run, true ideas do tend to drive out false ones. The problem is that the short run may be very long, that one short run follows hard upon another, and that we may become overwhelmed by the inexhaustible supply of freshly minted, often very seductive, false ideas.”\textsuperscript{61}

\textsuperscript{55} See Erwin Chemerinsky, Constitutional Law (2001), 529 (described in the context of the Equal Protection Clause).

\textsuperscript{56} The lack of expressivity in the conduct of biomedical research has been noted in Barry McDonald, Government Regulation or other “Abridgements” of Scientific Research: The Proper Scope of Judicial Review under the First Amendment, 54 Emory Law Journal 979; James Weinstein, Institutional Review Boards and the Constitution, 101 Northwestern University Law Review 493-561 (2007).

\textsuperscript{57} United States v O’Brien, 391 U.S. 367 (1968).

\textsuperscript{58} For example, McDonald, supra note 56. 1031.

\textsuperscript{59} See discussion in Id. at 1018.

\textsuperscript{60} Id. 1018.

A related avenue for pursuing freedom of scientific research has been through a proposed right of “thought and inquiry,” located either within the First Amendment or the due process clauses of the Fifth and Fourteenth Amendments. Under such a right, a regulation that forecloses an entire line of inquiry—such as a complete prohibition on certain forms of experiment—would be considered a “direct” restriction, while a regulation that dictates the manner or means by which an experiment is performed would be an “incidental” restriction. If the Court recognized such a right, it would only be likely to be infringed by exceedingly burdensome regulations—for example, a regulation that effectively forecloses an entire line of inquiry.

This leads to the question of how the model proposed in this paper may fare under First Amendment principles. The model regulates the testing of scientific propositions and data analysis, none of which evidences an intention to convey a specific message. This makes it unlikely that it would be characterized as a direct restriction on “expressive” activity. It could, however, be considered an incidental burden on the spread of new scientific information. If federal courts accept this as “constitutionally significant” it may be subject to First Amendment scrutiny, either on the basis of strict or intermediate scrutiny. There are compelling government interests for introducing the proposed restrictions, including establishing a reliable evidence-base for drug approvals, and minimizing potential race-based discrimination. The restrictions are narrowly tailored to achieving these interests. As such, the model is likely to satisfy intermediate scrutiny. Considering the notorious fatality of strict scrutiny, however, success is far from assured under that scenario. The restrictions do not appear stringent enough to invoke any “right to research.” In particular, race-based research is not cut off completely as a line of inquiry; rather, justifiable conditions are put forward for the manner in which such research should be conducted.

Finally, the above constitutional analysis has assumed that the proposed model was imposed directly on research institutions by law. In reality, it would apply only to institutions that receive federal research funding and, on that basis, are required to institute IRB review.

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63 Weinstein, supra note 56. 547.
Given the wide latitude the Court has accorded to government to attach conditions to the receipt of federal assistance, this is likely to render irrelevant any First Amendment problems.\textsuperscript{64}

**Equal protection**

Different constitutional issues are raised with regard to the conduct of race-exclusive clinical trials. Under the Equal Protection Clause, the government must not allocate societal benefits or burdens on the basis of race, other than where the disparate treatment is narrowly tailored to achieve a compelling governmental interest. This is likely to include the enrollment of subjects into race-exclusive clinical trials.

The first question that must be considered under Equal Protection Clause analysis is whether the research is being conducted by government. This will include research conducted by the FDA and public research facilities, but not private facilities (even if the research is government funded).\textsuperscript{65} If the research is conducted by government, a court must decide whether it imposes a benefit or burden on the basis of race. In their comprehensive article on the application of the Equal Protection Clause to race-based clinical trials, Eric Lillquist and Charles Sullivan suggest that merely recording data in racial terms is unlikely to pose a problem in this regard. However, they conclude that conditioning enrolment in a study on the basis of race would impose a burden or benefit and, therefore, give rise to strict scrutiny.\textsuperscript{66} The final question for consideration is whether any imposition of burden or benefit is justified by a compelling government interest. This will be considered on a case-by-case basis. In practice, the Supreme Court has accepted very few government interests as sufficiently compelling to validate a racial classification.\textsuperscript{67} However, there is judicial obiter that the use of racial classifications in medical research may, in some circumstances, satisfy the strict scrutiny test. In *Regents of University of California v Bakke*, Justice Powell commented that:

> As applied to research, grouping individuals by racial categories might be permissible, but only if the extant evidence of racial differences is sufficiently strong to justify further study and the categories used are properly tailored to study those differences.\textsuperscript{68}


\textsuperscript{67} Lillquist and Sullivan, supra note 65. 443.

