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A Critique of the Moral Economy of Pharmaceutical Development

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Abstract:
Drug development is widely recognized as risky, time consuming, and costly for pharmaceutical firms. Less widely appreciated is the fact that nonhuman animals and patients also bear risks and costs for pharmaceutical development. I argue that by participating in studies, nonhuman animals and patients commit some (or for nonhuman animals, all) of their welfare and labour to drive this process forward. I further argue that this commitment of welfare and labour is rendered invisible by discourses that present trial participation to patients as medical opportunity, despite evidence and principled reasons suggesting the contrary. This subsidy of welfare and labour, though nominal to moderate on a per patient basis, is significant when aggregated across patients and clinical trials and considered alongside nonhuman animal use. I close by arguing that this subsidy is grounded on defective consent, and that it generates two strong claims on researchers and states overseeing the research. The first is an obligation to economize on nonhuman animal and patient welfare and labour by conducting research efficiently. The second is an obligation to align drug development and policy with the aspirations that motivate the use of nonhuman animals and the motivations of patients in this endeavour.

Keywords:
pharmaceutical development, research ethics, clinical trials, labour, informed consent, nonhuman animals

1. Introduction

Drug development is enormously expensive, requiring on average upwards of $1.3B private investment for each new drug receiving regulatory approval (Wouters, McKee, and Luyten 2020). The expense and riskiness of pharmaceutical development is widely recognized. And it heavily informs policies on pharmaceuticals, including those pertaining to intellectual property, drug regulation, reimbursement, and purchasing. For example, permissive drug approval standards, or liberal pricing policies, are often defended by appealing to the necessity of large rewards to attract private investment in so lengthy and uncertain an endeavour.

Less widely appreciated is the large amount of time and welfare nonhuman animals and patients invest in drug development. Much of what is argued below pertains to both nonhuman animals and patients, but for reasons of exposition, the present article will focus more on the latter. To develop a drug, scientists and pharmaceutical companies require an army of patients willing to roll up their sleeves, drop their gowns, or sit in waiting rooms to support pharmaceutical progress. This willingness is often premised on a perception that participation in trials is medically advantageous for patients. Large numbers of animals are created and then euthanized in drug development research. But as we will see below, nonhuman animals and patients give their labour and welfare without receiving much in return medically. And they give their welfare and labour to entities- drug companies- who sometimes apply the proceeds of this subsidy towards activities that may work against the interests of patients and/or nonhuman animals.

In this essay, I will call this arrangement whereby nonhuman animals and persons debilitated by sickness provide a subsidy to private drug development efforts a "moral economy." In this term, I hope to capture the notion that drug development entails a sprawling system whereby things that have moral value (nonhuman animals and patients) are exchanged for other things of value (for example, future drugs, knowledge, healthcare or profits). In using this term, I make no commitments to any theory of moral philosophy. For example, formalizing the concept so that we could measure the value of these exchanges would greatly facilitate utilitarian analyses of research or policy choices. But deontologists might use the concept to get traction on the fairness of exchanges that characterize present day pharmaceutical research.

As large and vital as it is, this moral economy has almost no visibility in policy discussions about pharmaceuticals. The value associated with the nonhuman animal and patient's labour and welfare are unmeasured by economists. Policy debates around drug pricing almost never mention this subsidy. And despite pharmaceutical development being among the most heavily regulated industrial endeavors, this moral economy is scarcely noticed by oversight bodies and ethics committees, much less patients themselves. As I suggest below, the scale and obviousness of this appears to be actively constructed through what I call a "collusion of ignorance." What policy vistas open when we dissolve this ignorance and take notice of what nonhuman animals and patients contribute to private pharmaceutical development (and what they gain from the process)?

2. A Welfare Subsidy

The first task is to establish that drug development draws on large quantities of patient welfare and labour. Some basics about drug development will set the stage.

Policymakers typically divide the process of drug development into three stages. The first is preclinical research, conducted mainly in nonhuman animals, aimed at identifying promising drugs. The next stage, "clinical development," involves testing a drug in patients. Clinical development is often divided into three steps or "phases." In the first (phase 1), drug developers test the safety and establish conditions, like dose, for further testing. In many areas of medicine, phase 1 trials involve healthy volunteers who are paid to receive drugs in specialized testing clinics. In some areas of medicine, like cancer, most phase 1 trials involve patients. Such patients have generally exhausted treatment options and trial participation is their last hope of disease control. In phase 2, interventions are tested for efficacy in patients using outcomes that can be measured quickly and cheaply, and that are believed to predict meaningful patient outcomes (such outcomes are called "surrogate;" the meaningful outcome eventually sought is "clinical"). For example, in cancer, phase 2 trials typically measure tumour shrinkage, which occurs within weeks after a patient starts treatment, and is a surrogate for a clinical outcome like longer survival. Phase 3 trials aim at nailing down efficacy using clinical outcomes. They typically use randomization, run for longer periods, and enroll large numbers of patients. Because of their size and duration, they are the most expensive trials in the drug development process. The third stage of drug development occurs after a regulator, like the Food and Drug Administration (FDA), grants a license to the manufacturer to commercialize the drug for the condition against which it was tested. Subsequent research on the drug might gather further information on safety or test the drugs in different patient groups. There is lots to be said about the process of developing drugs but this sketch above is enough to support the present analysis.

