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The Trade-off between Impartiality and Freedom in the 21st Century Cures Act

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Abstract

Randomized controlled trials test new drugs using various debiasing devices to prevent participants from manipulating the trials. But participants often dislike controls, arguing that they impose a paternalist constraint on their legitimate preferences. The 21st Century Cures Act, passed by US Congress in 2016, encourages the Food and Drug Administration to use alternative testing methods, incorporating participants' preferences, for regulatory purposes. We discuss, from a historical perspective, the trade-off between trial impartiality and participants' freedom. We argue that the only way out is considering which methods improve upon the performance of conventional trials in keeping dangerous or inefficacious compounds out of pharmaceutical markets.

1. Introduction

In 1997, Harry Marks published *The Progress of Experiment*, a landmark history of the rise of randomized clinical trials (RCTs) in the United States (US). RCTs are standardized experiments for assessing the safety and efficacy of medical treatments. By design, RCTs control for a number of well-known biases that may interfere with the assessment. For instance, RCTs compare a new treatment to an already existing intervention (or a placebo). Physicians and patients are usually not indifferent to the treatments under study: for instance, patients often drop out of tests if they do not receive the drug they want. To prevent participants' preferences from interfering with the assessment, treatments are blinded so

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that participants cannot tell which intervention they are receiving. Blinding is a trial control intended to contribute to the *impartiality* of the experiment: controls prevent any of the trial stakeholders (researchers, clinicians, patients) from influencing the outcome according to their particular interests.[1] Impartiality plays a crucial role in Marks's account. As we will see in more detail in section 2, RCTs became the main tool for US drug regulators at a time when there was great public mistrust of the pharmaceutical industry. The impartiality of trials, based on many controls, delivered evidence that was prima facie free from industrial interests. In 1962, an amendment to the Food and Drug Administration (FDA) Act required that pharmaceutical manufacturers provide "adequate and well-controlled clinical studies" as proof of efficacy and safety. The FDA developed this in further detail the following year (Carpenter and Moore 2007, 355–356), although it took until 1969 to formally define what a well-controlled study meant (Podolsky 2015, 108–111).

Following in Marks's steps, historians and critics of the pharmaceutical industry have contested the claim that controls are enough to guarantee the impartiality of industry-sponsored trials, as the interests in conflict are too powerful. Dominique Tobbell (2011) explores industry strategies to silence critics in the 1950s and 1960s, either through marketing campaigns promoting misleading views or by undermining the authority of the FDA through problematic partnerships. For Tobell, RCTs were never sufficiently persuasive to settle the question of the efficacy of medical treatments. As to the industry scourges, Peter C. Gøtzsche (2013) shows the many ways in which the industry can manipulate RCTs to achieve a desired outcome—for example, deleting a few data points to achieve statistical significance. For Gøtzsche, the only solution would be more rigorous trial designs in which the industry has no say.

Paradoxically, many patient advocacy groups are demanding *fewer*, rather than *more,* trial controls. Trial participants want to see their preferences incorporated into trial design, rather than suppressed. They care about impartial evidence, but in the US they revolt against the *paternalistic justification of controls*.[2] In standard RCTs, patients are told that treatments are prima facie equivalent (until the trial proves otherwise)—this is *equipoise* (Freedman 1987). Blinding compels trial participants to accept this equivalence, depriving them of information about the actual treatment they receive. Trialists know better and they decide for patients which treatment they should receive using a randomizing device.

We know a great deal about the historical rise of impartiality in pharmaceutical regulation but, as we will see, historians have written little on the parallel rise of the FDA as a paternalistic gatekeeper of pharmaceutical markets—this article is an invitation to explore this issue further. Nonetheless, regulatory paternalism has been with us for almost half a century: after the 1962 FDA Act, patients in the US were only able to access those treatments that the FDA had declared safe and efficacious through RCTs.[3] Impartiality and paternalism

[1] As one reviewer of this article rightly observed, there is more than debiasing to the history of any of these controls. For instance, blinding played a crucial role in the experimental understanding of the placebo effect, helping researchers separate the causal effects of the treatment from participants' expectations about it. The success of randomization owes much to its appearance as a fair lottery for the allocation of scarce treatments. For more complex accounts of these two debiasing methods, see Teira (2013, 2016).

[2] From now on, we assume the standard definition of paternalism (Dworkin 2020): a third party interferes with the freedom of physicians/patients to prescribe/consume drugs for the sake of the patients' welfare. If that third party seeks the consent of physicians/patients to do so, we speak of soft paternalism. If there is no consent, it is hard paternalism. A trialist randomizing masked treatments to patients exerts a soft form of paternalism. A regulatory body preventing patients from consuming unauthorized drugs is strongly paternalistic. For a detailed discussion of pharmaceutical paternalism, see Teira (2020).

