

Biobusiness in brief: what ails clinical trials?

Gayatri Saberwal

Many academic researchers, while working on fundamental problems, hope that in due course their science will benefit humanity. Undoubtedly, they would be delighted if their science was to be the basis for drugs that reached patients. For that to happen, the candidate molecules must pass through clinical trials. Unfortunately, world over, trials have been beset with problems and have been heavily criticized on many fronts. Here we describe some of the points of contention, focusing on issues that have come to light in the West.

Keywords: Biotech industry, clinical trials, ethics, pharma industry.

BEN GOLDACRE, John Ioannidis, Donald Light and others are angry over the state of clinical trials in the world today. Here we discuss some of the problems that they are exercised about. We have focused on issues that come to light in the West, and leave those in the rest of the world for another day.

Badly or unethically designed trials

Imagine that I have to pass an exam. I prepare for it, set the exam paper, correct the paper and submit the results to the faculty. The faculty look at the preparations made, the question paper, and the marks awarded and decide that I have qualified.

One would laugh at this scenario, and probably consider it a rather poor joke. Although it is an oversimplification of the process of seeing a drug through approval, enough of it is true that it is a problem. A company has a candidate molecule, designs the trials, obtains permission from the United States' Food and Drug Administration (FDA) to conduct trials, conducts them or commissions someone to conduct them, analyses the data and submits the data to the FDA or equivalent authority in another country. In many cases the drug is approved. At no point does the FDA directly check the ethical underpinnings of the proposed trials, and nor does it dynamically monitor ongoing trials.

Overall, this process is obviously a prescription for corruption, the more so because clinical research is increasingly being commissioned by companies and not academia or nonprofits¹. In a review of Ben Goldacre's book *Bad Pharma*, Richard Smith, a former editor of *the BMJ* writes: 'you can get the results you want by doing trials that are too small or too short; by testing your drug against either too low a dose or too high a dose of your competitor's drug; by stopping trials either too early or

too late; by changing the outcome measures; by ignoring drop outs; by undertaking "dodgy subgroup analyses"; and by many other methods'². The inherent conflict of interest of industry sponsoring an evaluation of its own drug candidates has led to calls for the public sponsorship of trials that separates their funding on the one hand from their conduct and the analysis of the results on the other^{3,4}.

Other problems that plague trials are not so much that they are unethical, but that their outcomes may not be particularly useful to patients. Companies tend to conduct trials to gain product approval rather than to compare drugs with each other or with other types of interventions. Whereas this situation is not unethical, it is not useful to daily medical practice where a doctor has to choose one drug over another.

Another way in which trials are not designed well is captured in the concepts of efficacy and effectiveness. Efficacy is how well the drug works in ideal conditions, that is, on a small, carefully defined population of individuals. After approval, of course, the population to which the drug will be administered will be much larger, and will often be older and perhaps taking a battery of other drugs as well. How effective is the drug in the latter situation? That is called its effectiveness, that is, how well it works with 'real world' patients. Sponsors who launch a trial want to maximize the chance of success; so the number of restrictions imposed in recruiting adult patients in particular – the situation is different for pediatric cases – means that under 5% of patients are eligible for cancer trials, for instance⁵. This is a huge disservice to patients. Also, since pharmacovigilance – the longterm monitoring of a drug for adverse effects – tends to be poor, drugs may be on the market for a long time while harming, even killing, patients.

Recruitment of patients for trials

One large pharma company has stated that of the 10 years or so required to test a new drug, three years are spent

Gayatri Saberwal is in the Institute of Bioinformatics and Applied Biotechnology, Biotech Park, Electronics City, Phase I, Bengaluru 560 100, India. e-mail: gayatri@ibab.ac.in

identifying and enrolling participants (<https://www.wsj.com/articles/companies-try-new-ways-to-attract-patients-to-drug-trials-1468858289>). It also reported that up to 3% of trial budgets is spent on recruiting and retaining subjects, and the delay in recruiting them can be so significant that a trial may even be cancelled⁶.

There are various reasons for these challenges. Too many companies may use the same, preferred trial site and therefore be chasing too few subjects⁶. The diseases being targeted may be rare, and so the number of subjects is small to begin with. It can also be difficult for ill people to travel to designated hospitals. Some companies are trying to address this issue by bringing trials to people's homes. With the help of their mobile phones and other devices, patients are able to talk to staff members, fill up consent forms, report side-effects, transmit photographs of some side-effects, and so on. Yet another experiment is that of direct-to-patient trials, wherein patients can work with their own physicians and receive medicines by post. Either way, the patient does not have to travel to an authorized trial site (<http://medcitynews.com/2016/12/direct-patient-model-future-clinical-trials/>). Such modalities would be fairer to the poor, the old and those living in far-flung areas.

Therapeutic misconception and the Right-to-Try

There are many stories of people who cheated death by participating in a trial. This was, of course, essentially a miracle for the patient concerned. While undoubtedly such stories are a way to get people interested in clinical research, the idea that it will benefit the participants is a widely held 'therapeutic misconception'. Trials are designed to answer a question, and to guide future medical treatment. They are not primarily meant to help the participants. Under 6% of participants will benefit by being on a trial (<https://well.blogs.nytimes.com/2015/03/26/living-with-cancer-clinical-trials-looking-for-patients/>). Therefore, it is unethical to sell the idea of participating in a trial by emphasizing the benefit it might bring the patient.

