Doubly disadvantaged: on the recruitment of diverse subjects for clinical trials in Latin America

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ABSTRACT
Due to its allegedly diverse population and strong doctor–patient relations, Latin America has become one of the most attractive locations for international clinical trials. In the paper, I examine the case of recruitment of women and minority patients to serve as subjects of international clinical trials, through CROs operating in Latin America. In particular, the paper examines some of the strategies that CROs use to expand their services in the Latin American medical market, illuminating the mechanisms through which the current organization of medical research contributes to power imbalances in the Global South. After analyzing the epistemic and ethical shortcomings of such endeavor, I show how Latin American patients participating in clinical trials are located in a position of double disadvantage. First, they suffer the consequences of a lack of appropriate understanding of symptoms and reaction to treatment. Second, they suffer the consequences of being subjects in clinical trials which are not designed to meet their needs, but the needs of patients in the Global North. Accordingly, I conclude by highlighting the importance of this double disadvantage and suggesting that the problem can be understood in terms of a misalignment of commercial, ethical, and epistemic concerns in clinical research.

KEYWORDS
Commercialized medicine; patient recruitment; diversity in clinical trials; contract research organizations; clinical trials in Latin America

Duplicamente desfavorecido: Sobre o Recrutamento de Sujeitos Diversificados Para Ensaios Clínicos na América Latina

RESUMO
Devido à supostamente diversa população e às fortes relações médico–paciente, a América Latina tornou-se um dos locais mais atraientes para ensaios clínicos internacionais. No artigo, eu examino o caso de recrutamento de mulheres e pacientes pertencentes aos grupos de minoria para servirem como sujeitos de ensaios clínicos internacionais, por meio de CROs que operam na América Latina. Depois de analisar as deficiências epistêmicas e éticas de tal empreendimento, eu argumento que os pacientes latino-americanos que participam desses estudos estão localizados em uma posição de dupla desvantagem. Primeiro, sofrem as consequências de uma falta de compreensão apropriada dos
sintomas e das possíveis reações ao tratamento. Em segundo lugar, sofrem as consequências diretas de serem sujeitos de ensaios clínicos que não são projetados para atender às suas necessidades, mas sim às necessidades dos pacientes no Norte Global. Assim, concluo ressaltando a importância dessa dupla desvantagem e sugerindo que o problema pode ser entendido em termos de um desalinhamento das preocupações comerciais, éticas e epistêmicas na pesquisa clínica.

Doblemente desfavorecidos: sobre el reclutamiento de sujetos diversos para ensayos clínicos en América Latina

RESUMEN
América Latina se ha convertido en uno de los lugares más atractivos para ensayos clínicos internacionales, debido a su supuesta diversidad poblacional y a las relaciones fuertes entre médicos y pacientes. En este artículo, examino el caso del reclutamiento de mujeres y pacientes pertenecientes a minorías a través de Organizaciones de Investigación por Contrato (OIC) que operan en América Latina, para incorporarlos como sujetos de ensayos clínicos internacionales. En particular, analizo algunas de las estrategias utilizadas por las OICs para expandir sus servicios en el mercado médico latinoamericano, e identifico los mecanismos a través de los cuales la actual organización de la investigación médica contribuye a los desequilibrios de poder en el Sur Global. Después de analizar las limitaciones epistémicas y éticas de dicha labor, muestro las formas en las que los pacientes latinoamericanos que participan en estos estudios son situados en una posición de doble desventaja. En primera instancia, sufren las consecuencias de la falta de conocimiento de los síntomas y las posibles reacciones al tratamiento. En segundo lugar, sufren las consecuencias de ser sujetos de ensayos clínicos que no están diseñados para satisfacer sus necesidades, sino más bien las necesidades de pacientes en el Norte Global. De esta forma, concluyo subrayando la importancia de esta doble desventaja y sugiero que el problema puede ser entendido en términos de una desalienación de las consideraciones comerciales, éticas y epistêmicas de la investigación clínica.

1. Introduction

As emphasized by women’s health advocates, the inclusion of research subjects who have been traditionally excluded from medical research is the first major step to acquire more specific knowledge about diseases that affect that particular group of patients, as well as to develop better treatments. In addition to this epistemic gain, an appropriate diversification of research subjects aims to address issues of sexism, racism, and previous history of exploitation and abuse of research subjects (Gamble 1997). However, two important challenges arise. First, the recruitment of women and minorities for clinical research can be challenging, especially among groups with histories of clinical abuse and patient exploitation. Second, patients in high-income countries, where most revenues for pharmaceutical companies are located, tend to consume more medicines and thus become less ideal as subjects for clinical trials. In this scenario, Latin America has become one of the most attractive
locations for the recruitment of research subjects in international clinical trials, due to its diverse and treatment-naïve population (i.e. patients who have not undergone treatment for the condition to be studied), as well as strong doctor–patient relations, in which doctors enjoy positions of social privilege and respect, and where patients feel pressed to comply with doctors’ recommendations (Ukwu et al. 2011; Homedes and Ugalde 2014).