[3] Pharmaceutical regulation involves paternalism in varying degrees to the extent that it prevents compounds from gaining access to markets. In a nutshell, the 1906 FDA Act required drug testing to certify composition; the 1938 FDA Act prescribed testing for toxicity; and the 1962 FDA Act, as we will see, brought together safety and efficacy. Nontoxic but ineffective drugs were excluded from the market. In the eyes of many libertarian

in trials went hand in hand: the more controls on the experiment, the fewer options participants were given. In this article we want to show how this tight knot was severed, becoming a trade-off instead: the more participants' preferences a trial accommodates, the less impartial (controlled) the resulting evidence is.

In the last four decades, there has been an upsurge against regulatory paternalism, with US patients revolting against standard RCTs because of the constraints they impose on their preferences. And, finally, they have been heard. In 2016 the US Congress passed the 21st Century Cures Act, an ambitious Act reforming the organization of biomedical research in the US, with the overarching goal of bringing new treatments to patients more quickly. Some sections of the Act encouraged the FDA to use alternative sources of evidence to accelerate the drug-approval process. These new sources of evidence (alternative trial designs, observational studies, clinical experience) would enable the FDA to allow patients' preferences to be incorporated into studies, to varying degrees, and somehow satisfy the demands of the patients.

In this article, we first explore the evolution of the trade-off between impartiality and trial participants' freedom. In section 2, we discuss how trial impartiality was instrumental in the adoption of RCTs as regulatory tools in the US, and how impartiality went hand in hand with a paternalistic approach to both patients and trial participants. In section 3, we illustrate how trial participants' discontent with regulatory paternalism has grown slowly but inexorably since the 1980s, now reaching a point where standard trial controls such as blinding may not be enforceable anymore. In section 4 we discuss how the 21st Century Cures Act responds to these patients' initiatives with more flexible testing methods. We analyze the Salford Lung Study, a pragmatic trial that was used as a paradigm in a recent FDA workshop. We argue that the compromise it strikes between participants' preferences and outcome impartiality is far from satisfactory: dispensing with blinding comes at a price.

In the fifth and final section we respond to the more straightforward objection: there is no impartiality to preserve in trials; they have been predated by conflicts of interest right from the beginning. We suggest differentiating between interests outside the trial and experimental biases: controls can only neutralize the latter. But the contribution of controls should not be underestimated—if the goal of pharmaceutical regulation is to keep dangerous compounds off the market, the standard RCT has done a good job, setting a benchmark to match for new sources of regulatory evidence. This benchmark, we argue, should guide us in finding a real compromise between trial impartiality and participants' preferences.

2. The Social Consensus on Trials: Impartiality and Paternalism

According to Marks's landmark account, in the 1950s a minority of therapeutic reformers fought a "shadow war," marshaling arguments to persuade "a largely silent medical community" of the necessity of adopting RCTs to evaluate the therapeutic merit of drugs (Marks 1997, 155). Their most cogent case was based on the protection that controls such as randomization and blinding offered against subjective biases in medical tests—see, for example, Marshall and Merrell (1949). At the time, fair experimental comparisons were not popular among medical researchers: in a sample of about a hundred studies published in five leading American medical journals in 1950, Otho B. Ross Jr (1951) found that 45 per cent of the trials had been conducted without a comparison group and a further 18 per cent had an inadequate one.

critics, this was the last straw: if a compound was not poisonous, why should the FDA constrain patients' right to take their chances with it? This is where the contemporary debate on pharmaceutical paternalism started (Flanigan 2017).

According to Marks (2000), the case for impartial tests found much of its strength in a renewed mistrust of the pharmaceutical industry among US physicians and patients. The 1950s saw a boom in industrial drug production: some were *wonder drugs,* such as antibiotics and the contraceptive pill but many were combinations of compounds already available. There was a simultaneous explosion in pharmaceutical advertising that caused much confusion among practitioners regarding the therapeutic merit of each product (Marks 2000, 346). For therapeutic reformers, RCTs with a strict research protocol provided the information about drugs that "sleazy advertising" was trying to disguise with "badly scissored quotes," a "pharmaceutical numbers racket," "detail men" visits and so forth (Lasagna 1959, 460–461)—hence the necessity of advising physicians to prescribe on the basis of RCT evidence. Moreover, once medical tests became part of the advertising engine, controls were upheld as guarantees of the impartiality of the trial protocol regarding the sponsor's interests—see, for example, Dowling (1957); Sheps (1961) and Podolsky (2015) for further developments.

