

Position Paper

The coverage of medical injuries in company trial informed consent forms

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Received 6 July 2022

Accepted 18 January 2023

Abstract. Best practice consent forms in company clinical trials detail the financial coverage for medical treatment of injuries. In trials undertaken for licensing purposes these arrangements can raise concerns. We detail three cases in which elements of the consent forms appear misleading and designed to elicit a consent to participation that might not be forthcoming if volunteers for these clinical trials were aware that what is outlined in principle is not likely to happen in practice. Beyond clinical trial participants, these consent forms have wider implications. Medical coverage of injuries sustained in a clinical trial is a nexus where business, scientific and ethical considerations meet. It is not clear that anyone to date has grappled with the issues posed. This paper uses three clinical trials to illustrate the problems to be addressed.

Keywords: Consent, injuries, cause and effect, licensing applications, medical treatment, COVID-19

1. Introduction

This paper looks at the promised medical coverage for treatment induced injuries as outlined in the consent forms for three clinical trials: Study 329, a trial of paroxetine in minors [1], the recent phase 3 Pfizer BioNTech COVID-19 vaccine trial [2], and the phase 3 Astra-Zeneca COVID-19 vaccine trial [3].

The issue of medical coverage for injuries in clinical trials intersects with whether the injuries that happen have been caused by the agent under investigation. Where the trial is being done for licensing purposes, where little may be known about a novel agent, conceding that the agent in question may have caused an injury may have consequences for approval or for the label of the new treatment. (The label is written by the sponsoring company and covers the claims for benefits and harms that a regulator has licensed.)

This problem cannot be solved by a company simply taking responsibility for events in a trial, on both the investigational agent and placebo, unless the event is something like slipping on a banana skin. Any independent treating facility will need to assess what role the investigational agent may have had in the

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resulting clinical condition and what the best treatment for their patient might be in the light of this. Their assessment may be at odds with company views.

2. Study 329

From 1994 to 1998, SmithKline Beecham conducted Study 329, a trial comparing paroxetine (Paxil) to imipramine and placebo in depressed minors [1].

The consent form for participants stated [4]:

If I become ill or injured as a result of participation in this clinical study, medical treatment will be provided, and the reasonable cost of such treatment will be paid by SmithKline Beecham.

The trial report published in 2001 claimed an efficacy and safety for paroxetine [5]. There were suicidal events on paroxetine in this trial, but the implication was that paroxetine had not caused them. Prior company internal assessments and subsequent independent review did not support these claims for efficacy or safety [1,6]. The publication of the 2001 article, claiming efficacy and concealing life-threatening problems, boosted the sales of Paxil [7].

In 2004, when an internal SmithKline Beecham document came to light indicating the company knew the trial had been negative for paroxetine [6], New York State's Attorney General sued GlaxoSmithKline (GSK), for fraud [7]. As part of a resolution of this action, GSK made a commitment to transparency and said it would post reports from its trials on the company website. Study 329 later featured in a US Department of Justice action against GSK that was resolved in 2012 with a payment of \$3 billion [7].

The documents that became available through these legal actions revealed a statistically significant increase in suicidal and related serious behavioural events in this trial compared to placebo. Eighteen of ninety-three children, roughly one in every five, on paroxetine had a serious behavioural event and this was statistically significantly greater than the rate on placebo [1].

By then standard canons of medical causality, most of these children had a clear treatment induced injury. The events came on after treatment was initiated and resolved when it was discontinued. GSK did not let any of the trial participants know that paroxetine had caused their suicidality and that among other consequences for their health, they should approach further exposure to serotonin reuptake inhibiting antibiotics, analgesics, antihistamines and psychotropic drugs with caution. This holds true for other members of their family as well.

In response to questions from the team restoring Study 329 [1], GSK said it was up to the doctors of the patients in the trial to raise these issues with any injured parties; the company did not wish to intrude on the doctor patient relationship. The patients' doctors, however, were involved in the study and were authors on the 2001 ghostwritten paper that denied there were any significant injuries linked to paroxetine [5].

It appears that, to this day, the subjects in this trial have not been alerted to what likely happened them. They have not been compensated for or had treatment for their injuries informed by the best possible knowledge about what caused these injuries. Some may be dead as a result of this lack of what would be normal medical care. Their situation is comparable to that of someone who suffers an allergic reaction to penicillin but is told their problems are linked to the condition they were being treated for rather than penicillin. Such individuals are more likely to take penicillin in the future, with a likely bad outcome, than someone warned to avoid penicillin.

The Study 329 consent form states that the treatment subjects receive in a trial will not deviate from standard clinical practice. It is good clinical practice to attempt to assess what is happening when someone

gets worse on a drug, but this is discouraged by the algorithmic nature of RCT processes [8]. For instance, if a subject is more suicidal two weeks after taking the drug, the investigator will score this on a depression rating scale that has a default to seeing any deterioration as a manifestation of illness rather than an adverse event.

A suicidal attempt or event may be recorded but in trials investigators are not encouraged to link these to treatment and rarely do so. If an investigator judges that an event is likely to have been linked to treatment with paroxetine, these linkages judged 'possible' by the investigator are unlikely to lead to action on the part of companies for two reasons.

First, in the 1990s, many companies adopted a strategy of saying that unless a harm happened more frequently on drug than on placebo to a statistically significant extent no-one could say the drug was linked to the harm, even though it might appear to be. As such, harms an investigator might think linked, as a matter of company policy are not viewed as having been proven to be linked. GSK personnel have stated under oath there are no adverse events that can be definitively linked to paroxetine [9].

