CLINICAL INVESTIGATION

OPINION

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Information wants to be free, but when it comes to clinical trials can we afford to let it be?

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"The double-blind, placebo-controlled, randomized control trial (RCT) is undoubtedly one of the most elegant inventions of science; designed specifically not just to answer the question of whether a treatment is effective, but to do this with in-built safeguards to protect against human nature."

'Information (or data) wants to be free' – so goes the mantra of hackers and data activists. In the past this meant computer geeks hacking into secure private networks to fulfill their own curiosity or liberate secret knowledge. Today, voluntary 'data liberation', as practiced by governments and corporations, is relatively commonplace and semiorganized groups with data freedom agendas, such as Wikileaks and Anonymous, have entered the mainstream consciousness.

For me, it feels increasingly challenging to delineate the margins where free data is good or bad. A highly networked, mobile-enabled popular uprising is considered a 'revolution' when it's against an oppressive regime, but considered a 'menace' when it is a disenfranchised mob rioting in a western democracy. Bravely recorded videos of civilians attacked by autocratic regime military forces are essential in prosecuting crimes against humanity, but videos leaked from within a democratic military are a 'threat to national security'. So while data itself may want to be free, we don't always want it to be. And so, to clinical trials.

From a societal perspective, the requirement for any trials conducted in the USA to register on ClinicalTrials.gov can only be a good thing in preventing past sins, such as suppressing negative trials or changing end points. As the US government makes this data open, it also allows repurposing. For instance, PatientsLikeMe imports the complete dataset from ClinicalTrials.gov every night to let our membership know (free of charge) about the 30,000+ active trials for which they may be eligible. So far, so good. But what if even more clinical trial data were free?

The double-blind, placebo-controlled, randomized control trial (RCT) is undoubtedly one of the most elegant inventions of science; designed specifically not just to answer the question of whether a treatment is effective, but to do this with built-in safeguards to protect against human nature. In a well-conducted RCT, it is difficult (though not impossible) to systematically stack the deck by ensuring that the sickest patient or a young parent receives the experimental treatment and not placebo. In the somewhat artificial trial environment, patients, clinicians and researchers all agree to be 'blinded' to preserve the integrity of the trial, although inevitably all three groups make guesses; the accuracy of such guesses is even being reported in some studies. However, unblinding becomes more likely when a treatment is strikingly effective, has a known side-effect profile or when the stakes are particularly high.

I knew one young patient with amyotrophic lateral sclerosis (ALS) who was dissatisfied with the concept of placebos, so she sent her study medication off

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to a private laboratory. This laboratory determined whether she was on the treatment arm (and so, in her view, had a chance at slowing her illness) or on the placebo (in which case she considered participation a 'waste of time'). Needless to say, this caused some consternation, particularly when she blogged about it.

That was nearly 10 years ago and since then the internet has exploded in terms of utilization and tools available for trial participants. Technology now makes it easy for patients to find a clinical trial near them or watch a YouTube video explaining what the study involves and for experimenters to run a multicenter site with electronic outcome measures. However, the same technology also allows what might be considered less desirable behavior.

In 2008, a small study suggested that lithium carbonate slowed ALS [1]. Once that study was published, hundreds of ALS patients on PatientsLikeMe began taking the drug and a few used freely available tools such as Google Spreadsheets to 'crowd source' their own study. In response, PatientsLikeMe upgraded its tools and developed new analytical techniques to evaluate whether lithium was effective. Sadly, we could find no effect [2], but neither could the four subsequent RCTs that announced their results years after our preliminary findings were released [3].

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We felt that exploring the case for lithium carbonate was justified because it was a widely used and relatively safe drug being used at a lower dose than is typically used in psychiatry. Patients obtained the drug off-label, but still under the guidance of their clinician. If we hadn't built our study tools, patients would have still tried to study the effects of lithium on their own. Our concern was to avoid repeating a previously established pattern where, sadly, several experimental treatments in Phase III RCTs have caused death faster than placebo.

But what happens when patients, such as those on PatientsLikeMe, start using online tools to determine whether they are on the treatment or placebo arm of an organized clinical trial? Or try and determine whether the treatment is having any effect? Currently on our site, a little over 400 patients have added a treatment that indicates they have been participating in a clinical trial across 76 studies, mostly in ALS, multiple sclerosis, fibromyalgia and Parkinson's disease. Indeed, a small number of patients are collating and aggregating data from other trial participants to try and unblind themselves and determine whether the experimental treatments are effective. How should we respond to this as researchers or as a company?

On the one hand (as a scientist), I would argue that the blinded RCT is one of the best methods we have in advancing the cause of good medicine. Patients unblinding themselves may inadvertently affect others that didn't want to be unblinded. These people may feel that other participants are unfairly thwarting the good intentions of their altruism. With access to only a small subset of the data and only basic statistical tools, it will be very easy to conduct a flawed analysis. If negative findings are broadcast, this may harm recruitment or cause drop out (a valid critique aimed at PatientsLikeMe by those running lithium trials after we released our own preliminary results). If positive findings are broadcast, this may drive demand for off-label compassionate-use prescriptions of questionable benefit. If the drug later turns out to be harmful, this could be a major problem for patients and a concern for the pharmaceutical industry. New treatments take many years to go from discovery to approval, at a cost of hundreds of millions of dollars. No matter what one's views on the pharmaceutical industry are, nobody else has the resources to take risks such as these and undermining the clinical trial infrastructure in this way is likely to slow the research enterprise. Finally, if patients successfully unblind themselves, this could jeopardize the approval of a crucial new treatment.

On the other hand (as a patient advocate), I want to live in a world where data about patients are theirs to own, to learn from and to share for the benefit of all. When it comes to disease management, the clinicians I speak with are enthusiastic for this notion; when it comes to trials, however, it is more important to them for patients to be kept blinded. Some patients, particularly those with rare or serious diseases, know a lot about their condition, perhaps as much as or even more than their clinician. They are smart, insightful, self-aware people and blinding them is asking them to switch those talents off, or at least to pretend to. That seems unsustainable and unfair, perhaps even unjust. Are we being unreasonable in asking patients to be altruistic and risk their health and their lives for the greater good? A small subset of trials are, in truth, for 'me too drugs' that advance the cause of patients little; trials which are under-powered and unlikely to yield conclusive answers; or even worse, 'seeding trials' that are meant to increase market share of new treatments. Such truths are not to be found in informed consent documents.

More pragmatically, what we are witnessing is the opening salvo of asymmetrical information warfare. A crackdown is only going to foment revolution;

patients could easily organize themselves to 'occupy' and so de-rail a clinical trial. It's not hard to imagine and it could happen anywhere, not just the developed world. They don't even need powerful tools such as PatientsLikeMe, they could do it via Twitter with a simple hashtag. The opposite extreme, that of total transparency, would require new methodologies that control for expectations and placebo effects, which could take decades to develop.

So where is the middle ground? I hope there is a way where we can preserve the value of blinding to maintain scientific integrity, but not to continue pretending that patients must be 'kept in the dark'. There is no stopping the information revolution and stakeholders (patients, industry, academia, payers and regulators) must all deal with transparency as a new reality. The contract for the future must be founded upon patient value. From there we can work through all the other needs that must be met for us to move forward into a world where we can know with confidence which treatments work best for individual patients.

One thing is clear, the status quo cannot be maintained; but herein lies opportunity to upgrade our methods in a way that puts patients at the center of the research enterprise.

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