But who was to enforce research protocols? According to Daniel P. Carpenter (2010, 228–297), a group of pharmacologists at the FDA were somehow more radical: they thought the agency should assess whether industry-sponsored trials incorporated all the necessary experimental controls to deliver a reliable outcome. After becoming the director of the FDA's Bureau of Medicine in 1950, Ralph G. Smith recruited and led a generation of pharmacologists who formed an informal coalition with like-minded researchers and physicians at the FDA's headquarters and in its delegations. Like the therapeutic reformers studied by Marks, they shared the conviction that drugs should be tested for safety and efficacy. However, there was no agreement on what sort of proof was required. Daniel Carpenter and Colin Moore (2007) claim that this ambiguity was instrumental in the formation of a common discourse for efficacy among this cohort of public officers. Even before the 1963 Act, it was clear that the Bureau of Medicine was considering efficacy in the assessment of each application. No precise definition of efficacy was given (Carpenter and Moore 2007) but it was generally linked to a demand for stricter tests, often expressed in public by FDA officers—even if it was beyond their duty to establish what qualified as a proper clinical test.

This approach to testing allowed the officer in charge of the thalidomide application, Frances Kelsey, to be very strict in her demand for additional evidence of safety from the American manufacturer (the Richard Meller Corporation), in order to prevent cases of phocomelia among pregnant patients—as had already happened in Europe (Carpenter 2010, 228–297). Despite initial industry objections, Kelsey was proved right once the link between the drug and the babies' malformations was established. Defenders of a more severe pharmaceutical regulation in the US Congress found in the thalidomide scandal the boost they needed to pass what would become the 1962 Drug Efficacy Amendment to the Food, Drug and Cosmetics Act. It required from applicants "adequate and well-controlled clinical studies" for proof of efficacy and safety. The FDA developed this indication in further detail, creating the modern clinical trial industry (Carpenter and Moore 2007). In the next three decades, pharmaceutical funding would propel the use of RCTs in the US (and elsewhere).

The purported impartiality of RCTs thus played a key role in articulating the political consensus that brought about the 1962 FDA Act. However, our first hypothesis is that regulatory paternalism was equally crucial in building this consensus, even if it has been somehow neglected in the standard accounts (for a discussion, see Teira 2020). After the passing of the 1962 FDA Act, patients could only access those treatments that had been deemed safe and efficacious by the FDA, regardless of their preferences or any medical

advice. Following the example of Kelsey, the FDA became the gatekeeper of the pharmaceutical market, charged with acting in the best interests of patients. At the time, this may have been interpreted as a form of collective risk aversion: US pharmaceutical consumers did not want thalidomide-like catastrophes to happen ever again and they were apparently happy to reduce their pharmaceutical freedom in exchange for a superior degree of collective protection against dangerous compounds.[4]

This form of paternalism was epistemically grounded in the asymmetry of knowledge between the FDA and the individual judgment of either physicians or patients. If safety and efficacy are to be assessed exclusively on the basis of big, long, complicated experiments like RCTs, only well-funded public or private institutions can afford them. Individual physicians or patients cannot claim that their own judgments about treatments count as much as RCT evidence. Their own preferences therefore become dispensable in trials. For instance, most patients are not indifferent about which treatment they want to receive in a test (Mills et al. 2006) but they are unable to choose one (allocation is randomized) and, if possible, they will not be informed which treatment they are receiving (blinding), so that their preferences do not contaminate the outcome (Teira 2013). The standard argument to justify this form of paternalism in bioethics is based on the superiority of RCT evidence (Levine 1988): the treatments under study are, in principle, equivalent (equipoise) until the trial outcome eventually breaks the equivalence. In other words, regulatory agencies knew better than patients about treatments, and this superior knowledge allowed them to decide on treatments on behalf of physicians and patients.

There is, of course, a gap in this argument: superior knowledge does not straightforwardly justify moral paternalism. But US pharmaceutical consumers seemed happy to have the FDA as gatekeeper of their interests (see Carpenter 2010), and we do not find in the literature many attempts to justify regulatory paternalism. There are only a handful of staunch libertarian critics advocating for the right of patients to self-medicate (Flanigan 2017). Unlike impartiality, we do not know much about how regulatory paternalism emerged and the particular coalition of interests that brought it about.

But even if we do not know how this form of paternalism appeared or how it was originally justified, it is nonetheless there: the FDA has been acting for the last six decades as a paternalist body—hence, our claim that the consensus on the 1962 FDA Act was based on two normative pillars: impartiality and paternalism. RCTs provided a crucial foundation for both pillars—trial controls warranted the neutrality of the test and the trial outcome justified the superior knowledge of regulatory authorities. But then support for paternalism began to crumble.