The paper provides a philosophical analysis of patient recruitment, especially women and minority patients, as subjects of clinical trials in Latin America. The paper follows recent work in social epistemology of science (Longino 1990; Solomon 2001; Kourany 2010; Harding 2015) and in philosophy of medicine (Solomon 2015; Solomon, Simon, and Kincaid 2017; Stegenga 2018; Valles 2018), which emphasizes that medical research is both a social and an epistemic endeavor, and that any philosophical account of such practice ought to consider not only its epistemic goals but also its social dimensions. In addition, the paper also acknowledges recent contributions from scholars working on science and technology studies, who have unpacked the social complexities of clinical research today, mostly managed by multinational pharmaceutical companies at a global scale (Epstein 2007; Petryna 2009; Fischer 2009; Mirowski 2011; Sismondo and Greene 2015; Rajan 2017).

In the paper, I examine the case of recruitment of women and minority patients for clinical trials through contract research organizations (CROs) operating in Latin America. In particular, the paper examines some of the strategies that CROs use to expand their services in the Latin American medical market, illuminating the mechanisms through which the current organization of medical research contributes to power imbalances in the Global South. After analyzing the epistemic and ethical shortcomings of such endeavor, I show how Latin American patients participating in clinical trials are located in a position of double disadvantage. First, they suffer the consequences of a lack of appropriate understanding of symptoms and reaction to treatment in women and other underrepresented groups, which has led in turn to unnecessary suffering and death. Second, they suffer the direct consequences of being subjects in clinical trials which are not designed to meet their needs, but the needs of patients in the Global North. Accordingly, I conclude by highlighting the importance of acknowledging this double disadvantage to understand how commercial interests influence the ethical and epistemic concerns of clinical research at the global scale.

2. Recruitment of women and minority subjects for medical trials

Efforts to diversify the pool of subjects for clinical trials became a concern as gender and racial biases were uncovered in medical research (Dresser 1992; Rosser 1994; Van Ryn 2002). Women and minority groups were traditionally excluded from clinical trials, where the white-male was taken as the human standard (Simon 2005). This meant that research results were inaccurately generalized to treat everybody, ignoring variations in patients’ physicality, symptomatology, disease development, and reaction to treatment. Although the problem has not completely disappeared (Westervelt 2015), important efforts have been made to change the idea of the white-male as the standard human subject and to diversify the pool of participants in clinical trials. The participation of previously marginalized groups of patients in clinical trials aims to be inclusive and egalitarian, insofar as the knowledge produced should favor the common good and not only a small privileged group.
In the early 90s, the FDA took a step towards the inclusion of marginalized groups in clinical trials through its “Guideline for the Study and Evaluation of Gender Differences in Clinical Evaluation of Drugs,” which states that

The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug response. (FDA 1993, 1C)

Similarly, inclusion efforts became salient in the NIH Revitalization Act of 1993, which states that NIH-funded clinical research has to ensure that: “(a) women are included as subjects in each project of such research; and (b) members of minority groups are included in such research” (NIH 1993, 492B(a)(1)).

Traditionally, clinical trials have been conducted in the Global North, especially in high-income countries, such as the US, the UK, Canada, Germany, and France. Even today, 66% of clinical trials worldwide are concentrated in these five countries (clinicaltrials.gov). Despite initiatives from the FDA, the NIH, and other funding and regulatory agencies, the inclusion of marginalized groups in trials located in the Global North has not been easy, facing at least three major problems. First, given the history of clinical abuse and patient exploitation, traditionally underrepresented groups are skeptical about participating in clinical trials and do not trust medical researchers, as many have documented (Gamble 1997; Corbie-Smith, Moody-Ayers, and Thrasher 2004; Dancy et al. 2004; Moreno-John et al. 2004; Branson, Davis, and Butler 2007).