This issue dovetails into the 'Right-to-Try' issue. Whereas this is not a direct criticism of trials, it is closely related to them. Many states of the US have passed 'Right-to-Try' laws. Under such a law, a terminally ill person could petition a company to permit access to a drug candidate which has passed a phase-1 safety trial, but not yet completed efficacy testing through phase-2 and phase 3-trials. The molecule is still an experimental therapy, and has not yet been approved by the FDA as a drug. In a famous case that played out in March–April 2014, seven-year-old Joshua Hardy battled to stay alive after his adenovirus levels shot up. This was the latest installment of medical issues that had started when he was diagnosed with cancer as a nine-month-old. In an intense 'Save Josh' campaign that – involving a large number of

very effective people around the US – snowballed on social and regular media, the company that was developing an experimental therapy for adenoviral infections was brought to its knees and compelled to provide it to the child. A detailed account of this battle has been written up (<http://www.kidsvcancer.org/wp-content/uploads/2016/01/Hardy-Case-Study-final-March-9-2016.pdf>). To those who are trying to help a patient, the issue is simple: Give us the experimental drug because you have it and it is the only chance to save the person. To the company concerned, to the FDA and to ethicists, it is not that simple. Issues to be thought of include: (a) the cost of manufacturing the test doses, which are manufactured in very small amounts at this stage of their development, and the inability of many to afford the test dose even if it is available because insurance will not pay for it until it is an approved drug; (b) the danger that a bad outcome could doom the drug's chances of being approved; (c) the converse danger that success could raise expectations unrealistically; (d) the inherent conflict between the gain of the one person who succeeds in getting access versus the good of the rest of the patients who may not have been able to access the test molecule and whose chances of getting it are delayed as the small company's limited resources are diverted by the 'compassionate use' cases; (e) the potential subsequent flood of requests that the company may not be able to service; (f) patients having the good luck of their doctor knowing about the experimental drug or being part of a social media-savvy group that is able to champion their cause. After learning much more about such issues, one of the most active people in the 'Save Josh' campaign today agrees with the CEO of the company who had initially denied Josh the drug. Today this activist too would resist giving Josh the drug⁷.

Having seen, however, that trials do help some patients, various states in the US have passed a 'Right-to-Try' law. First approved in Colorado and Louisiana in 2014 (ref. 8), today close to 40 states in the US have such a law. It must be hard to withstand the pressure when faced with a sick person, but that does not make the ethical issues disappear. The ethicist Arthur Caplan argues that if there needs to be a 'Right-to-Try' law, let it apply to phase 3 trials, when there is at least some data on the efficacy of the molecule⁹.

The need for timely, comprehensive and accurate reporting of trial data

The whole purpose of launching a clinical trial is – or ought to be – to collect data on whether or not a molecule works. However, a longstanding problem has been that trial data is not reported in a thorough and public manner, such that others may examine it and determine whether or not they agree with the conclusions. Due to perceived problems with the reporting of trials, there have been

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Table 1. More problems with clinical trials

Problem	Effect	Reference
Industry influence over Congress: Industry lobbied the US Congress to significantly reduce funding for the FDA. Then, the Prescription Drug User Fee Act (PDUFA) was introduced, which requires industry to pay fees to the FDA for its applications to be examined.	This puts the FDA in the pay of industry, a situation of 'institutional corruption'.	20
The 'clean up' of the language associated with trials: The pressure to enrol people in trials has led to the use of milder words being used to describe trials. Illustratively, the word 'experimentation' is being replaced, and even the Helsinki Declaration does not use it any more.	This masks the dangers that undoubtedly exist while participating in trials.	21
Most trial participants are educated, male and white: Although Blacks and Hispanics are 12% and 16% of the US population respectively, their trial participation rates are 5% and 1%.	Since different ethnicities have seen some differential effects in the clinic, minorities will be denied medical insights that affect them. Some outcomes may also be due to socioeconomic determinants.	22, 23
Conflicts of interest of doctors conducting trials: In the first ever death – of Jesse Gelsinger – in a gene therapy trial, one of the researchers had a US\$ 25–30 million financial stake in the company sponsoring the trial.	The doctor may be more concerned about his/her financial or other interests than in the well-being of the patient.	24
There are various programmes under which the approval of drugs can be expedited 'to reach patients faster': Such molecules are not tested for as long as others, are tested on fewer patients, and are not put through post-marketing trials as much as mandated.	Patients are being administered drugs that have not been rigorously tested.	25
The phenomenon of hypothesizing after the results are known (HARKing): In one study, the authors looked at five criteria – including the primary objective and the sample size – that had been defined before the start of the trial and compared these with the subsequent reports of the trial; 61% of the cases did not report on all of these five points.	This reduces the value of the trial, since sheer chance can give rise to certain patterns which can then be reported as the result of the trial.	26
The existence of seeding trials: These trials are deliberately conducted by many doctors, each with very few trial participants. These are meant to get doctors used to prescribing the new drug.	Extra sites mean extra costs in drug development. This is finally borne by the payer, whether the patient or the insurance company. Further, doctors' prescribing habits are altered, and this may be for the better or for the worse.	27
The use of unvalidated surrogates: Surrogate markers are often easier and quicker to track than actual disease outcomes. However, the surrogate used as the endpoint to a trial may not be validated.	Patients do not actually benefit from such trials.	28
Composite outcomes: Researchers may report composite outcomes that have no rational basis for being reported.	Patients do not actually benefit from such trials.	28
Missing data: Large fractions of patients enrolled in a trial may not be tracked. This is captured in the '5 and 20 rule', which states that if less than 5% of the data is missing, then there is no bias, but if there is more than 20% missing, then there is a large bias.	Patients do not actually benefit from such trials.	28