3. **Patients Revolt against Paternalism**

The pharmaceutical industry is still widely mistrusted when it comes to drug testing. The public success of campaigners like Ben Goldacre (2013) and Gøtzsche (2013) shows that Western audiences, at least, are still sensitive to the need for strong trial controls and unbiased medical evidence. In that respect, the situation is not fundamentally different than half a century ago. We argue, rather, that the public perception of paternalism has changed. Over the last three decades, terminally ill patients have been advocating for quicker access to experimental treatments, lately rallying behind the "right to try" movement (Carrieri, Peccatori and Boniolo 2018). Their opposition to pharmaceutical paternalism goes hand in hand with a general critique of regulatory experiments, arguing that new sources of evidence would serve their interests better (Teira 2017). Our claim is that, more and more

[4] We will never know whether this interpretation actually captures the zeitgeist, since, as far as we know, there was no opinion poll documenting collective risk aversion among US citizens at the time.

frequently, trial participants have become not only more vocal in expressing their preferences but also more capable of acting upon those preferences and breaking the trial protocol. US politicians and regulators are trying to accommodate patients' demands by sacrificing controls that block their preferences and taking new forms of evidence into consideration. We illustrate this gradual erosion of regulatory paternalism with a couple of vignettes in which patients revolted against trial protocols. These vignettes hinge on blinding, a device disliked by patients, which regulators try to bypass with alternative testing methods. These are, of course, vignettes of a much broader process, but we hope they will be persuasive enough to make our claim worth exploring.

Our first quick vignette of a patient revolt against blinding is well known in the literature, thanks to Steve Epstein's landmark study on the early trials of AZT (azidothymidine), one of the first antiretroviral treatments for AIDS, conducted in the US in the 1980s (Epstein 1996). Many of the potential participants had been involved in the gay liberation movement of the 1970s and they used this network to organize themselves and have a say in the organization of the trials, which was at that point unheard of in medical experiments. Organized in movements like the AIDS Coalition to Unleash Power (ACT UP), these patient activists did not believe in the hypothesized equivalence between AZT and the placebo, and they disliked both randomization and blinding. In a coordinated effort, many trial participants resorted to all sort of tricks to make sure they received AZT and not the placebo (exchanging pills, taking them to labs to test whether they had an active principle, and so on), disrupting the research protocol to the point that the experiment was made unfeasible. The FDA was forced to initiate the compassionate use program, in which patients were given early access to experimental treatments (Carpenter 2010, 428–461).

The ACT UP movement made it explicit that not all patients are equally willing to play by the trial protocol rules, which they saw as justified on paternalistic grounds. As Epstein (1996) points out, the ACT UP activists subverted the distinction between lay participants and expert researchers: they learned about the methodological foundations of clinical trials and demanded to be part of the various boards where the research agenda for potential treatments was discussed. They openly questioned those aspects of clinical trials that they found went against their expectations regarding outcomes and procedures, sometimes in the name of science—many ACT UP activists genuinely believed in the power of RCTs to assess a treatment's efficacy. And, crucially, they vindicated their right to take their chances with experimental treatments. We find in their arguments a first intuition of what we call the trade-off between impartiality and trial participants' freedom. As Larry Kramer, a founder of ACT UP, put it in a *New York Times* op-ed, "Double-blind studies were not created with terminal illnesses in mind. It is, again, inhumane to withhold drugs from terminally ill patients willing to take them, Phase One trials having been completed safely" (Kramer 1987). He added, "AIDS sufferers, who have nothing to lose, are more than willing to be guinea pigs." That is, under certain conditions, paternalism provides no justification to blind control for patients' preferences in a test through randomization and blinding. According to this argument, if impartiality should be sacrificed for the sake of patients' right to try, so be it.

The AZT trial was nonetheless exceptional in the 1980s, if only for one reason: the trial participants had a preexisting network, whereas most other patients had no easy way to contact each other and coordinate their actions. Our second vignette illustrates how fragile blinding becomes once patients reach this degree of coordination via social media. Patient communities have grown hugely on the internet, ranging from simple mailing lists or Facebook groups to dedicated websites. PatientsLikeMe (PLM) is one such digital platform: in 2011–2012 a group of ALS (amyotrophic lateral sclerosis) patients taking part in an early

clinical trial used its message boards to share their experiences during the test, unblinding the treatment they were receiving and breaking the protocol (for a full discussion, see Tempini and Teira 2019).

The Neuraltus phase II trial of NP001 started in February 2011. It was a two-arm, double-blinded trial in which ALS patients were randomly allocated either NP001 or a placebo. What eventually made this trial unusual was that some of the participants were registered PLM users. Through the forums and the pages where patients record first-person evaluations of treatments, some of the trial participants organized themselves to try to find out which treatment they were receiving, NP001 or placebo. The patients assumed that any effect they could register on the questionnaires was most likely caused by the active treatment (NP001), be it in the form of self-registered improvement or any other side effects. Consequently, they were trying to devise the composition of the treatment and the placebo arms of the trial by grouping together patients with usually uncommon, yet repeated side effects, and putatively attributing them to the treatment arm. In other words, they were explicitly breaching the trial protocol with a concerted attempt at breaking its blinding.