That clinical development exacts welfare from nonhuman animals is patent. Almost all nonhuman animals used in research are sentient. That is, they possess the capacity to have pleasant and aversive experiences. According to many different philosophical and religious traditions, this capacity engenders obligations to avoid or at provide morally compelling reasons to override an injunction against causing sentient beings harm (for brief and readable introductions to animal ethics, see (DeGrazia 2002) and (Nussbaum 2023)). The EU is one jurisidiction where the volume of nonhuman animals used in research is monitored. In 2019, the EU used 10.4M nonhuman animals for scientific research. Most of these animals were bred, raised, and ultimately euthanized to advance science. About a third of these animals are used in experiments involving severe pain, suffering or distress ("Commission Staff Working Document - Summary Report on the Statistics on the Use of Animals for Scientific Purposes in the Member States of the European Union and Norway in 2019," n.d.).

Patients also give up at least some well-being to drive this process forward- though nowhere near the intensity or volume for nonhuman animals. The high rates of failure in new drug development evidence this. For every 100 drugs entering clinical development, 10-15 will demonstrate sufficient safety and efficacy to win regulatory approval (Hay et al. 2014). To a rough approximation, this means that the remaining drugs are ineffective, or they involve unacceptable side effects (Wouters, McKee, and Luyten 2020). A large number and proportion of patients who participate in drug development trials receive drugs that are unsafe and ineffective. As a rule of thumb, the earlier in drug development, the greater the probability of receiving an unsafe and/or ineffective drug increase. A bit more than half of cancer patients who participate in intervention trials are enrolled in early phase trials (Gumnit et al. 2021). Also as a rule of thumb, the later a drug is tested in drug development- that is, the time elapsed since a drug is first put into testing- the greater probability of the drug being ineffective (Hutchinson et al. 2023).

There are many other factors in trials that exact welfare from participants. Participation in most drug development trials involves research procedures that are performed solely for scientific reasons. Many patients receive blood draws so that scientists can monitor a drug's metabolites. Some cancer patients receive organ biopsies so that scientists can determine whether a drug is reaching its target. Some patients in neurological disease trials might receive lumbar punctures to collect cerebrospinal fluid. Patients might receive extra imaging, or they might run treadmill tests, etc. Some welfare losses are nonmedical. Patients in randomized trials, for example, are generally kept from knowing whether they received the experimental treatment or a comparator, like a placebo. Patients intensely care about their treatment assignment. Preventing them from knowing treatment assignment is not generally thought to be medically harmful. But it exposes participants to an uncertainty to which they are averse. Many of these procedures are merely annoying or unpleasant. A few are risky and/or painful. Very rarely but still occasionally nevertheless, they can be fatal or lead to disability. When aggregated together across the duration of a trial, and across all patients in a trial, they add up.

Many drug trials involve a particularly burdensome research procedure: patients in comparator groups are given a treatment that falls below standard of care. This is common where drugs are developed for symptomatic conditions (i.e. medical conditions where patients report outcomes), like rheumatological or psychiatric disorders. For example, for rheumatological disorders, the standard of care when a patient no longer responds to one line of treatment is to escalate treatment to a more aggressive, second line treatment. Many trials in rheumatology instead randomize patients to either a new drug or to continued use of a treatment they failed plus placebo. Drug regulators set a ceiling on risk in such circumstances, limiting placebo use to situations where a patient is not put at risk of death or lasting disability (International Council for Harmonisation 2000). This ceiling sets a high regulatory bar on tolerance of welfare loss. Imagine all the circumstances you went to the doctor for conditions that were short of being life threatening or that threatened lasting disability.

In all, learning whether drugs are safe and effective enough to market requires large numbers of nonhuman animals, all of whom are significantly harmed, and it requires large numbers of patients, most of whom will lose at least a little welfare. According to major ethical codes like the World Medical Association's Declaration of Helsinki or nonhuman animal protections policies like the 3R's, such welfare losses are ethically acceptable provided certain conditions are met. These conditions include minimizing harm (National Research Council, n.d.), and for patients, obtaining informed consent from those possessing decisional capacity, and justifying harms by the prospect of advancing medical science (World Medical Association 2008; International Council for Harmonisation 1996; Council for International Organizations of Medical Sciences (CIOMS) 2016). Absent this conditional moral license for harm, pharmaceutical development as we know it would otherwise be impossible. Summed together across all participants and trials, nonhuman animals and patients provide a large welfare subsidy to drug developers. This is a constitutive feature of the moral economy of pharmaceuticals.