Second, patients in high-income countries, where most clinical trials have been traditionally conducted, tend to consume more medicines and thus tend to be less ideal subjects for clinical trials. In the US, for example, patients expended $1,174 dollars per capita in pharmaceuticals in 2016, according to the latest OECD Health Statistics (2018). As Petryna claims, “‘Treatment saturation’ is making Americans increasingly unusable from a drug-testing standpoint, as our pharmaceuticalized bodies produce too many drug-to-drug interactions, providing less and less capacity to show drug effectiveness and making test results less statistically valid” (2005, 185).

Third, and related to the last point, the fact that patients taking multiple medications are systematically excluded from clinical trials plus the fact that more and more patients in the Global North are taking multiple medications, opens a gap between the sample population used in clinical trials (i.e. treatment-naïve patients) and the eventual treatment population (i.e. patients taking multiple medications), which in turn questions the external validity of trial results (see, e.g. Masoudi 2003). In other words, it is not clear why patients taking multiple medications should trust results of clinical trials which study only treatment-naïve patients, and not patients with drug-to-drug interactions.

Given the over-medicalization of the overall population, the search for exclusively treatment-naïve patients, and the history of medical abuse towards marginalized populations, finding appropriate individuals to participate in clinical research is becoming more and more difficult. Accordingly, pharmaceutical companies, driving around 80% of international clinical trials (Atal et al. 2015), have developed different strategies for the more efficient recruitment of research subjects. Patient recruitment tactics have become so specialized and elaborate that some are talking about a science of recruitmentology, i.e. “the empirical body of studies scientifically evaluating the efficacy of various social,
cultural, psychological, technological, and economic means of convincing people (especially members of 'hard-to-recruit population') that they want to become, and remain, human subjects” (Epstein 2008, 801). Let me mention just two of these recruitment tactics.

First, recruitmentologists have shown the advantages of participatory research, in its various forms, scientifically identifying better ways to recruit underrepresented groups of patients. For instance, community-based participatory action research has proven successful for the recruitment of African Americans (Dancy et al. 2004; Branson, Davis, and Butler 2007) and Latinos (Sheppard et al. 2005), and even more effective than traditional population-based recruitment methods (Gilliss et al. 2001; Cabral et al. 2003). For example, Branson and his colleagues state that:

A multifaceted approach to enhancing minority enrollment in clinical trials includes involvement of local opinion leaders, culturally competent programs and investigators, honest and appropriate discussion of risks, use of multiple formats for presentation of procedures and risks, and community consent. (Branson, Davis, and Butler 2007, 38)

On the other hand, of course, participatory research may offer a simple and effective tactic to sign research subjects, i.e. “to get the ‘bodies’ that they [the investigators] seek for the research they already have determined to conduct” (Epstein 2007, 197). Either way, recruitmentologists encourage pharmaceutical companies to use participatory recruitment practices as an effective way of engaging women and minorities in clinical trials (see, e.g. Getz 2015; Experientia 2016).

Second, and as a consequence of over-medicalization in high-income countries, treatment-naïve patients, i.e. patients who haven’t been exposed to particular treatments, are scarce. Thus, search for research subjects has moved overseas, particularly to Eastern Europe, Asia, and Latin America (Thiers, Sinskey, and Berndt 2008; Drain et al. 2014). Between 2005 and 2012, Latin America presented the second largest average annual growth rate of clinical trials (12%), only after Asia (30%) (Drain et al. 2014). As of July 2018, 2114 of the 47,345 recruiting trials worldwide are located in Latin America (https://clinicaltrials.gov).

Specialized CROs have been particularly successful in recruiting patients for major pharmaceutical companies worldwide. CROs have been carefully manufactured to have a flexible structure so that they are not tied to particular geographic locations or academic settings (Mirowski and van Horn 2005), making them ideal for mobilizing recruitment efforts to emerging regions with treatment-naïve populations and massive urban centers (Petryna, Lakoff, and Kleinman 2006). As expected, CROs have adapted quickly to new research markets in Latin America (Ukwu et al. 2011).

Take for instance the case of Pharm-Olam, a global CRO in the business of performing international clinical trials. Among other services, Pharm-Olam specializes in “global patient recruitment”:

We start by accurately identifying target patient populations through feasibility assessments and by implementing cost-effective strategies and tactics to complete enrollment on time. Due to time constraints and high cost of delays commonly encountered in clinical trials, feasibility research is essential to planning a clinical trial. Our recommendations, based on feasibility analysis, have saved sponsors millions in clinical development costs through enhanced protocol design modifications and reduced recruitment periods. Our feasibility
research provides specific insights into enrollment, screening failure/completion rates, and retention. (www.pharm-olam.com)