Furthermore, when PLM noticed the exchange of trial information on their platform, they decided not to stop it, since the company felt its primary loyalty was to its users, not to the trial sponsor (Neuraltus), so they allowed the exchange to proceed. Two years later, PLM justified its decision in a letter to the *British Medical Journal,* where they called for "a new social contract that maximizes both scientific discovery and patient autonomy, setting the stage for better trials with more engaged participants" (Wicks, Vaughan and Heywood 2014). This would be necessary, they claimed, to reduce the risk of "patient-led 'disobedience'" against trial protocols.

The debate on the PLM incident exposed even more vividly the trade-off between impartiality and trial participants' freedom. The title of the PLM piece is telling: "Subjects No More: What Happens When Trial Participants Realize They Hold the Power?" (Wicks, Vaughan and Heywood 2014). Indeed, randomization and blinding are only possible if trial participants agree to play by the rules established in the testing protocol. But if they challenge the standard informed consent for its unjustified paternalism, trial controls collapse. The "scientific altruism" of trial participants, assuming their indifference towards treatments and withholding their preferences, gives way to a simple strategic approach: access the trial and then coordinate with other patients to see if you are getting the treatment you want. Participants' freedom goes directly against impartiality because the trial outcome becomes directly dependent on their preferences, in violation of the testing protocol.

In these two vignettes we see the trade-off between impartiality and trial participants' freedom in RCTs at work: the less control on the patients' preferences, the more biases will affect the trial outcome. It is worth recalling here the so-called therapeutic misconception: against the intuitions of many trial participants, RCTs are not primarily carried out for their benefit, but rather to generate evidence that will protect future patients from unwanted harms. Misunderstanding this point leads patients to overestimate the benefits of trial participation and downplay its risks (Candilis and Lidz 2010). At the same time, we may have reached a point in pharmaceutical history where patients can easily rebel against trial protocols, making medical experimentation unfeasible unless patients' preferences are somehow accommodated. Let us now discuss the regulatory response of the US authorities facing this dilemma.

4. **Sacrificing Impartiality in the Name of Trial Participants' Freedom**

The FDA has adjusted its testing standards in response to patients' demands. The demand for shorter/quicker trials was met in the 1990s with the rise of surrogate outcomes (Kemp and Prasad 2017; Stegenga 2015). Instead of following patients until the absolute end of the treatment (for example, death), the trial focused on a surrogate variable that could reliably predict the true outcome. Objectionable as surrogate outcomes may be, trial design was left untouched: controls were left in place and impartiality was not sacrificed to accommodate patients' preferences. In the 2010s, the rise of medical Big Data, in the guise of electronic health records (EHRs), created a potential new source for regulatory evidence, in which standard trial controls were not strictly necessary (for a full discussion, see Tempini and Teira 2020).

Whenever patients visit medical facilities, they leave a digital trail, through their exchanges with the staff (for example, clinical interviews, anamnesis and assessments, or diagnosis in an emergency room), or through the supplementary evidence generated by any kind of testing. Furthermore, there is an increasing number of EHRs gathered by measurement devices that patients wear and use while away from the point of care (for example, glucose sensors inserted under the skin). And there is also indirect evidence about treatments, such as medical claims and billing data.

EHR systems are "electronic platforms that contain individual electronic health records for patients and are maintained by health care organizations and institutions" (FDA 2019, 4). There are multiple sources of EHRs and many different ways to exploit them. There are hospitals and all sorts of medical institutions (from physician offices to multi-specialty practices) but also insurance claims databases and registries. The standardization of EHRs and the interoperability of EHR systems would generate a wealth of data about, among other things, treatment effects.

Whereas the 1962 FDA Act relied exclusively on RCTs to assess new treatments, the 21st Century Cures Act (section 2,062) opens up the possibility of using EHRs to assess new indications for treatments already approved (through conventional RCTs). Instead of running new trials to assess alternative uses of these treatments, the 21st Century Cures Act mandates the FDA "to use of evidence from clinical experience (in place of evidence from clinical trials)" and to "establish a streamlined data review program" in order to support approval of a drug for new indications.

This regulatory shift has already yielded a 2019 FDA framework document on the use of real-world evidence.[5] This shift may be interpreted as a response to patients' demands. According, again, to Paul Wicks, Timothy Vaughan and James Heywood (2014), patients want to "prioritize the outcomes they truly value" and, through patient-led research, they may "help us learn what works in the real world, not just in trials." Exploiting real-world evidence is one of the principles inspiring the 21st Century Cures Act and, as of today, there is an ongoing debate at the FDA on the best methods to assess treatments on the basis of EHRs. We now discuss the trade-off between impartiality and trial participants' freedom, focusing on one of these methods—what are known as *pragmatic trials*.