3. A Labour Subsidy

The fact that nonhuman animals and patients may give up some welfare in drug development is at least something that physicians, regulators, patients and oversight bodies are aware of. Human research regulations ask research sponsors to justify risk. Companies sometimes stop trials early because of safety concerns. Consent forms go to great lengths to alert potential participants to risks.

The labour nonhuman animals and patients provide for drug trials, however, is almost invisible to drug developers, oversight bodies, patients or policy makers. For animals, we are generally not habituated to thinking of animals as labourers, even if we routinely make use of expressions that suggest otherwise (e.g. "working dogs," "service animals," "draft oxen"). Yet pressing touchpads for monkeys, or running on rotorods for rodents, or abiding afflictions for animals that are disease model, would seem to meet the definition of labour (for further discussions, see (Donaldson and Kymlicka 2019)).

For human beings, there is one narrow exception where labour aspects of trial participation are part of the conversation: healthy volunteers in phase 1 trials aimed at testing safety. These typically pay participants. There is a healthy debate in Bioethics about whether healthy volunteer participation represents a form of work (Grady 2005; J. A. Anderson and Weijer 2002; Malmqvist 2019). This debate is primarily aimed at informing fair remuneration for such work. Should research participants be paid like temporary wage labourers? Should they be paid more? Or does too much pay set this medical undertaking up for some of the odious dynamics- for example, principle-agent conflicts- that are corrosive of the fiduciary obligations that physicians- even physician-researchers- are said to owe study participants. Sociologist Jill Fisher has written extensively about the work experience of healthy volunteers (Fisher 2020).

However, most persons participating in trials are patients, not healthy volunteers. To my knowledge there is almost no accompanying literature on the labour of patient participation in trials (one exception is provided here (Cooper and Waldby 2014)). While there are many competing theories of work, one simple definition posits work as any activity that produces objective value in the world (Cholbi 2023). Work can be defined in opposition to leisure, an activity that brings value to the self. Trial participation meets this definition. It involves a host of physical, emotional, and cognitive activities that bring value to pharmaceutical firms and to future patients.

Patients (and often their caregivers) must transport themselves to a research clinic, which are often specialized medical centers and located farther away than clinics providing usual care. In some cases, patients temporarily relocate to participate in trials. Patients produce information: they answer queries, fill out surveys, and provide symptom ratings so that physicians can determine whether a drug is working. Patients must regiment their lives in accordance with the research goals. This means taking a medication on a scientifically specified schedule, abstaining from protocol-proscribed activities like unprotected sex, or organizing their calendars to make clinic visits at designated timepoints. Patients typically need to muster emotional resources to sustain participation. For example, many patients dread receiving placebo. But because trials are blinded, they are prevented from knowing whether they have been assigned to receive placebo or an experimental treatment. Patients must thus withstand doubts about whether they are receiving a placebo. Patients must also muster emotional resources to tolerate unpleasant research procedures, like blood tests or MRI scans, or the indignities of close medical inspection. Sometimes these procedures can be painful, such as when researchers take biopsies of organs, or when patients are asked to forgo a standard of care and take a placebo. Patients must take in and interpret information. They must read and interpret consent forms, which contain information about risks, benefits and procedures. They also need to understand instructions for taking a medication. Patients must stand watch over their symptoms, so that they can be reported back to the study team. Though participants are always free to exit a trial, they are asked to sustain this labour for the duration of the study, which can be several weeks, months, or sometimes a year.

We can then think of research participants as research labourers, and surveys or testimonials of patients who participate in trials reveal that participation is experienced as requiring work (de Jorge et al. 2015; Small 2005; Gubar 2020; Tengbeh et al. 2018). This labour force almost certainly outnumbers personnel traditionally considered research labourers, like physicians, research nurses and statisticians. I've already described the animal volume. For human beings, one analysis of the U.S. pharmaceutical industry reported that it employed 409K persons in research and development in 2022 (Mikulic 2024). By contrast- and using very crude methods- my research group estimates that at least 5 million individuals participated in U.S.-based clinical trials of interventions in 2022 (On file with author).