To guarantee the recruitment of research subjects, Pharm-Olam has a global network of recruiting agencies, and strongly promotes patient recruitment in emerging markets, where they can find “easy access to patients who are either treatment-naïve or modern-treatment naïve,” and where patients are “as a rule, very willing to take part and very motivated to remain compliant with their treatment regime” given that “participating in trials gives patients in these countries access to the latest therapies and often, closer medical supervision, more advanced diagnostic equipment, and more extensive follow-up care than they would otherwise receive” (Pharm-Olam 2016, 3). Nowadays, Pharm-Olam is strongly advertising Latin America as a “world of opportunity” to register clinical trials, highlighting among others its “diverse patient population” which “allow for broader array of inclusion and exclusion criteria” (www.pharm-olam.com).

Pharm-Olam is hardly an exception. A quick google search of “CROs in Latin America” offering services to pharmaceutical companies renders similar results. As shown in Table 1, CROs operating in Latin America frequently highlight the region’s diverse population, treatment-naïve patients, and strong doctor–patient relations, as assets for patient recruitment in clinical trials.

Pharmaceutical companies frequently claim that the high price of drugs is directly related to the high costs of research. According to PhRMA (Pharmaceutical Research and Manufacturers of America):

[Developing new medicines is an incredibly difficult, long, and costly process. It takes on average 10 to 15 years and $2.6 billion to bring a new medicine to patients. And because of the complicated nature of biology, most drugs that are tested never make it to market. (Zirkelbach 2014)

Although we have good reasons to doubt the accuracy of these numbers, e.g. a recent study shows that the average cost to bring a new drug to market ranges more likely between 180 and 231 million dollars (Light and Warburton 2011), the truth is that pharmaceutical companies strive to reduce the cost of putting a new drug in the market. Within this process, the recruitment of research subjects is seen as a particularly inefficient aspect, in which around 80% of trials fail to meet enrollment deadlines (Drennan 2002). Both the use of participatory research recruitment and the outsourcing and off-shoring of patient recruitment are commonly used tactics of the pharmaceutical industry to satisfy regulatory demands and shorten clinical trial timelines, thus speeding up their drug approval process.

The success of CROs depends on their capacity to render results in an efficient and cost-effective manner and in particular on their ability “to recruit patients quickly and more cheaply than academic medical centers” (Petryna 2005, 186). Accordingly, Latin American countries are portrayed as ideal locations for overcoming recruitment limitations. As FOMAT Medical Research, another CRO operating in the region, claims: “Latin America enjoys excellent patient retention. Physicians and patients in these areas have strong bonds that result in high rates of patient compliance and study retention,” and moreover, “Latin America offers vast diversity for a rapid recruitment, most countries are multicultural and had become a great location to develop a broad-spectrum research” (FOMAT 2015, 6).
Table 1. Summary of CROs operating in Latin America.

| CRO                                      | Countries where it operates (locations) | Emphasis on region's ethnic diversity | Emphasis on trial and treatment-naive patients | Emphasis on strong doctor/patient relations | URL                                      |
|------------------------------------------|----------------------------------------|--------------------------------------|-----------------------------------------------|--------------------------------------------|------------------------------------------|
| Cidal                                    | Latin America and the Caribbean (12 countries) | X                                    | X                                             | X                                         | www.cidal.net/                            |
| Chiltern                                 | Argentina, Brazil, Chile, Mexico       | X                                    | X                                             |                                            | www.chiltern.com/#home                     |
| Clinipace Worldwide                      | Argentina, Brazil, Peru                | X                                    | X                                             |                                            | www.clinipace.com/                         |
| Covance                                  | Argentina, Brazil, Chile, Mexico, Peru, Colombia | X                                    | X                                             |                                            | www.covance.com/                           |
| ESTERN Medical                           | Argentina, Brazil, Chile, Colombia     | X                                    | X                                             |                                            | www.esternmedical.com/                     |
| Fomat Medical Research                   | Ecuador and other countries not specified (4 countries mentioned) | X                                    | X                                             |                                            | www.fomatmedical.com/                      |
| ICON                                     | Argentina, Brazil, Chile, Colombia, Mexico, Peru | X                                    | X                                             |                                            | www.iconplc.com/                           |
| Intrials                                 | Argentina, Brazil, Chile, Colombia, Mexico, Peru | X                                    | X                                             |                                            | www.intrials.com.br/                        |
| Syneos Health (INC Medical Research + inVentive Health Clinical) | Argentina, Brazil, Colombia, Mexico, Peru | X                                    |                                               |                                            | www.syneoshealth.com                       |
| MDS                                      | Argentina, Brazil, Chile, Colombia, Mexico, Peru | X                                    | X                                             |                                            | www.mdspcs.com/                            |
| Medpace                                  | Argentina, Brazil, Mexico              | X                                    | X                                             |                                            | www.medpace.com/                           |
| Paralex                                  | Argentina, Brazil, Chile, Colombia, Mexico, Peru | X                                    | X                                             |                                            | www.parexel.com/                           |
| Pharm-Olam                                | Latin America: Brazil, Mexico          | X                                    | X                                             |                                            | www.pharm-olam.com/                         |
| PPD                                      | Argentina, Brazil, Chile, Colombia, Mexico, Peru | X                                    | X                                             |                                            | www.ppd.com/                               |
| IQVIA (former Quintiles)                 | Argentina, Brazil, Colombia, Mexico    | X                                    | X                                             |                                            | www.iqvia.com/                              |
| ReSolution Latin America                 | Not specified                          | X                                    | X                                             |                                            | www.resolutioncrs.com/                      |