calls for trial registries for decades¹⁰. Finally, steps were taken to 'pre-register' trials before the first patient was enrolled. The International Committee of Medical Journal Editors decided that, starting from July 2005, if a trial not been preregistered in a repository then the results of the trial could not, in due course, be published in any of their

journals, which include some of the most prestigious in the field¹¹. The FDA subsequently decided that starting from 2007 many categories of trials will have to be compulsorily logged with the US government registry, viz. ClinicalTrials.gov (CT.gov). CT.gov has grown into the largest such registry, with almost 300,000 trials in its

database today. All of these are freely available to anyone who wishes to look for specific trials or to analyse data concerning a large number of trials.

Although their holdings are imperfect, the existence of trial registries has proven useful. In 2015, for instance, it was shown that there has been a significant increase in the ‘null effects’ of preregistered trials compared to those that were not¹². By not pursuing such ineffective experimental treatment, many lives must have been saved.

As alluded to above, the intended function of registries is not being fully met. The sub-standard reporting of a large fraction of registered trials includes a good number that is not reported at all, or not done so in a timely manner¹³. A company trying to bring out a drug has a clear incentive to report only results that reflect well on the molecule, and to suppress those that paint it negatively. This selective reporting of trials is highly problematic, leading to the undeclared dangers of particular drugs, to the unethical duplication of trials and to the biasing of the evidence base.

Academics have poor reporting habits too. Only about a third of them report their results within two years of completing the trial and another one-third does not report them at all¹⁴. It is not as clear as to why academics would not want to publish the results of their trials. It could be that they have links with industry, that they do not have the money to follow through this last step, or are simply too preoccupied.

All of this non-reporting is despite the fact that any organization that does not report the results of a trial in the US could be fined US\$ 10,000 per day. However, this rule has never been implemented. Adding his voice to those who have been railing against this situation for years, the former Vice-President of the US, Joe Biden, threatened to stop all federal funds to any institution that failed to report any trial that it had conducted¹⁵. From January 2017, new rules have been implemented in the US. Amongst other steps taken to tighten up the situation, it is now mandatory to register trials with CT.gov, that were earlier exempt¹⁶.

The fact that so many studies have not been reported means that the evidence base for medicine is contaminated. In general, we need analyses to identify gaps and redundancies in the reporting of trials, as further illustrated by the following. A few years ago it was discovered that citizens in Guatemala had been experimented upon by the US, and that some of them had been intentionally infected with syphilis. Then President, Barack Obama, asked the US Presidential Commission for the Study of Bioethical Issues to ascertain whether this could happen in any studies funded by the US government today. In due course the Commission was forced to conclude that whereas such a situation was unlikely, it could not be definitively ruled out since various government departments did not have the data required to determine the same¹⁷.

The lack of records is a serious issue, with scientific, ethical and economic ramifications. In a response to the current situation, the Laura and John Arnold Foundation, USA, has donated US\$ 3.6 million for improving the integrity and transparency of clinical trials (<http://www.arnoldfoundation.org/laura-john-arnold-foundation-announces-3-6-million-grant-increase-clinical-trial-transparency-fda-approved-drugs-interventions/>). An important initiative to improve the situation is the All Trials campaign, which calls for each trial to be registered and the results of each to be published¹⁸. The campaign is supported by 700 organizations and almost 90,000 people¹⁹.

Here, we have described some of the problems afflicting trials. Are there others? Certainly. Table 1 provides a gist of a few others.

It is important that trials be done right, from start to finish. Aside from the medical value, the availability of verifiable data from each step helps build trust with the public, without which there could be a backlash, as evident in other fields such as GM-crops and vaccination. For commercial or other reasons, there may be lobbies and counter-lobbies on any particular issue, and it is only accurate, comprehensive, readily available and independently verifiable data and analyses that will prevent or terminate unwarranted controversies. It is in the interest of each of us, and of future generations, that we take only as many drugs as are truly useful, and this can be determined only through proper trials. This will happen only if potential participants have faith in the whole trial enterprise.

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ACKNOWLEDGEMENT. I thank H. S. Subramanya, Institute of Bioinformatics and Applied Biotechnology, for discussions.

Received 28 June 2017; revised accepted 6 June 2018

doi: 10.18520/cs/v115/i9/1648-1652