The work of human research participation is occasionally problematized by the research establishment. This problematization is mainly oriented towards reducing frictions in data collection. A fifth of trials fail to recruit or retain research volunteers. Often this reflects that participation is too onerous. Any attrition of participants during a study presents a threat of bias and reduced statistical power for the sponsor. There are many efforts to reduce the amount of work patients need to commit to clinical trial participation (Smith et al. 2021; Lingler et al. 2014; Ulrich et al. 2018). However, in this formulation, labour of trial participation is not regarded as a moral problem. For example, there is little to no discussion about the fairness of workloads or how work is distributed. Little said about what patients might be owed for their labour, and discontinuities between what protections normal workers have and those available to research volunteers (for example, many normal workers have access to compensation in the event of work-related injury; the same is generally not the case for research participants). Little is said about the textures or experience of that labour, and how it might differ from other forms of labour, including other volunteer work. Consent forms elaborate on research procedures and sometimes provide visit schedules. However, in my experience, they generally do not position study participation as labor by enumerating the estimated number of hours or days a participant will need to devote to study participation.

As with welfare, the labour of animals and patients is a constitutive element of the moral economy of pharmaceutical development. It is difficult to conceive of an efficient way of developing pharmaceuticals that would not ask patients to do some work. But it is almost invisible as a moral problem.

4. Compensations

One reason the welfare and labour of research participation might have little visibility is a perception that each are compensated by the prospects of accessing superior healthcare. As we will see in the next section, this view- I will call it the “therapeutic creed”- is deeply entrenched among individuals and institutions pursuing drug development. Is there evidence to support it? Obviously, with exceedingly rare exceptions (Gordon et al. 2009), nonhuman animal research participation is nontherapeutic.

For patients, there are principled grounds for skepticism. The scientific rationale for running clinical trials is to resolve uncertainty about whether a new drug is therapeutic. If drugs tested in trials were known in advance of the trial to be therapeutic, there would be no reason to run the trials in the first place. It follows from this logic that, *a priori*, there should be no reason to think that accessing an unproven drug in a scientifically justified drug trial would be therapeutic. As indicated above, the high failure rate of drug development logically implies that benefits do not generally exceed risks for most drug exposures in trials.

Another fallacy in the therapeutic creed is that trial participation almost always entails extra research procedures that have no therapeutic value whatsoever. Imagine, for the

moment, a clinical trial where accessing the experimental drug, and the extra monitoring, confers 20 units of therapeutic value to the patient as compared to what they would receive if they didn't enter the trial. For purely scientific reasons, the scientists also collect tissue samples and perform some extra tests. Together, suppose these subtract 1 unit of health-related value for the patient. The trial thus presents 19 units of therapeutic value and is good choice for the participant. However, the subtraction of that one unit of value is not a price of receiving the therapy itself. It is a price of entering a scientific experiment. The experimental drug could have been administered, absent the tissue procurement, and the participant would have experienced 20 units of therapeutic value. Even if it were the case that overall patients benefit from going into trials, they sacrifice some of that welfare because a new treatment exacts side effects, but because evaluation of a new treatment exacts some sacrifice.

Another reason to question the therapeutic creed derives from a somewhat subtle statistical point. When we speak of risk and benefit in medicine, we usually use populations as our reference class. Thus, when we say that a drug is safe and effective, what we mean is that when we give a drug to a population of patients and we add the risks and burdens together, the overall benefits exceed the burdens. A drug can thus be therapeutic for a population, even though some individuals in that population do not respond or suffer side effects. According to many moral philosophies, what matters most when we speak of harm and benefits is a reference class of the individual. Suppose that, when measuring outcomes in a population of 100 patients, we discover that overall, 100 units of benefit are achieved, along with 50 units of harm, leading to a net population benefit of 50 units, or 0.5 units per person. This outcome is compatible with a scenario where 50 of the individuals experience 2 net gains in benefit, but the other 50 experience 1 unit of net harm. According to many moral philosophies, the harm caused to the 50 patients is not redeemed by the net benefits experienced by the other 50 patients. This matters in drug development, because even if some patients come out ahead after receiving experimental drugs in trials, there are many individuals who come out behind. These latter individuals have sacrificed welfare and labour without compensation.

These principled reasons are complemented with abundant and often ignored evidence against the therapeutic creed for patients. Many researchers have attempted to quantify the benefits associated with clinical trial participation using a technique, meta-analysis, that pools estimates derived from many different individual epidemiological studies (Vist et al. 2008; Peppercorn et al. 2004). My own research team has published three such meta-analyses.

The first looked at whether accessing unapproved cancer drugs extended the survival of patients relative to patients receiving the standard of care in the control group. Studies in our sample included phase 2 and 3 trials. We found that there was a small survival benefit associated with accessing experimental cancer drugs. It conferred about five weeks extra survival. Yet this advantage was purchased at the expense of greater risk of life-threatening toxicity. These overall welfare gains are nominal. They are further diluted by the fact that

many patients entering such trials are randomized to receive the same therapy they would have received had they not entered the clinical trial (Iskander, Moyer, Fergusson, et al. 2024). Another study we performed looked at trials for neurodegenerative disorders like Alzheimer's disease. In this study, patients accessing the new drug did not do better than patients receiving the placebo in terms of efficacy. In terms of safety, they did worse. For trials involving difficult to treat diseases, there is an overall net loss associated with accessing experimental drugs, even when drugs are in late phases of testing (Feustel et al. 2020).