3. Ethical and epistemic costs

Merely demanding a diverse pool of subjects in clinical trials is not enough to achieve the epistemic goal of obtaining better medical knowledge or the ethical goal of successfully
treating patients. This section shows that pharmaceutical companies can easily comply with regulations demanding diverse subjects without caring at all about understanding health differences or appropriately treating these patients. I examine two aspects of the current implementation of clinical trials in Latin America to illustrate this point. First, when clinical trials include a diverse pool of subjects, but the experimental design does not reflect this diversity; and, second, when doctors have conflicts of interests, especially strong financial incentives to recruit subjects for clinical trials, which can lead to the inclusion of unsuitable subjects.

Despite the pharmaceutical industry trying to comply with FDA regulations in the recruitment of women and minority subjects in clinical trials, it is not clear that the tactics used can grant a better understanding of health differences. In fact, a mere compliance with FDA guidelines, without the required oversight of the whole research process leads in turn to significant ethical and epistemic costs. Diversity might be a necessary condition for the study of diseases and drug benefits in underrepresented groups, but it is obviously not sufficient. In order to obtain results relevant for underrepresented groups, the study design and the data collection and analysis have to be consistent with this aim. However, in many cases, this is not being done. As Steve Epstein reports:

While various populations (women, in particular) are being included in greater numbers, either the subgroup analyses are not performed or the results are not being reported and published. Thus, the premise that underrepresentation matters because results cannot necessarily be generalized is not actually translating into a careful study of when or where generalizations break down – let alone an investigation of the underlying causes or mechanisms that bring about medical differences between human groups. (Epstein 2007, 167)

In 2000, a study on NIH-funded clinical research evaluating the impact of the 1993 Revitalization Act concluded: “In addition to finding that women are still excluded from a considerable proportion of clinical research studies, we found that analysis of outcomes by sex is sorely lacking” (Vidaver 2000, 502). Specifically, “Only one quarter to one third of the studies that included women analyzed data by sex of the subjects” (2000, 495). A 2011 systematic review of NIH-funded studies looking at outcome reporting by sex and race/ethnicity found no significant improvements: “Seventy-five percent of the studies did not report any outcomes by sex, including 9 studies reporting <20% women enrolled” (Geller 2011, 315). The study also identifies a similar issue regarding race/ethnicity reporting: “Among all 86 studies, 21% did not report sample sizes by racial and ethnic groups, and 64% did not provide any analysis by racial or ethnic groups” (2011, 315). This is particularly worrisome given that treatment recommendations tend to be neutral regarding sex or race/ethnicity, even in cases where the analysis has not been sex or race/ethnicity specific, which in turn obscures our understanding of potential differences in response to treatment (Charney and Morgan 1996). The FDA has also acknowledged this point recently: “Inclusion did not necessarily mean that the data on patient subgroups was sufficient for meaningful analysis or to detect relevant subgroup effects” (2013, 5). So even when researchers comply with regulations demanding the inclusion of women and minorities as research subjects, this does not guarantee the epistemic gain that ought to come from such inclusion, and in some cases, it might even give the false impression that the research is, for example, sex-specific when it is not.
In addition, complying with the inclusion of a diverse pool of subjects without a real concern for understanding health differences has worrying ethical implications. To continue with the example of sex differences, historically underrepresented groups have been medically treated according to data obtained from clinical research on white males (Ramasubbu, Gurm, and Litaker 2001, 757), while sex-specific clinical research has shown significant sex differences on drug-metabolizing enzymes (Fletcher, Acosta, and Strykowski 1994; Bigos et al. 2009), cancer etiology (Tseng 1999), heart disease symptoms and reaction to treatment (Maxwell 1998), and so on. Accordingly, a lack of appropriate understanding of symptoms and reaction to treatment in women within clinical research has led to unnecessary suffering and death.