Pragmatic trials are designed in a way that balances patients' demands for care with the investigation of treatment effects. These trial designs include elements resembling regular clinical practice, such as interventions administered in routine clinical care, settings seeking access to more patients under the variations that are typical of routine care (Ford and Norrie

[5] This document defines *real-world data* as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources," and *real-world evidence* as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data" (FDA 2019, 4).

2016). Specifically, pragmatic trials exploit EHRs generated in regular medical setups to track treatment effects without the sort of controls about which patients complain in standard RCTs. In 2017, the FDA ran an experts' workshop with the National Academy of Sciences to discuss one such trial (together with three observational studies) as a paradigm for further regulatory action (NAS 2017).[6] This pragmatic trial was the Salford Lung Study (Woodcock et al. 2017).

The trial took place in Salford, in the greater Manchester area in the United Kingdom, between 2012 and 2016. It was an *open label* study: clinicians and patients knew what treatment was being administered. The treatment under study was Relvar©, an inhaler combining two compounds for the treatment of asthma and obstructive pulmonary disease. The safety and efficacy of the inhaler had been established by means of standard RCTs, and its commercial use was approved in 2013 by both the FDA and the European Medical Agency. The Salford Lung Study focused, rather, on the effectiveness of the inhaler, drawing patients from 74 primary care centers with broad eligibility criteria, targeting a representative population of potential users.

Pragmatic trials exploit randomization in a conventional setup. Treatments were allocated by patient (not by center) to three different interventions: the inhaler with two different amounts of one compound (fluticasone) and their usual treatment. The main outcome variable was the "Asthma Control Test" (Nathan et al. 2004), a questionnaire measuring the patients' control of their symptoms. This is a patient-reported outcome, a choice justified by the authors (Woodcock et al. 2017) since they argued that the sample size was not large enough to detect less subjective events such as asthma exacerbations (episodes in which the usual symptoms worsen) with enough statistical power. Participants were followed over the course of a year, either through the EHRs generated during their visits to their primary care centers and Salford Hospital, or via quarterly phone interviews. Although not the primary focus of the study, follow-up also registered the number of exacerbations, the use of rescue inhalers (controlled through the EHRs generated at the community pharmacies where they were acquired) and eventual hospitalizations. It also monitored the patients' adherence to the trial protocol.

The study recruited 4,233 patients, 2,114 of whom received the inhaler and 2,119 their usual treatment (Woodcock et al. 2017). Roughly half (1,364 + 1,381) were finally included in the analysis. Both groups increased their baseline scores in the "Asthma Control Test," although those who received the inhaler had, on average, 1.6 points more than those in the control group—a statistically significant difference, although its clinical relevance was less clear. The secondary outcomes were not particularly revealing: no significant difference in exacerbations, but the patients in the control group used more rescue inhalers (Woodcock et al. 2017).

The Salford Lung Study thus illustrates a compromise between regulatory demands and the accommodation of patients' preferences. Its prominence in the FDA workshop suggests that it could become a paradigm for future regulatory trials. And indeed, Robert Califf, then the FDA commissioner, highlighted in his workshop intervention that randomization at the point of care provides protection against biases while generating real-world evidence for regulatory purposes (NAS 2017, 11).

In our view, however, the trade-off is still at work and the Salford Lung Study illustrates how impartiality is sacrificed to accommodate patients' antipaternalism demands.

[6] A reviewer of this article observed that it is not clear what regulatory purpose is being served in the study. The workshop organizers remain ambiguous in this regard: it was a case study highlighting "how real-world evidence has been incorporated into medical product development and evaluation processes," allowing participants to discuss the opportunities and challenges arising from such designs (NAS 2017, 5).

Physicians and patients knew the treatment administered and the effects of lack of blinding could have interfered in the trial, at least, on two accounts. Firstly, a usual consequence of patients' dissatisfaction with the treatment they are receiving (because it does not suit their preferences) is trial dropout. And, indeed, 18 per cent of the patients in the Salford's experimental group abandoned the inhaler and returned to their usual treatment. Three patients from the control group were given access to Relvar© instead. Secondly, we may wonder how this knowledge interfered with their responses to the "Asthma Control Test." Patient-reported outcomes are by definition dependent on the patients' experience and are very sensitive to biases: it has been documented in meta-analyses how nonblinded assessment of a patient-reported outcome magnifies the treatment effect (Hróbjartsson et al. 2012). Since the Salford Lung Study did not check for the effects of the lack of blinding, we can only gauge the potential impact by comparison with other trials of the experimental treatment.