A third meta-analysis from my group pooled epidemiological studies aimed at determining whether patients who participate in cancer trials live longer than those who don't but who receive the same treatment. Unlike the previous two studies, this one aimed at studying the effects of receiving extra care in a trial, rather than accessing an unproven drug. Our unadjusted analysis found that patients in trials seemed to live longer than patients who don't. The abundance of such studies likely fosters the belief that trial participation is benefit. However, this overall benefit may simply reflect that patients who enter trials tend to be younger and more able than patients who have the same illness, but do not enter trials. When we pooled only those studies that addressed various confounds and biases, benefit regressed to the null. The conclusion is that the extra monitoring and care associated with trial participation does not confer a detectable survival advantage for cancer patients (Iskander, Moyer, Vigneault, et al. 2024).

There are many methodological limitations of our studies and those of others. For example, trial participation could be associated with better quality of life than not participating in trials. However, quality of life is not generally measured and reported for patients in trials and outside them, making comparison of the two impossible. Bearing this and other provisos in mind, the broad point is this: many researchers have attempted to detect a benefit from clinical trial participation. Efforts aimed at synthesizing these studies have recurrently failed to detect evidence that patients benefit medically from trial participation. Overall, patients transfer welfare and do work for drug development. The benefits of trial participation do not zero out this subsidy. For nonhuman animals, this transfer is wholesale.

5. A Collusion of Ignorance

That pharmaceutical development runs in part on a welfare and labour subsidy from nonhuman animals and patients has, as I have suggested above, little visibility in economic, policy and moral discussions of the enterprise. For example, numerous economists have estimated the costs of developing new pharmaceuticals. These analyses include direct spending on research and development, the costs of capital, and opportunity costs (Sertkaya et al. 2024, 2000–2018; Wouters, McKee, and Luyten 2020; DiMasi, Grabowski, and Hansen 2016). None has ever priced the value of the labour or welfare nonhuman animals and patients contribute to develop drugs, much less more tangible costs, such as those associated with patient travel or lost wages. Along similar

lines, there are numerous analyses of pharmaceutical workforces. These consider medical scientists, engineers, chemists, pharmacists, sales representatives, janitors, and customer service workers; they exclude research participants and their caregivers (Lydia and Schumacher 2024; "Pharmaceutical & Medicine Manufacturing | Data USA," n.d.).

Policy debates around pharmaceuticals generally ignore this welfare and labour subsidy. Consider, for example, debates about price controls for pharmaceuticals. Critics of price controls generally appeal to the power of free markets to coordinate supply (in this case, investment in innovation) with demand (the need for treatments). That individuals and governments pay high prices for life saving drugs attracts investment in developing treatments against dread diseases like cancer, Alzheimer's etc. Enact price controls, according to this logic, and everyone loses. These arguments, however, never address the fact that this free market socializes some of the costs of drug development. They also ignore the fact that the labour market nourishing this effort is not free, owing to the limited mobility and eligibility of patients. For example, in a free patient labour market, patients would lend their bodies to firms most likely to pursue drug development in a manner that is most aligned with their values and preferences. However, patients generally do not have a choice among multiple trial options. Proponents of price controls, for their part, often point out that private drug development is heavily subsidized via public funding for basic science or tax breaks for research investment. Such subsidies, they argue, give taxpayers a claim on setting price. I have yet to see nonhuman animal and patient welfare and labour subsidies, however, invoked as a reason to enact price controls.

Two dynamics, each set in motion to various parties to drug development, contribute to the invisibility of this moral economy. The first is a sustained and remarkably resilient construction of trial participation as a therapeutic endeavor for patients. Medical centers encourage this in the U.S. by proclaiming their clinical trials offerings as a reason to seek care with them (London and Kimmelman 2018). Medical professional societies endorse a therapeutic creed by issuing policy statements that endorse even phase 1 cancer trials- a category of trials associated with the greatest burden but lowest prospect of benefit- as having "therapeutic intent" (Weber et al. 2015). In the U.S., Medicare covers medical expenses associated with participation in such trials. Clinical practice guideline committees issue recommendations that present trial participation as "the best management for any patients with cancer" (Shalowitz and Miller 2024). Patient advocacy groups, like the U.S. Alzheimer's Association, describe the benefits of participation as including "Giv[ing] access to potential treatments before they are widely available, [and] offer[ing] expert medical care at leading health care facilities — often free of cost" ("Why Participate in a Clinical Trial?," n.d.). Public funders like the NIH offer reasons to participate in a trial as "to possibly receive the newest treatment and to have the additional care and attention from the clinical trial staff" ("Why Should I Participate in a Clinical Trial?" 2015). Or in the NHS in the U.K.: "If you take part in a clinical trial, you may be one of the first people to benefit from a new treatment" ("Clinical Trials" 2022). Cancer Research in the UK states "you may have a treatment which is only available as part of a trial… the new

treatment may work better than the standard treatment (no one knows this for sure, which is why the trial is being done)" ("What You Should Be Told about a Clinical Trial" 2022).