Another shortcoming of the pharmaceutical industry’s tactics for the recruitment of research subjects is, not surprisingly, the different conflicts of interest that it creates. To give just one example, CROs offer important sums to doctors to help them recruit patients, and in some cases, they also offer benefits based on how quickly they succeed. According to former editor-in-chief of the New England Journal of Medicine, Marcia Angell:

To get human subjects, drug companies or contract research organizations routinely offer doctors large bounties (averaging about $7000 per patient in 2001) and sometimes bonuses for rapid enrollment. For example, according to a 2000 Department of Health and Human Services inspector general’s report, physicians in one trial were paid $12,000 for each patient enrolled, plus another $30,000 on the enrollment of the sixth patient. One risk of this bounty and bonus system is that it can induce doctors to enroll patients who are not really eligible. (Angell 2004, 30–31)

Homedes and Ugalde (2014) raise a similar concern regarding incentives for investigators in Latin America, who might not only enroll patients who do not fulfill the criteria but also might retain patients “who should be excluded due to adverse effects” (58). Of course, the inclusion of non-eligible patients in clinical trials compromises not only the epistemic adequacy of the study but also patients’ health. Homedes and Ugalde also report that paid patient recruitment in low and middle-income countries, with weaker regulatory environments, encourages other unethical behavior:

It is known that in Latin America there are researchers who recruit their own patients, even to the point of reviewing medical records in public facilities to identify possible participants; some pay other physicians per patient referred, and some contact academic centers to recruit students when health participants are needed. Other methods include the use of media to advertise and broadcast information about the study, frequently exaggerating the possible benefits without including the risks, and offering money to participants. (Homedes and Ugalde 2014, 58)

In general, incentives per patient recruited create a conflict of interest for researchers and doctors, which might compromise both the epistemic and ethical aspects of clinical trials. Conflicts of interest in the recruitment of research subjects of clinical trials compromise the quality of the knowledge achieved (an epistemic cost), as well as patients’ health (an ethical cost). For instance, by encouraging doctors to recruit or maintain patients who do not meet the criteria for the study, conflicts of interest affect both the quality of the results obtained as well as the well-being of the patients involved. In addition, a systematic exploitation of patients for clinical trials has the risk of eventually undermining the relation of trust that Latin American patients commonly have with their doctors. If we understand
trust as a fundamental value for the proper production and dissemination of scientific knowledge (De Melo-Martín and Intemann 2018), this erosion of trust would further complicate the proper production and dissemination of medical knowledge relevant for Latin American patients.

As the examples examined in the previous sections have shown, strategies to increase the diversity of research subjects in medical research are susceptible of being distorted in favor of commercial interests with significant epistemic and ethical costs. For instance, misusing strategies to diversify the pool of subjects in clinical trials seems to harm the epistemic appropriateness of clinical research under the banner of allegedly good social and ethical goals, e.g. patient empowerment, diverse subjects of study, attention to the health needs of particular groups, etc. Not only are these goals devious, since they are not the main goals behind the pharmaceutical industry’s support of clinical trials (Rajan 2017), but they become also double-edge swords; they hurt the epistemic goals of clinical research and they also end up compromising the ethical and social impact that research could accomplish.

As the example of patient recruitment illustrates, merely diversifying the pool of research subjects does not lead to a better understanding of health differences, which in turn does not allow for adequate treatment of patients belonging to underrepresented groups. In this sense, one should notice that the epistemic and ethical costs, at least the ones identified in the cases examined in this paper, are intertwined. Conflicts of interest, for example, have both ethical and epistemic costs for the recruitment of research subjects in clinical trials. This connection between the epistemic and the ethical costs opens the door to questions pertaining to the relation between the ethical and epistemic aspects of research.