\textsuperscript{68} Regents of the University of California v. Bakke, 438 U.S. 265 (1978).
The model proposed in this paper is closely attuned to the requirements of the equal protection clause. In particular, a race-exclusive study has the greatest chance of satisfying the strict scrutiny test where race-targeted clinical trials demonstrate compellingly that further research is only justified in persons of specific races or ethnicities. This evidence will go a long way towards meeting the requirements of the equal protection clause.

Federal and state legislation

Various state and federal statutes, including civil rights acts and anti-discrimination laws, also might impact on the lawfulness of the model, particularly with respect to the conduct of race-exclusive research. Two federal law provisions could apply to the use of racial or ethnic categories in medical research: 42 USC § 1981 and Title VI of the Civil Rights Act of 1964. 69 42 USC § 1981 prohibits race discrimination with respect to contracts involving public or private parties. It is unclear, however, whether a contractual relationship exists between a researcher and a clinical trial subject. 70 Accordingly, the provision likely has limited applicability in this context. Title VI of the Civil Rights Act of 1964 prohibits race discrimination on the part of federally funded programs. Recourse under this provision will depend on whether a person seeking to participate in a clinical trial is an “intended beneficiary of, an applicant for, or a participant in a federally funded program.” 71 Characterizing a potential participant from another race or ethnicity as an “intended beneficiary” appears unlikely if there is compelling scientific evidence that further research on the intervention would only be safe or efficacious on persons of a specific race or ethnicity. However, in the absence of such evidence, the study could breach the title’s requirements.

In addition, the majority of states have enacted civil rights statutes that proscribe making a distinction on the basis of race in connection with goods or services offered in a place of public accommodation. 72 Some states expressly extend this protection to goods and services offered in other establishments such as clinics and hospitals. Once again, definitional issues are likely to

69 For an in-depth discussion of this issue, see Hoffman, supra note 66.
70 In Ericka Grimes v. Kennedy Krieger Institute, Inc., 366 Md. 29 (2001), the Court held that an informed consent form for nontherapeutic research could, in some circumstances, create a contract. The Court did not determine whether informed consent in a therapeutic context could generate contractual obligations. Limited or no contractual relationship exists between a research participant and the sponsor company: Suthers v. Amgen Inc., 441 F. Supp. 2d 478 (2006); Abney and Others v. Amgen Inc, 443 F.3d 540 (2006).
72 See discussion in Hoffman, supra note 67.
arise; in this case, as regards whether enrolment in a clinical trial is a “service” for the purpose of the provision. A court’s answer to this question will depend on whether it defines clinical research as a process intended to achieve scientifically generalizable results, or a service intended to provide benefits to individual participants. If the study is characterized as a “service”, the legality of excluding persons of certain races or ethnicities will require compelling scientific evidence, as discussed in the context of Title VI of the Civil Rights Act.

The proposed model differs in several respects to the requirements of the NIH Revitalization Act. Most notably, the proposed model advises against separate racial and ethnic analyses of race-inclusive research, while the Act demands that such analyses be performed for all publically funded clinical research, subject to limited exceptions. In the author’s view, this statutory requirement goes against the goals of scientific value and validity. Accordingly, the Act should be amended to reflect the requirements set out in this paper.

Policy critiques

The legality of the proposed model says nothing about its policy merit. While a number of arguments have been set out in the body of the paper for instigating the proposed model, several arguments are likely to be raised against it. First, that by imposing limits on the conduct of race-based research it closes the door on potentially constructive avenues of scientific research; and, secondly, that IRBs are already overburdened and that no more obligations should be placed on them. Finally, the use of race or ethnicity in medical research may highlight the need for more sweeping changes to the ethical requirements under the Common Rule—in particular, a requirement to protect communities.

Closing the door on avenues of scientific inquiry

One criticism of the proposed model is its potential to close the door on the identification of unanticipated racial and ethnic differences. That is, that by restricting “blue sky” analyses of clinical research based on racial or ethnic subgroups, potentially valuable evidence of racial disparities will not come to light.