Human protections may also foster the therapeutic creed. For one, they rarely question the vague language about benefit in informed consent forms. As an example, typical phase 1 cancer trial consent forms state "you may or may not benefit by participating in this trial." Sometimes they say "if you participate in this trial, benefit is not guaranteed." Mathematically, these two statements are the equivalent of saying that the probability of benefit is greater than equal to zero percent and lesser or equal to 100% (in the first case) or less than 100% (in the second case). Imagine waking up to a weather forecast this uninformative. These proclamations defy numerous meta-analyses that fail to demonstrate survival benefits associated with phase 1 trial participation; they also prevail despite a massive literature suggesting that cancer patients overestimate the prospect of benefiting from trial participation (Bittlinger et al. 2022).

Human protections policies encourage review committees to determine that risks in a study are outweighed by direct benefit (if any) and scientific value. The first phrase implies that there are circumstances where the therapeutic benefits of an experimental drug are known in advance to outweigh their risks, and that these benefits are sufficient to redeem the risks. The question is: benefit relative to what? At the point where many trials are run, experimental drugs might already be known to be better than leaving a patient untreated. But the relevant comparison for this judgment is what a patient would receive outside a trial. Generally, the reason why a trial is run is because the value of an experimental drug is uncertain relative to a standard of care.

It is difficult to overstate the historicity of this therapeutic creed. Before the 1990s, trial participation was generally viewed as medically burdensome. Indeed, public discourses often merged conceptions of animal and human ethics, speaking of human research participants as "guinea pigs." It is also difficult to overstate how discordant the creed is with the very enterprise in which it occurs. The raison d'etre for running trials is to generate high quality evidence. It is founded on skepticism about anecdote and on an awareness of theory and bias affect the collection and interpretation of evidence. That the therapeutic creed persists in this environment can only be explained by what scholars of agnotology might call active ignorance (Proctor and Schiebinger 2008; Oreskes and Conway 2010). I term this a "collusion of ignorance."

6. The Moral Economy of Drug Development

This moral economy of drug development I have sketched out has much to commend it. First, it supports a robust drug development enterprise that has produced many life-saving drugs and vaccines. In so doing, it also fulfills many of the moral aspirations motivating the engagement of patients, caregivers, scientists and others in this enterprise. Second, it does this while asking for little from individual patients. Specifically, per patient welfare losses are generally modest. While some trials, like those in early phases, require a considerable

amount of labour (probably one sixth of cancer patients survival time is spent visiting clinics for a trial) (Iskander, Magnan Robart, Moyer, et al. 2024), others require little more work than a patient and caregiver would do outside a trial. Third, patients engage in this moral economy voluntarily. Canons of informed consent and oversight systems prevent coercion and constrain manipulation. At least ostensibly, that private and profitable drug developers benefit from this large subsidy takes nothing away from the fact that future patients benefit from this as well.

Fourth, consider the alternatives. What if it were the case that patients benefitted from accessing new drugs in trials? What if there were survival advantages to receiving care within a drug development trial? In the former case, it would imply that the state, by withholding approval of life saving drugs and conditioning access to them on participation in trials, uses its coercive powers to conscript patients into the social project of developing drugs. It would also imply that pharmaceutical firms collude with states in that project. It would also likely entail injustices in the way access and care benefits are distributed. Participation in early phase cancer trials, for example, requires travel and a substantial commitment of time. The resources needed for trial participation are inaccessible to many. That patients do not benefit from accessing unapproved drugs, or receiving extra care in trials- that participation in drug trials entails burden- to some degree preserves a fair, progressive arrangement where the greatest burdens of developing drugs fall on those with greater advantage.

Another alternative: what if we paid patients for their welfare and labour? While this might rectify their undervaluing, payment would introduce other dynamics that work against a sound moral economy. For one, it would introduce a principal-agent dynamic into clinical trials, whereby researchers and patients instrumentalize each other and vie for advantage. This dynamic is ill suited to an enterprise where one party to the transaction is debilitated by illness, and information asymmetries abound. Another problem with payment is that it would dramatically increase the costs of drug development, which would be reflected either in more expensive pharmaceuticals or (in the case of price controls) less private investment in drug development. Third, the volunteerism of patients binds present patients, future patients, and ultimately states in solidarity. Patient subsidies to drug development have many of the same qualities Richard Titmuss extolled for voluntary blood donation (Titmuss 2018): they foster altruism and a sense of community, and they head off an arrangement where the disadvantaged- in search of research wages- bear a disproportionate burden for future patients.

