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Do No Harm: Balancing Medical Due Diligence and Clinical Outcomes to Garner Trust in Novel Therapeutics

On March 13th, 2006, a man named Rob Oldfield walked into Northwick Park Hospital in the United Kingdom. He was by all accounts perfectly healthy, yet within a few hours, he and five other patients were experiencing multi-organ failure and complete immune system shutdown with fluid gradually inundating their lungs. While all six people survived after fighting three long weeks straddling the precipice of life and death, many were left irrevocably scarred, be it with long-term immune compromise or even physical amputations.

The cause of their nightmarish ordeal was an untested drug named TGN1412, for which they had been participating in a clinical trial. Oldfield recalls signing the 11-page consent form vividly, later telling a BBC reporter that he "had no idea [the drug] altered the immune system" and that the consent form's description of "'potential hazards' could have resulted in him needing life support" (Caffrey 2016). Later investigations revealed that Parexel, the parent company behind the clinical trial, knew of the drugs' capacity to induce a terrifying immune overreaction called a cytokine storm, which was the causal factor behind their organ failure. However, simultaneously, the investigations concluded that Parexel had "acted within the protocols" (Caffrey 2016) and thus faced little liability (they ultimately agreed to provide monetary compensation).

The case of TGN1412 speaks to a long-standing, overarching conundrum within the sphere of medical therapeutic development. Newly developed drugs require clinical validation in humans to be verified as effective, yet exactly how much theoretical investigation and biological research should be required before clinical testing commences? And how should that information be communicated to prospective patients in the trial? The first question itself is already quite slippery to pin down—pharmaceutical companies themselves don't want to invest resources into testing an ineffective or even potentially toxic drug on humans. However, there is at least an empirically-tested albeit continuously-updating set of guidelines to broadly screen for biological toxicity. For example, Parexel knew of TGN1412's potential side effects. It is the critical second question relating to ethically disclosing information and maximizing public trust that is nebulously defined.

Perhaps the most intuitive solution to maximize public trust and safety is to prolong the pre-trial validation phase and introduce stricter regulations to require complete transparency. This way, all nuances can be thoroughly explored and all data freely perused by the public. Indeed, this is a popular school of thought, and all scientists should feel beholden to the underlying principles behind encouraging stringent requirements, as it does fundamentally protect patient safety. Recent examples include the 2016 rules modification to NIH grants, which closed a critical "loophole" that meant laws requiring "researchers… to include information about their methods and results" were "hard to enforce" (Reardon 2016). The change was almost universally praised, as it meant scientists were no longer able to conduct statistical manipulation through so-called "p-hacking" and refuse to report data for failed clinical trials. This was clearly a case where information should have been disclosed, yet had been withheld for profiteering reasons. Other historical examples involve introducing obvious rules by modern standards, like

the requirement to publicly track and render care to all patients. This arose from the ethically disastrous and individually traumatizing events of the Tuskegee syphilis experiment, where sick participants were denied penicillin for the sake of continued research. One would be hard-pressed to find scientists who lambast these boons for transparency in our scientific process.

However, increasingly in the modern age, introducing regulations on clinical trials to protect patient safety often refers to two things: requiring stringent side effects disclosure and enforcing ever-increasing eligibility requirements for participating in the studies. However, neither are as clear-cut positive as the Tuskegee or 2016 NIH regulations in terms of maximizing both clinical benefit and public trust.

The most intuitive to understand is side effects disclosure. How could it ever be detrimental to inform prospective participants of the dangers or effects they may face? Notably, one of Oldfield's most significant laments in the TGN1412 case was the fact that he "didn't know it was dangerous" (Caffrey 2016). Wouldn't Parexel have engendered more public trust if they had at least made it immediately obvious that cytokine storms were an inherent part of the risk, as they had known? In the case of TGN1412, yes. In hindsight, Parexel would have mitigated much of the fallout by being upfront about the risks with patients. But in everyday trials, the answer is more complicated. In "To Tell the Truth, the Whole Truth, May Do Patients Harm: The Problem of the Nocebo Effect for Informed Consent," author Rebecca Wells discusses the concept of the "nocebo effect." Clinical trials naturally require a control arm where participants are given a placebo, yet during the informed consent process, they are told they are being treated with the new therapeutic and may experience its accompanying side effects just like anyone else. Wells elucidates that "in the very process of describing side effects" during informed consent, "physicians may… cause harm rather than relieve suffering… because of

patients' negative expectations, anticipations, and anxiety" (Wells 2012). The implications of side effects disclosure are significant in terms of patient health. "Psychological distress, significant excess costs because of increased medication non-adherence, extra treatment visits, and additional medicines prescribed" have all been empirically identified (Wells 2012). The harms of the nocebo effect to trust can also be personally experienced through a simple hypothetical scenario: imagine you are enrolling in a clinical trial in hopes of benefiting science, yet the very first sentence uttered by your physician warns you about a sundry of ghastly side effects including disability, disease, and death. Would you feel inclined to trust this drug, and more broadly the therapeutics-development sphere?

Wells proposes a solution of "contextualized informed consent," which essentially enables physicians to make a case-by-case judgment for each study and cohort of participants on how to address this issue of side effects disclosure. While non-standardized and imprecise, this seems to be the best solution at the moment.