Undoubtedly, the model involves a trade-off between freedom of scientific inquiry that, on the one hand, may spark a useful path of inquiry but, on the other, may be scientifically and socially destructive. Such a balancing act is central to the work of IRBs generally. For example, many possible advances are likely to have been held up because of difficulties of seeking
informed consent. Yet the delay is necessary to uphold the autonomy of research participants—an ethical principle on which the US places a particularly high value. In the context of race-based research, there are good reasons for placing a premium on the presumption of racial and ethnic similarity, given the atrocities that previously have been justified in the name of medical research. Where researchers suspect that there may be differences in the efficacy or safety of the intervention among racial groups (based, for example, on unexplained health disparities or a high degree of inter-subject variability in drug response), they may analyze this through race-targeted studies. If these studies show compelling racial or ethnic differences, a researcher may seek IRB approval for a race-exclusive study. This process appears to be far more likely to generate clinically useful racial or ethnic information than current shotgun approaches.

Concerns about the model’s potential to detract from the research enterprise also could be diminished by applying it only to “confirmatory” or “hypothesis-testing” clinical trials, in which race or ethnicity is used as a surrogate marker to test the safety and efficacy of a drug for a set of patients.73 The classifiers used in these studies warrant far greater ethical and scientific critique than, for example, early-phase exploratory studies. Richard Simon has commented, for example, that: “The process of classifier development may be exploratory and subjective, but the use of the classifier in the pivotal trial must not be.”74

**Resourcing and time constraints on IRBs**

Membership of IRBs is in a voluntary capacity and boards already are burdened with a multitude of responsibilities. This raises the question of the desirability of adding yet more considerations to their purview. Relevantly, a 1996 study by the GAO reported that the sheer number of studies on their agenda meant that an IRB rarely spent more than one or two minutes reviewing each study.75 The counter argument is that the proposed model is based only on those ethical requirements on which IRBs already must satisfy themselves. An IRB that has

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73 Defined as follows: “Also known as “confirmatory” clinical studies, hypothesis-testing studies are always well-controlled and are intended to provide meaningful results by examining pre-stated questions (i.e., hypotheses) using predefined statistically valid plans for data analysis, thereby allowing firm conclusions to be drawn to support product claims. Hypothesis-testing studies may occur at any stage of drug development and include all phase III studies, some earlier-phase studies, and many studies of marketed products.” ClinicalStudyResults.Org, GLOSSARY OF TERMS, http://www.clinicalstudyresults.org/glossary/ (last visited Dec 9, 2010).


been satisfying its obligations should already have been considering these issues, albeit in the absence of formal guidance. To the extent that implementing the model would add to an IRB’s overall workload, strategies should be implemented to improve the broader framework in which IRB reviews are conducted. This may include, for example, single ethical review of multisite clinical research, which would minimize the duplication of resources incurred by multiple reviews of research proposals.

The need for broader systemic changes

Ethical standards for research with human subjects historically have been developed in response to concerns about the protection of individual study participants. To the extent that vulnerable groups, such as the mentally ill, are expressly considered in research ethics guidelines, it is in the context of preventing wrongful inclusion in or exclusion from clinical trials. In recent years, however, growing attention has been given to the need for ethical guidelines to codify protections for communities. Key features of guidelines directed towards the protection of communities involved in human research include consultation in protocol development; involvement in research conduct; access to data and samples; and involvement in the dissemination and publication of results. The inclusion of community protection standards in clinical research could have widespread implications for studies that seek to use race or ethnicity as study variables—most especially, race-exclusive research projects.

To date, community-level protections that have been included in research ethics frameworks have focused on indigenous populations. The extent to which such protections should be applied more broadly is subject to debate. Some commentators have concluded that there are “substantial problems” with applying protections developed for indigenous communities to other less cohesive communities, especially ones without legitimate political authority. However, they did suggest that for communities such as the Amish, which are localized and highly cohesive, the protections found in guidelines for indigenous communities

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77 Id.
may be an appropriate template. The role of community involvement in the development and approval of race-exclusive research warrants consideration in future research.