Yet pharmaceutical development is different from blood and organ distribution in one important respect. Whereas blood and organs are generally not sold in a free market, pharmaceuticals (and the intellectual property on them, which patients help create) are. The moral economy I've described is deficient in three respects.

First, it rests on defective consent. It contradicts one of the most important tenets of human research ethics. Patients enter this moral economy in pursuit of therapeutic

outcomes- and expecting their realization. These expectations are reinforced by states, sponsors, medical centers and some physicians. Consent documents, as we have seen, do little to correct the record, offering statements that are mathematically consistent with exaggerated benefit. As we have seen above, however, the benefits of participation in late phase trials are, on balance, nil; in earlier stages of drug development burdens are generally exceeded by medical benefits. It seems likely that, if patients understood that trial enrolment offers somewhere between a nominal and moderate net loss of welfare, fewer would enroll in trials, and drug developers and medical centers would need to make different appeals to sustain an enterprise this robust. To some degree, the drug development enterprise we enjoy today rests on a collusion of ignorance about the therapeutic status of trials.

Second, the moral economy I describe makes profligate use of this donated welfare and labour from patients, and extracted welfare and labour from nonhuman animals. Many trials and drug development efforts are marvels of science. The rapid development of safe and effective vaccines and treatments for COVID testifies to how well- and efficiently- drug development can work. But before these successes, much of the clinical research directed towards COVID was scattershot, redundant, poorly designed and analyzed, and reported in a biased manner (London and Kimmelman 2020). The early days of the COVID pandemic recapitulated research dynamics observed with Ebola trials of vaccines and treatments during the West Africa outbreak of 2013-16. (Dodd et al. 2019) These spectacular fails reveal what occurs, quietly, in normal research. My own team has estimated that roughly 73% of randomized trials (accounting for a third of patients enrolled in trials) are unlikely to have informed medical decisions (Hutchinson et al. 2022). A five part series published in the medical journal *Lancet* documented numerous ways patients and research efforts are "wasted"(Glasziou et al. 2014; Macleod et al. 2014; Chan et al. 2014). Ethics review committees routinely approve studies that enroll more patients than needed to resolve a clinical hypothesis (Hey and Kimmelman 2014). Nonhuman animal research is also plagued by deficient design and biased reporting (Begley and Ioannidis 2015; Baker et al. 2014). The literature on deficient research in medicine too large to summarize here.

In some spheres of medical innovation, market forces press drug developers to make judicious use of nonhuman animals and patients. Experiments using animals that have longer life spans and richer emotional lives- like nonhuman primates- are expensive. Trials are even more expensive, and drug developers are under considerable pressure to run the smallest ones possible, over the shortest period, and to make them as convenient as possible for patients. These same market forces work against efficiency in other areas of innovation. Drug developers often have strong incentives to develop me too drugs- where the gain in medical value is smaller per patient randomized in a trial. After drug approval, companies often have incentives to run large trials to habituate clinicians to using a new drug (London, Kimmelman, and Carlisle 2012). Such forces combine with a somewhat casual attitude towards clinical research that has taken hold in the last two decades. Perhaps this casual attitude is reinforced by the therapeutic creed. The result is that many

drug development efforts use patient welfare and labour gratuitously, and in ways that participants would probably not endorse.

Third, nonhuman animals and patients participating in this enterprise make strong claims on those conducting and overseeing the research. The latter include researchers, sponsors, medical centers, states and actors to whom they have delegated oversight, such as ethics review bodies and regulatory agencies. Patients are recruited to give up time and commit uncompensated work for one of the most powerful sectors of the modern economy- the pharmaceutical industry- in part on the prospect their participation will advance medical science. At medical journals, funding agencies and the corridors of the academic medical center it is common knowledge that clinical trials vary widely in terms of their rigour and prospect of advancing future care. Patients participating in trials are not privy to this knowledge- they are generally offered only anodyne statements like "your participation may help doctors improve treatment for future patients." Because of this- and a host of other reasons- patients are in no position to leverage their labour power to align research with their moral aspiration. This task is tacitly delegated to sponsors, scientists, medical centres and above all- as the sole research actor backed by the coercive force of the state- regulators.

The claim nonhuman animals and patients make extends in space and time. The medical value of drugs and evidence produced by trial participation is promissory. Many conditions must materialize for the social value embodied in a patient's subsidy to be realized. Here are five: 1) Trial results must be reported and circulate among decision-makers. 2) More trials must be run to confirm safety and efficacy. 3) Regulators need to approve the drug in accordance with evidence. 4) Physicians must prescribe the therapy appropriately. 5) The drug needs to be accessible to those who need it. Many of these conditions that redeem the promissory value grounding this patient welfare and labour subsidy materialize long after trial participants exit this moral economy. This places strong moral obligations on downstream actors to ensure these conditions are met and make good on the promissory value grounding clinical research.