Recent work in social epistemology of science and philosophy of medicine has examined the relation between the ethical and the epistemic aspects of research. Various authors (see e.g. Longino 1990; Kincaid, Dupré, and Wylie 2007; Carrier, Howard, and Kourany 2008; Douglas 2009; Kourany 2010; Elliott 2011) have tried to clarify the character and the appropriate extent of the influence of ethical and social values in scientific research. Without undermining the importance of such work, these proposals tend to focus on one direction of the relation between the ethical and the epistemic aspects of research, i.e. how ethical/social values affect (or ought to affect) the process of knowledge production. Less attention has been paid to the ways in which the epistemic and ethical aspects of scientific research are closely intertwined, so that changes in one aspect frequently trigger changes in the other. In this sense, as others have emphasized, the relation between the ethical and the epistemic aspects of scientific research is more complex (Tuana 2013; Hicks 2014; Katikireddi and Valles 2015; Fernández Pinto 2018).

As the argument of this paper shows, the ethical and the epistemic aspects of research are intertwined, so that decisions taken during the research process, for instance, the decision to pay doctors for the recruitment of research subjects in clinical trials, has both ethical and epistemic costs. And even if we can conceptually differentiate between the two types of costs, ethical and epistemic, they are both implied by the same decision. In fact, the ethical and epistemic aspects of scientific research are so intertwined that different decisions in the research process, for instance, decisions to improve the epistemic quality of the research, induce changes in the ethical aspects and vice versa. If, for example, a measure is taken to ban doctor compensation per patient recruited in...
order to avoid including patients who do not meet the criteria for the trial, this will not only benefit the results of the study but also the health of the patients (both the patients who might benefit from the drug, and the patients who are not qualified to participate). Thus, the recruitment of research subjects examined in this paper presents a good example of the close relation between the epistemic and ethical aspects of research.

Part of the problem with current recruitment tactics for clinical trials is driven by the influence of commercial interests in scientific research, in this case, the interests of the pharmaceutical companies. As many have emphasized, the epistemic and ethical challenges of commercially driven research today are plenty (Brown 2000; Krimsky 2003; Radder 2010), and clinical research driven by the pharmaceutical industry has proven to be particularly problematic (Elliott 2003; Goldacre 2013; Whitaker and Cosgrove 2015; Rajan 2017; Fernández Pinto 2018); although it has also been successful in some cases (Biehl 2007; Carrier 2008).

Without trying to unpack this problem in all its details, my aim is to suggest a possible reading or diagnostic. I suggest that the tensions uncovered in commercially driven research today, including clinical research, can be characterized as a \textit{misalignment} of the multiple goals of science. Clinical research has at least three different goals: an \textit{epistemic} goal (to achieve better medical knowledge), an \textit{ethical} goal (to procure the well-being of patients), and a \textit{commercial} goal (to achieve a profitable product). As the example of recruitment illustrates, these goals are not well-aligned. Instead of using the ethical value of diversity to \textit{complement} the epistemic appropriateness of medical research and the commercial success of the medication under study, leading to more empirically accurate, socially responsible, and commercially successful medical knowledge (as suggested, for example, by Harding 2015), commercial interests have encouraged researchers to misuse the value of diversity which has \textit{compromised} the epistemic and ethical appropriateness of the research, while favoring only commercial goals.

Commercial interests might not necessarily compromise the ethical and epistemic goals of research (Carrier 2009), in so far as private companies can also thrive in tandem with proper medical knowledge and human health, as the development of antiretroviral drugs for the treatment of HIV illustrates (Epstein 1995). In my view, problems arise when there is a misalignment of research goals. More specifically, in cases in which commercial goals are given priority over ethical and epistemic goals, as the present case exemplifies, ethical and epistemic costs seem to follow. Accordingly, the organization of medical research should strive for maintaining a proper alignment of the different goals of research (for further details on this view, see Fernández Pinto 2018).

4. A double disadvantage

So far, I have argued that some of the strategies implemented to diversify the pool of subjects in clinical trials have been compromised to favor commercial interests, which comes at a significant ethical and epistemic cost. I have also suggested that the problem arises when the ethical, epistemic, and commercial goals of research are not properly aligned. In addition, given that clinical trials are currently conducted at a global scale, an adequate understanding of recruitment strategies should also take into account how efforts to increase diversity impact populations outside high-income countries. In this section, I
argue that women and other traditionally marginalized patients, who are recruited as diverse subjects for clinical trials in Latin America, experience a double disadvantage (both in ethical and epistemic terms).