**Conclusion**

Despite ongoing controversy, racial and ethnic analyses are an established component of American clinical research. Drug regulatory frameworks, including IRBs, should play an active role in ensuring that the use of race and ethnicity in clinical research is scientifically and ethically robust. However, for IRBs to satisfy this role, they need far greater clarity about the relationship between the Common Rule requirements for approving clinical trials, and the issues raised by the use race or ethnicity in clinical research. In this paper, I have suggested that separating out the pertinent scientific and ethical issues in accordance with a three-pronged framework can promote such clarity. Namely, the manner in which an IRB reviews clinical research should take into account whether it is: (1) *race-inclusive research*, which does not seek to analyze racial or ethnic differences; (2) *race-targeted research*, which sets out to study possible differences between racial or ethnic groups; or (3) *race-exclusive research*, which uses the results from race-targeted research to justify studying the intervention only in specific racial or ethnic groups.

The three-pronged model also is likely to have relevance for other components of the drug regulatory framework; most notably, FDA drug approval and labeling processes. This is an issue that should be explored more closely.

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79 Weijer, Goldsand, and Emanuel, *supra* note 76.
## Appendix A: Currently recruiting trials with race-based inclusion requirements

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
</tr>
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<tbody>
<tr>
<td>A Study of Alimta/Cisplatin/Gefitinib for Asian Non-smoking Patients With Non Small Cell Lung Cancer</td>
<td>Eli Lilly and Company</td>
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<tr>
<td>A Study of Early Immunologic Response in Asian Patients With Chronic Hepatitis B, Treated With Pegasys (Peginterferon Alfa-2a (40KD)), Nucleoside Analogues, or Both</td>
<td>Hoffmann-La Roche</td>
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<tr>
<td>Aromatase Activity and Ovarian Growth Factors in African-American Versus Caucasian Women</td>
<td>Massachusetts General Hospital</td>
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<td>Comparison of Brivanib and Best Supportive Care to Placebo for Treatment of Liver Cancer for Asian Subjects Who Have Failed Sorafenib Treatment (BRISK-APS)</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>Effect of Entecavir in Blacks/African Americans and Hispanics With Chronic Hepatitis B Virus (HBV) Infection</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>Effect of Race/Ethnicity and Genes on Acetaminophen Pharmacokinetics</td>
<td>Tufts University</td>
</tr>
<tr>
<td>Efficacy and Safety of Linagliptin (BI 1356) in Black/African Americans With Type 2 Diabetes With a MTT Sub-study</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
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<tr>
<td>Impact of Conversion From Tacrolimus to Sirolimus in African American Renal Transplant Recipients</td>
<td>Temple University</td>
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<tr>
<td>Irinotecan in Treating Asian Patients With Solid Tumors</td>
<td>National Cancer Centre, Singapore</td>
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<tr>
<td>Open Label Study to Evaluate the Safety, Efficacy, Viral Kinetics, Genetic, Epigenetic, and Proteomic Expression of Weekly Peginterferon Alpha 2a and Ribavirin Therapy for Chronic Hepatitis C in Latino Subjects With and Without HIV Co-infection</td>
<td>National Institute of Allergy and Infectious Diseases (NIAID)</td>
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<tr>
<td>OSI-774 in African American Patients With Advanced and Previously Treated Non-Small Cell Lung Cancer</td>
<td>Ohio State University Comprehensive Cancer Center</td>
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<td>Pathophysiology of Cardiometabolic Risk Factors in African Americans</td>
<td>Vanderbilt University</td>
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<td>Prevascar in African Continental Group Scarring</td>
<td>Renovo</td>
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<tr>
<td>Sirolimus Conversions in African-American Renal Transplant Recipients</td>
<td>Medical University of South Carolina</td>
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<tr>
<td>Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE)*</td>
<td>Henry Ford Health System</td>
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<td>Study of Ixabepilone in Asian Subjects With Unresectable or Metastatic Gastric Cancer</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>Study to Determine the Effects of Nebivolol and Hydrochlorothiazide in African Americans With Hypertension (NASAA)</td>
<td>InVasc Therapeutics, Inc</td>
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<tr>
<td>The Effect of Docetaxel or Gemcitabine-Based Chemotherapy in East Asian and Caucasian Patients*</td>
<td>National University Hospital, Singapore</td>
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<tr>
<td>The Effect of Nebivolol on Endothelial Dysfunction in African Americans With Hypertension</td>
<td>Emory University</td>
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<tr>
<td>The Effect of Non-Surgical Periodontal Therapy on Glycemic Control and Bacterial Levels in a Mexican-American Population With Type 2 Diabetes</td>
<td>The University of Texas Health Science Center</td>
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</table>

* Race/ethnicity not specified as an inclusion criterion but race/ethnicity restrictions inferred from the study description.