Processes and structures are in place to see these conditions through. Laws are in place, for example, that require sponsors to report trial results promptly and accurately ("FDAAA 801 and the Final Rule" 2020). Regulators have authority to, and generally press for evidence of safety and efficacy before approving a drug. Healthcare systems generally strive to make safe and effective pharmaceuticals accessible to those who need them. However, many of these processes and structures are failure prone. And some of this failure proneness likely reflects the ability of pharmaceutical firms to convert their earnings into political influence. As illustrations, consider the five conditions mentioned above.

1) Trial results must be reported within a year of completion. This policy only applies to a subset of trials that are regulated by drug regulators (in the U.S., for example, the rule does not apply to the most burdensome trials, phase 1), and compliance with reporting has generally been under 50%.(M. L. Anderson et al. 2015; DeVito, Bacon, and Goldacre 2020;

Dal-Ré and Mahillo-Fernández 2023) Regulators have rarely fined sponsors for noncompliance. 2) Trials need to be run to confirm safety and efficacy. Regulators frequently approve drugs for life-threatening diseases based on preliminary evidence of efficacy, on the expectation that sponsors will later confirm the drug's value. This confirmation is frequently delayed, and even where it occurs, study designs are inadequate to the task of confirmation. (Shahzad, Naci, and Wagner 2023; Liu, Kesselheim, and Cliff 2024) For example, sponsors frequently use indirect measures of efficacy. Regulators rarely remove drugs from the market because sponsors have not conducted properly designed confirmation studies (Gyawali et al. 2018). 3) Regulators need to approve the drug in accordance with evidence, and physicians must prescribe the therapy appropriately. However, regulators often approve drugs that have not demonstrated efficacy. Two prominent examples are the FDA approval of aducanumab for Alzheimer's (approval came after two trials were stopped for futility) and approval of eteplirsin for muscular dystrophy (the drug hadn't- and as of this writing still hasn't- shown any effect on patient outcomes). 4) Physicians need to prescribe the drug appropriately. Many drugs are prescribed liberally for indications for which they are not approved (off-label prescription), and for which evidence of efficacy is weak. Several studies suggest that many trials are run to promote such off-label prescription, and regulatory authorities create legal safe harbour for such promotion. (Federico et al. 2019; Grabitz et al. 2024; Carlisle, Federico, and Kimmelman 2018) The opioid epidemic in the U.S. provides an instance where effective drugs were not prescribed appropriately, and where regulators and medical licensing bodies failed to stem inappropriate prescription (Keefe 2021). 5) The drug needs to be accessible to those who need it. In jurisdictions like the U.S., high drug prices and/or a lack of insurance coverage compel many patients to forgo treatments, cut back on dosing, (Conwell et al. 2011; Tseng et al. 2004) or take extreme measures- like seeking bankruptcy protection- to access drugs (Dusetzina et al. 2018).

For the foreseeable future, pharmaceutical development will continue to rely on nonhuman animals and patients. Individually, these patients give nominal to moderate amounts of welfare and labour to drive pharmaceutical development. Nonhuman animals give their lives. Summed together, these contributions are large, and because of them, nonhuman animals and patients exert strong claims on states to oversee and orchestrate pharmaceutical development in a way that minimizes their sacrifices and that aligns drug development with their aspirations. These claims have received little policy attention- perhaps because the moral economy of drug development has been constructed as a win for all parties engaged except perhaps animals, whose interests can be ignored anyway. Once it is appreciated, however, that patients and animals give something of value up, many aspects of policy surrounding the development and disposition of pharmaceuticals come into question.

7. Conclusions

Drug development runs on a large labour force of sick individuals and nonhuman animals. For the most part, this labour force is not directly compensated by the prospect of medical

benefit. Instead, patients participating in trials generally experience small to moderate losses of welfare; animals give up large amounts of welfare. When aggregated across patients and across trials, this amounts to a large welfare and labour subsidy for drug development. This subsidy generates treatment options for future patients. It also supports private drug developers. This subsidy unfolds in front of sponsors, physicians, regulators and ethics committees, many of whom persistently discount the moral implications of animal research and regard human trial participation as therapeutically advantageous, despite reasoning and a robust evidence base suggesting otherwise.

The moral economy of pharmaceutical development has many virtues we should celebrate. Among other things, it supports an immensely productive and successful effort at developing treatments. But it is also shot through with problems and contradiction, including defective consent, exploitation of nonhuman animals, and a casual regard for the moral claims patients and nonhuman animals- as labourers and as sentient beings sacrificing some of their welfare for a common good- assert on the oversight and disposition of pharmaceuticals. Patients (and delegates of laboratory animals) apprised of this moral economy and their power to shape it have before them a world to win.

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