First, the lack of an appropriate understanding of symptoms and reaction to treatment in women and other underrepresented groups (an epistemic cost) has led to patients’ unnecessary suffering and death (an ethical cost). Take for instance the case of cardiac disease. Given that women were not included as subjects in clinical trials, we used to have no knowledge of the development of cardiac disease and reaction to treatment in women, which in turn led to a great number of women suffering and dying from a treatable disease (Nanda and Keser 2015). These are costs that patients in Latin America share with women and other traditionally underrepresented groups in medical research in the Global North. Second, these patients suffer the direct consequences of being subjects in clinical trials which are not designed to meet their needs, but the needs of patients in wealthier regions. These are additional costs not necessarily suffered by their counterparts in the Global North. This is a problem that becomes more salient given the strong doctor–patient relations in Latin America, which CROs and pharmaceutical companies exploit to secure recruitment in clinical trials. Moreover, this puts Latin American patients in a further position of disadvantage, feeling pressed to comply with their treating physician’s recommendation to participate in ongoing trials (e.g. FOMAT 2015, 6). This is also different from the relation between doctors and minorities in the US and other countries, where a history of exploitation has led to a lack of trust in doctors and clinical studies.

The majority of clinical trials conducted in Latin America are sponsored by multinational pharmaceutical companies (around 60%, according to clinicaltrials.gov), which are not interested in financing or conducting research on neglected diseases heavily concentrated in the region, such as dengue or Chagas (Da Silva 2018). Other relevant research, targeting diseases that affect both high-income and Latin American countries, such as research on diabetes or cardiovascular disease, involve treatments which are simply inadequate for current health care resources in Latin America (Perel 2006). In addition, many of the drugs tested in Latin America are not registered or marketed in the region after FDA approval, and when they are in fact available, they are unaffordable. For instance, a course of treatment of Afilbercept, a drug tested in Latin America to treat wet age-related macular degeneration and recently approved by the FDA, can cost 46 times the minimum wage in Brazil and up to 58 times the minimum wage in Argentina (Homedes and Ugalde 2016, 5).

Hence, Latin Americans do not gain a better understanding of the diseases and treatment that specifically affect them. Instead, patients who participate in clinical trials in Latin America contribute to the understanding of diseases and treatment that affect populations in the Global North. Moreover, even for Latin American patients who suffer from such diseases, their contribution is not particularly beneficial, given that tested drugs are not marketed in the region or they are marketed at unaffordable prices. In this way, given their particular socioeconomic and geographical status, Latin Americans frequently do not have access to the relevant medical knowledge to protect themselves from the diseases that specifically affect them (an epistemic cost) or they do not get the optimal treatment because it is unavailable or unaffordable, which leads to human suffering and even death (an ethical cost).
In sum, patients recruited overseas as a strategy to diversify clinical trials suffer a double disadvantage. First, they belong to traditionally underrepresented groups, who cannot protect themselves from irrelevant and harmful effects of trials; and second, they do not belong to the target population who would benefit from the outcome of the research.

5. Conclusions

The exclusion of women and minority subjects in clinical trials is now considered a worrisome methodological and ethical gap in medical research. To counteract this problem, government agencies in high-income countries, such as the FDA and the NIH, demand the inclusion of such underrepresented groups in clinical trials. Although the effort to diversify clinical trials is necessary to overcome the problem, it is also clearly not sufficient. Changes in experimental design and data analysis are also needed to obtain the relevant medical knowledge for these groups. Otherwise, women and minorities remain in a position of disadvantage regarding the production of medical knowledge.

In addition, pharmaceutical companies now work in tandem with specialized CROs to find properly diverse subjects for clinical trials and thus comply with regulations. Given the history of exploitation of minority groups in medical research in the US, as well as the over-medicalization of the population in high-income countries, CROs are now in the business of recruiting patients overseas. Given its diverse population, Latin America is a particularly attractive location for the recruitment of clinical subjects. Despite the many advantages of conducting clinical trials in Latin America, benefits for research subjects are not clear. In particular, given that the drugs tested are not targeted for regional diseases and they are not appropriately marketed or priced, these patients also seem to be in a position of disadvantage with respect to their counterparts in the Global North. In this sense, patients recruited overseas as a strategy to diversify clinical trials suffer what I have called a double disadvantage: they are in a position of disadvantage because they belong to traditionally underrepresented groups, and they are in another position of disadvantage in so far as they live in less wealthy regions, where the population does not necessarily benefit from the clinical research they help to develop.

In conclusion, to understand the scope of the ethical and epistemic costs of clinical research in commercial settings, particularly regarding the cooptation of strategies to diversify subjects in clinical trials, one must not only identify these costs and their mutual relation, but also acknowledge that they have different dimensions, just as in the case of the double disadvantage that I identify in the paper. Acknowledging the different interests at play in current clinical research, as well as their possible misalignments, is a first step to identifying, understanding, and possibly counteracting the social injustice produced by this social organization of science.

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