The issue of enforcing stricter eligibility requirements in trials to garner more trust and ostensibly protect against adverse reactions is also multifaceted. Often, patients do feel that companies have done their due diligence when people with certain traits (i.e. immunocompromised) are excluded for safety reasons. However, piling on more and more restrictions on who can participate decreases access to potentially life-saving drugs, which fundamentally damages the patients' belief and trust in the healthcare-patient relationship. For example, currently, patients on QTc (QT-interval) prolonging medication are not allowed to enroll in clinical oncology trials for fear that the cancer therapy will interfere with their heart rhythm. However, recent analysis indicates that "a substantial proportion of individuals with lung cancer will be prescribed QTc-prolonging medication" sometime during their life (18.4% of

280,068 patients studied), which means a significant proportion of cancer patients will be unable to receive potentially life-saving treatment (Le 2019). Furthermore, while a prolonged QT heart rhythm in healthy humans can cause life-threatening arrhythmias leading to cardiac arrest, "not all QTc prolongation, particularly if mild, will be dangerous. In addition, QTc prolongation is relatively common among individuals with cancer" anyways, so comparatively, QT-prolonging medication may not actually create an elevated risk for heart failure (Le 2019). While Le concludes by stressing more research is needed to truly uncover the association between QTc-prolonging medication and oncology drugs, it is abundantly clear that eligibility rules in clinical trials require more careful consideration. Indeed, in "Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015," author Susan Jin corroborates how "eligibility criteria for current cancer clinical trials tend to narrowly define the study population," resulting in both loss of generalization to the broader population and also a minimization in active clinical benefit (Jin 2017). Increased scrutiny has been placed on "common yet rarely justified exclusion factors" like "HIV diagnosis, reduced renal function, and a history of brain metastases" by organizations like the National Cancer Institute and the American Society of Clinical Oncology (Le 2019, Jin 2017).

Evidently, introducing new regulations in the area of clinical trials is a complex topic. While many new proposed guidelines at first glance seem to indisputably support patient health or increase transparency, the reality is that there are often many unintended effects downstream. Modern medicine is at the point where additional due diligence past well-established clinical guidelines (i.e. adding more eligibility criteria or listing negligibly probable side effects) actually may clash with patient comfort and positive outcomes. Thus, it becomes extremely tempting to argue that our status quo is sufficient—after all, if adding more regulations is so complicated and

modern clinical trials almost always conclude without devastating tragedies like TGN1412, what else is there to do?

The issue is that there are still many cases where additional regulations around theoretical due diligence and clinical validation are much needed, many of which relate to technology that doesn't cleanly fall into current definitions of innovations that require clinical trials. One particularly egregious example that may initially seem to lie outside of the clinical trial framework is Theranos and its blood testing fraud. However, the impact of Theranos's claims—that they could conduct hundreds of different tests from a few drops of blood—actually eclipses that of many therapeutics undergoing formal drug trials. Thus, as coined by Dr. Ioannidis, Theranos should not be allowed to undergo "stealth research" (Ioannidis 2015). Instead, what Theranos intends to do should fall within the clinical trial regulatory framework, where such important and life-altering tests should be validated with verifiable, non-invasive, and provable data in humans like any other clinical trial before they're permitted to sign multi-million dollar deals with Walgreens to broadcast their technology. This way, the "ambiguity about what evidence can be trusted in a mix of possibly brilliant ideas, aggressive corporate announcements, and mass media hype" can be clearly identified (Ioannidis 2015). Companies like Theranos should face greater regulations and scrutiny to force them to complete their due diligence honestly. However, incorporating biotechnology companies into the existing clinical trial framework will require additional regulations and guidelines. This, in turn, will once again spark conversation about what information to disclose, when we can be sure such technology is mature, how to protect intellectual property, and much more.

Another striking example of an industry that requires more regulatory oversight is the clearance of medical devices, which is governed by the FDA. Within the rules of medical device

clearance, there exists a “510(k) submission process” that “does not require companies to provide safety or effectiveness data from clinical trials” (Le 2021). Instead, they just have to show that the device is “substantially equivalent” to another device that has already been previously approved. Here, the balance between supporting patients and maximizing efficiency is grossly skewed: pushing top-of-the-line new medical devices to patients who ostensibly need them is prioritized over due diligence. The result is horror stories like that of Angie Rodriguez and similar class-action plaintiffs, who after undergoing DePuy’s new metal-on-metal hip replacement that had used the 510(k) pathway for clearance, had a “pseudotumor” form because of “metal debris” and “toxic ions” (Bartley 2017). Similar to Theranos, these so-called “low-risk” medical devices should nonetheless undergo more strict scrutiny of their safety, much like how the clinical trial framework currently operates.

Ultimately, the issue of inspiring public trust while simultaneously encouraging positive patient outcomes when developing novel therapeutics is a complex, multifaceted question with no easy solution. Transparency, validating theoretical safety, and actually helping patients often conflict with one another, and thus there is no prescriptive solution that easily balances all three perfectly. There are clearly sectors of healthcare that require more regulation to improve all three factors, but how we approach implementing these restrictions is challenging. I believe Wells's solution of “contextual” informed consent can be generalized to clinical trials and medical innovation as a whole. While regulations and guidelines do need to be codified, communities of scientists (not just individual physicians like Wells suggests) must congregate regularly to evaluate on a case-by-case basis which measures are appropriate for what trial. Furthermore, with the recent boom in biotechnical research, we must also be willing to alter our strategy at a moment’s notice to best adapt to breaking literature. It is only then that issues like patient

eligibility and side effect disclosure can be considered comprehensively, and ultimately, the patient feels most comfortable and healthy. And while our solutions may be imperfect and even imprecise, if we are able to constantly iterate and improve to the best of our ability, trust—that ever-elusive term in healthcare-patient relationships—naturally follows.

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