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Disease-mongering through clinical trials

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ABSTRACT

Our goal in this paper is to articulate a precise concept of at least a certain kind of disease-mongering, showing how pharmaceutical marketing can commercially exploit certain diseases when their best definition is given through the success of a treatment in a clinical trial. We distinguish two types of disease-mongering according to the way they exploit the definition of the trial population for marketing purposes. We argue that behind these two forms of disease-mongering there are two well-known problems in the statistical methodology of clinical trials (the reference class problem and the distinction between statistical and clinical significance). Overcoming them is far from simple.

1. Varieties of disease-mongering

Disease-mongering generally refers to a purported commercial strategy of the pharmaceutical industry, consisting in tinkering with the definition of a given disease (sometimes to the point of creating a new one) in order to promote the sales of one of their drugs. Disease-mongering has been featured prominently in special issues of the *British Medical Journal* (2002) or *Plos Medicine* (2006), although its existence is for some controversial—and it has probably been so for more than four decades, since the earliest discussions about *medicalization* or the more current debates about *pharmaceuticalization* (Abraham, 2009, 2010; Williams, Gabe, & Davis, 2009). The controversy is fueled, of course, by the huge advertising budgets of the pharmaceutical industry and the growing influence of their marketing arms in the drug development process. It starts at its very inception, with identification of the most interesting target patient from a commercial standpoint, and it certainly conditions the way in which clinical trials for drug approval are designed, conducted and published. It is open to discussion though whether the advertising power of the pharmaceutical industry goes as far as some authors claim (e.g., Moynihan, Gøtzsche, Heath, & Henry, 2002; Payer, 1992). For instance, the transformation of a collection of minor medical phenomena into a treatable condition: e.g., turning baldness into a generalized anxiety process (Moynihan et al., 2002), female sexual dysfunction (Lexchin, 2006) into so-called *premenstrual dysphoric disorder* (Moynihan, 2003), or shyness into *social anxiety disorder* (Wolinsky, 2005).

In this paper we want to articulate a more precise concept of DM. We want to show how pharmaceutical marketing can commercially exploit certain diseases when their best definition is given through the success of a treatment in a clinical trial. We will distinguish two types of disease-mongering according to the way it exploits the definition of the trial population for marketing purposes. We are going to argue that behind these two forms of disease-mongering there are two well-known problems in the statistical methodology of clinical trials and overcoming them is far from simple. But let us first introduce the discussion step by step.

Clinical trials are comparative experiments in which hypotheses on treatments are tested, usually with a methodology grounded in

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one particular view of probability, frequentism.[1] Namely, we judge the outcome of the experiment by assessing, e.g., the size of the observed difference between treatments with the distribution of outcomes that we would observe in an infinite series of repetitions of the trial, under the hypothesis that there is no difference between treatments. If we observe a large one, either our hypothesis is false or we have observed a very rare event.

In a frequentist approach, the probabilities of observing a given outcome are tied to one particular experimental design: if we repeat the same experiment time and again, we will observe a distribution of outcomes that will make our initial hypothesis about this distribution more or less credible. One crucial point, in making our experiment repeatable, is to define the population of patients that we are sampling in the trial. We are trying to ground an inference about the effect of the treatments in this population from the outcome we observe in the group of patients on which we are conducting the test. The probability of observing this outcome is indeed tied to a given reference class, the population of patients defined by the eligibility criteria in the trial protocol. Outside this population, the trial does not say how the treatment will work. The probability of observing a difference between treatments provides the significance of the test. If the probability is very low, the event is rare enough to deserve a reconsideration of our initial hypothesis (there was no difference between treatments) and declare one of these treatments superior.

From a purely commercial standpoint, the industry wants any treatment to: (a) work on a given class of patients, in order to earn regulatory approval and get market access; and (b) ensure that this class is as large as possible, in order to increase sales. Pharmaceutical marketing has exploited a methodological misconception about trials that prevails among both physicians and patients. Namely, that they provide a general assessment of treatments independently of the reference class they are tested on. Hence, physicians may prescribe them off-label, assuming that a patient will benefit from them as much as the participants in the trial, even if this patient would not have been eligible.

However, sometimes the definition of the trial population is so loose that physicians can be persuaded that it would suit most patients they see. We call this *mild disease-mongering*, since it does not target the trial as such, but medical prescription based on its outcome (b). However, there is also *strong disease-mongering*, where the very definition of the patient population (a) is targeted for marketing purposes. The goal here is to find a growing group of patients where we can reach a statistically significant difference between treatments. Inasmuch as the latter is obtained, there will be grounds to get regulatory approval for the drug and sell it to this larger audience.