There were three conventional RCTs of Relvar©, comparing it with a placebo, an inhaler with less therapeutic power (one active component alone, fluticasone), and an inhaler of similar power (fluticasone + salmeterol) (O'Byrne et al. 2014; Bateman et al. 2014). It is a well-established fact in respiratory medicine that a combination of an inhaled corticosteroid and a long-acting beta-agonist, such as Relvar©, represents an escalation of therapy, compared to using either of these compounds alone. According to the standard clinical guidelines (Bateman et al. 2008), two-compound inhalers are only recommended to intensify the treatment when one-ingredient interventions are not enough. Therefore, the only fair comparison would have been between Relvar© and a combination of similar power (such as fluticasone + salmeterol). It is not strange then to observe a better response to Relvar© by comparison to weaker interventions. But when compared to a two-ingredient alternative in a blinded trial, there is no significant difference between the outcomes on hard and soft endpoints, exacerbations, and quality of life questionnaires (Woodcock et al. 2013).

The Salford Lung Study then measures the self-reported improvement of patients who knowingly received Relvar©, compared to their previous treatments. In our view, this sort of information may perhaps be useful for a physician interested in prescribing inhalers but it is dubious that a regulatory agency would be able to make much use of this real-world evidence without compromising impartiality. The risk of potential bias due to the lack of blinding has been simply written off in the discussion. Interestingly, the Salford Lung Study would not easily fit within the FDA real-world evidence framework, where we read:

> When blinding of treatment is infeasible, FDA will seek to identify situations when bias resulting from lack of blinding can potentially be controlled using outcomes that are less likely to be influenced by knowledge of treatment assignment, such as clinically objective outcomes (e.g., stroke, tumour size). However, even when using objective assessments, approaches to ensure consistency in outcome ascertainment and reporting will be important. (FDA 2019, 19)

That is, rather than focusing on patient-reported outcomes (through the "Asthma Control Test"), the Salford Lung Study should have focused on exacerbations and checked for consistency with the former. Maybe the Salford Lung Study was just a preliminary proof of concept at a point when the FDA was exploring potential paradigms. But it illustrates our point very well: trading off controls for better accommodation of patients' preferences may only yield evidence about what those specific patients want, not about treatment effects on a general population.

5. But What Impartiality Are We Trying to Protect?

Our argument so far has presupposed that the impartiality in the trade-off is real. Trial controls such as randomization or blinding warrant a degree of neutrality of the outcome regarding participants' preferences. One quick rejoinder would be to contest whether such impartiality actually exists. Why try to preserve something that is a mere pretense, whereas patients' preferences are real?

Historians of clinical trials have developed arguments that certainly would support this objection (for a review from a philosophical standpoint, see Holman and Elliott 2018). Trial impartiality often appears as a rhetorical device for the promotion of self-serving interests. Various studies have shown how, in the United Kingdom, during the 1940s, the rhetoric of trial impartiality helped the medical authorities to control both physicians and patients (see, for example, Toth 1998; Edwards 2007; Valier and Timmermann 2008). RCTs are centralized experiments: physicians should follow a single protocol, rather than testing new treatments independently. Thanks to RCTs, the British Ministry of Health was able to control the way physicians used new treatments until they were declared efficacious. Moreover, all British patients wanted access to new miracle drugs, such as the antibiotic Streptomycin, of which there were often not enough doses. Trial controls such as randomization allowed the Ministry of Health to persuasively justify why some patients did not receive it. In other words, methodologically impartial experiments can be a vehicle for advancing the goals of the British medical authorities.

Historians have also shown how apparently impartial RCTs can help the pharmaceutical industry to turn physicians' judgment in its favor. For instance, Jeremy Greene (2007) has shown how trial evidence can be used to justify the transformation of risk factors into medical conditions: if a statin reduces the mortality of apparently healthy patients in a trial, this is a reason to treat their cholesterol levels as a disease. Tobbell (2011), among many others, has documented many other ways in which clinical trials became part of the marketing strategies of the pharmaceutical industry in the second half of the twentieth century.

Historians' reaction to the 21st Century Cures Act is precisely neutral, as exemplified in a recent paper published in a leading medical journal: "We find ourselves at a crucial point in the history of RCTs. Originally designed to reduce bias in research, RCTs have become sites of conflicting interests that merit careful scrutiny" (Bothwell et al. 2016, 2179).

Even though RCTs were developed to generate universal biomedical knowledge, they have remained entangled in local social conditions. Methodological impartiality is just an illusion. According to a recent review piece, the historian's role is to scrutinize the interests in conflict in every test without taking sides. The argument is that all evidence is biased to varying degrees, so let the stakeholders decide which biases should matter when making regulatory decisions.[7]

Historians are absolutely right in showing the different interests behind every test, be it on the part of health authorities (enforcing their regulatory power), companies (obtaining regulatory approval for their compounds) or, of course, patients (as in the AZT and NP001 trials). However, the methodological point of trial controls is to prevent these underlying interests from becoming experimental biases contaminating the trial outcome. In our view, debiasing methods like randomization and blinding can do nothing about the interests

[7] This is how we read, at least, the non-committal conclusion of "Assessing the Gold Standard: Lessons from the History of RCTs" (Bothwell et al. 2016, 2179): "Originally designed to reduce bias in research, RCTs have become sites of conflicting interests that merit careful scrutiny." The role of the historian, according to the authors, is to scrutinize those interests but, despite the paper's title, we do not find any guidance to assess, for instance, whether RCTs were successful at managing them.

outside the trial but they have been reasonably effective in controlling biases arising from the preferences of the participants in the experiment (researchers or patients) when handling the treatments. A randomized allocation prevents a self-serving assignment of treatments on the part of the sponsor; double blinding prevents physicians from treating patients differently depending on the intervention they are receiving, and so on. In this regard, they contribute to the internal validity of the experiment, even if they do not control for many other forms of bias distorting the assessment of treatment effects in trials.

An experiment can be thus full of interests and yet impartial, in our sense. The key point is that an impartial conclusion is not one that serves the general interest (for example, *the view from nowhere*) but rather a conclusion reached in an experiment that incorporates all the debiasing procedures that the scientific community considers necessary. For instance, if a pharmaceutical company decides to compare its new drug to a treatment (a placebo) that will likely yield a positive outcome, the choice of the comparison obviously serves the sponsor's interests. But if the trial incorporates the relevant controls, the outgoing evidence will be free from the biases neutralized by those controls. Such a trial may not provide the most useful information for a pharmaceutical regulator but the evidence would be as impartial (free from experimental biases) as it could possibly be. If a majority of experimenters comes to agree that self-serving placebo comparisons should be ruled out, this trial will cease to be impartial. Experimental impartiality is not an absolute benchmark: it is always relative to the number of biases that a community of experimenters acknowledge as potential threats, and the agreed methods to correct them.

A case in point is the standardized checklist to assess the risk of bias in a trial, often promoted by independent bodies like the Cochrane Collaboration (Sterne et al. 2019). These lists are silent on trial sponsors' interests and consider instead how they may affect the measurement process of the target variables in the test, so that the quality of the evidence can be assessed by the end users.

These lists of biases and controls are periodically revised and updated. Hence, they are a matter of historical negotiation subject to all sorts of particular interests. Still, we should not underestimate their contribution to the quality of regulatory decisions. There may be a plethora of interests behind every trial control but in the end these controls should contribute to the goal of every regulatory trial: the assessment of treatment safety and efficacy. As we have already seen, RCTs were adopted as a regulatory yardstick to fulfill a normative mission: they should keep out of the markets drugs that could kill patients or cause serious adverse effects. In our view, RCTs have been reasonably successful in this regard. When the FDA makes a wrong decision and approves a harmful drug, the agency withdraws the treatment from the market as soon as the effects are observed. The FDA's error rate provides a simple empirical benchmark for assessing the success of regulatory RCTs. According to a recent survey, less than 2 per cent of new drug approvals by the FDA between 1950 and 2011 (about 130 compounds) were withdrawn (Onakpoya, Heneghan and Aronson 2016). It is important, however, to note that this figure has been criticized (Rawson 2016).[8]

[8] Assessing the success of RCTs in preventing harms is far from simple. In fact, philosophers like Osimani (2013) have argued precisely the opposite: RCTs are not good regulatory tools for the assessment of adverse effects. Elsewhere, we have argued that success assessment is always comparative, and we need an empirical benchmark (such as market withdrawal rates) to assess the alternatives to RCTs (Andreoletti and Teira 2019). And then we would have to find out how much it would cost to achieve a better result with different sources of evidence and under similar external pressure. For instance, Osimani (2013) advocates for a more complex decision procedure, using multiple sources of evidence feeding a Bayesian algorithm to yield a decision but, as of today, it is a purely theoretical exercise without a clear assessment of the costs and benefits of implementation.

Depending on how you appraise it, this 2 per cent may seem a more or less reasonable figure (see Andreoletti and Teira 2019 for a discussion). Our point is that any alternative source of regulatory evidence should do just as well, assuming that we still agree on the paramount goal of pharmaceutical regulation being patient protection from harmful compounds. If we are to sacrifice trial controls in favor of alternative testing methods that are more accommodating of patients' preferences, it is worth asking whether these new methods improve on the performance of controls. Or perhaps, more radically, we should wonder how to balance our respect for trial participants' preferences with the protection of any future patient who may receive the same treatment. This, in our view, is the ultimate touchstone to decide on any solution to the dilemma between impartiality and trial participants' freedom.

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