Why call these two marketing strategies *disease-mongering*? We are going to defend the claim that randomized clinical trials (RCTs, from now on) have provided an implicit definition of at least some diseases in terms of (successful) treatments. In the 1950s RCTs came to provide a statistical proof of the safety and efficacy of medical treatments. At this point, physicians often did not know much about the full range of biological mechanisms by which a drug succeeded in healing individual patients. Under this veil of ignorance, RCTs provided at least statistical evidence about the safety and efficacy of the drug in a given population. Once RCTs became the regulatory standard to judge the effects of a drug, pharmaceutical research adopted an operational definition of disease that extensionally captured the group of patients targeted by the drug in the trial: a disease is just the condition cured in a trial on a given group of patients by a certain treatment.

Under such circumstances, RCTs can be used for either research or marketing purposes. As to the former, we can use RCTs to study different groups of patients on which the treatment may be effective, refining thus the working definition of the disease provided in the trial. This approach would resemble the epidemiological search for multifactorial definitions of disease (e.g., Broadbent, 2011). As to the latter, RCTs become marketing tools when the definition of the population is intentionally loose, so that it can be expanded for commercial rather than clinical purposes. However, if we judge the trial protocol alone, it is difficult to tell whether it is mainly conducted for marketing or research purposes: after all, they may well overlap.

The only conclusive evidence for the true intentions of the industry in sponsoring a trial is often found in confidential documents that become publicly accessible in court, in the case of litigation over a treatment.[2] Short of this, evidence of disease-mongering is always indirect and open to debate. By way of illustration, let us consider the comparison treatment in a trial, which is often considered a reliable sign of the intentions of the industry. But the interpretation of this comparison is, of course, controversial.

For instance, Pierre Azoulay (2002) has suggested distinguishing between RCTs as *market-expanding science* if they use a placebo or any active substance other than the antiulcer drugs competing in the market under analysis; if RCTs compare any of these competing drugs, they constitute *comparative science*. Whereas the former feature the more innovative products, complying directly with regulatory requirements, Azoulay suggests that the latter may well originate in the firms' marketing departments, since there is statistical evidence for their differential effects on sales.[3] However, even placebo-controlled trials are often suspect of commercial maneuvering: for instance, if we are dealing with subjective outcomes (often the case in psychiatric trials), Peter Gøtzsche (2013) has argued that a poor blinding either of the treatment (e.g., a placebo that does not properly mimic the effects of the active treatment) or the assessment may distort the comparison, making the treatment substantially more effective than it actually is. In summary, if we lack documental evidence for the intentions of the industry in sponsoring a trial, the discussion of whether it is conducted for commercial or research purposes should proceed on a

[1] RCTs are a tool for causal inference, but the problem we analyze is created by the particular statistical rendition of RCTs that we find in medicine. Here the current regulatory standard hinges on frequentist trials. If Bayesian trials were accepted, the problem we are tackling in this paper would change dramatically: a Bayesian probability is not tied to the replication of an experiment, but rather to a degree of belief conditional on the evidence available, wherever it comes from. For a Bayesian, conducting the same experiment on different populations may yield one single probability. For a frequentist, the probability is tied to one experimental design on a given population, so we would have a different *p*-value whenever we change the population, even if the rest of the experiment rests the same. Hence, inasmuch as disease mongering, in our sense, depends on tinkering with populations, Bayesians and frequentists would have different types of disease-mongering. See [David Teira, "Frequentist versus Bayesian Clinical Trials", in Fred Gifford, ed., Philosophy of Medicine, Amsterdam, Elsevier, 2011, pp. 255-297.] for a presentation and discussion of the difference between Bayesian and frequentist trials.

[2] For instance, Sismondo (2009) has made this point about ghost-writing practices in the pharmaceutical industry.

[3] Azoulay (2002, pp. 583–584) measured the cumulative citations of both types of trials, analyzing how responsive the demand elasticity was to each of them. He found that comparative trials proved to be "a particularly effective business-stealing weapon" for the second drug to enter the antiulcer market he studied. At the same time, he also shows that pharmaceutical investment in medical detailing grew with the increasing stock of citations in market-expanding trials (2002, pp. 579–580). Even if the data show as well that trials were not the main drive behind the marketing strategies and sales of pharmaceutical companies, Azoulay concludes that RCTs "represent investments whose effects on the product market are both substantial and long-lived" (2002, p. 582).