The Tobin v SmithKline trial in Wyoming in 2001 was one in which a jury found SmithKline culpable for familicide. In this trial, Ian Hudson, then head of safety within GSK, and later the head of Britain's medicines regulator, made the argument that clinical trials have not shown that paroxetine can cause suicidal events [9]. The jury rejected this argument and decided that in the Tobin case paroxetine had caused both suicide and multiple homicides [10]. The Tobin legal trial is the only legal process in which the claim that clinical trials rather than medical assessments are the true measure of causality has ever been tested. This jury verdict came before the 2001 version of Study 329 was published, with its claim that paroxetine was safe and effective in children.

SmithKline, therefore, had cause to pause and consider whether their approach in this article was appropriate. The 2001 article, however was published after the company had decided to submit this and other trials to the Food and Drugs Administration (FDA) as part of an application to license claims that paroxetine works as an antidepressant for children.

Second, had SmithKline assessed these injuries as they happened in the course of Study 329, and made what in many cases was an obvious link to treatment, they would have had to declare this to FDA as part of their application for a license to claim paroxetine is an antidepressant for minors. GlaxoSmithKline told FDA that paroxetine was lacking in efficacy in this and other trials done in minors [6]. The safety issues were therefore paramount. GlaxoSmithKline did not brief FDA on the safety profile of this drug in children. Taking the absence of evidence as evidence of absence, in 2002, FDA issued an approvable letter for the use of paroxetine for minors on the basis of what was submitted [6]. A more detailed look into what had been submitted later led to Black Box Warnings for suicide [6].

3. Pfizer-BioNTech COVID-19 Vaccine Trial

In August 2020, in Argentina, 36-year-old Augusto Roux volunteered to participate in a trial of Pfizer-BioNTech's COVID-19 vaccine, hoping to benefit his family, compatriots, and the wider world.

The site specific injury section of the consent form (translated from Spanish) states that [11]:

The sponsor, Pfizer, undertakes that, in the event that you suffer any harm, meaning an injury or adverse effects or consequences on your health, related to the study vaccine or with procedures performed as part of this clinical trial, you will immediately receive the necessary medical attention and treatment.

Pfizer will cover the costs of medical care and treatment.

To that end, you will need to communicate (in person or by phone 24 hours a day) with:

Dr. X, (011) 15 XXXXXXXX. Phone 24hs (011) XXXXXX

To guarantee cover of the risks or potential harm that could occur as a result of the study, the sponsor, Pfizer S.R.L, has taken out insurance with the firm

La Meridional Compañía Argentina de Seguros S.A., located in Tte.General Juan D Perón No. 646 4th floor (C1038AAN), C.A.B.A., Argentina, policy number: 406483 as amended.

By signing this informed consent, you do not waive the rights you have according to the Civil and Commercial Code and Argentine laws on civil liability for damages that may apply to you in case you suffer any injury as a result of your participation in this trial.

Here is a more general statement of the same:

Pfizer covers the cost for medical treatment for any injury or illness that occurs as a direct result of taking part in a Pfizer-sponsored study at no cost to the research subject. Pfizer does not use any exculpatory language in informed consent documents that will prohibit a research subject from obtaining appropriate compensation for research injuries [12].

Mr. Roux had mild vaccine induced injuries after his initial dose of vaccine and marked injuries almost immediately following his second dose of vaccine. These included what may have been an initial rhabdomyolysis, pericarditis and what appears to be hepatitis or other hepatic injury.

It is established that he was given the active vaccine and not placebo. There are radiological scans and blood tests in support of these injuries. He was hospitalized for his injuries and on discharge his hospital records offer a diagnosis of a vaccine induced injury. He has since been examined by 4 doctors who concur that he had/has a vaccine induced injury [13].

After his injuries, with ongoing clinical problems, as per protocol, Mr. Roux contacted the research team to inform them of his situation and requested that the blind be broken in order to obtain the right treatment. He was told the blind could not be broken while he was in the study. He withdrew from the study for this reason and found after a complaint to the Argentine medicines' regulator that he was on active vaccine.

In the clinical trial documents, he was recorded as a protocol deviation, withdrawn for personal reasons rather than discontinued as a result of vaccine related injury. After his contact with them, the research team entered a diagnosis of Suspected Covid-19 in the adverse event log for the trial, and also diagnosed him as anxious; these are the final entries in paperwork sent from Pfizer to FDA [14].

There is a mismatch between Mr. Roux's contemporaneous medical record and the records kept by the research team. His medical record from an independent hospital records a vaccine induced pericarditis. This does not appear in Pfizer's final submissions to FDA or in FDA documents laying out their view of what injuries occurred in this trial. A later FDA summary of events from this trial does not include his pericarditis [15].

A submission by Pfizer to the European Medicines Agency review of significant adverse events from this trial includes 7 deaths of which 4 were linked to myocarditis [16]. In these cases, Pfizer note the investigator did not link the myocarditis to the vaccine, although a link between myocarditis and these vaccines is now widely accepted. Mr. Roux made submissions to FDA and EMA about his pericarditis and other problems, but current FDA and EMA public documents do not include this.

The failure to endorse an obvious link between treatment and a closely related event fits with current World Health Organization advice to investigators in trials to make every effort to avoid linking injuries to vaccines [17–19].

As a result of this, Mr. Roux has not had the agreed coverage from Pfizer and has had to pay his own medical costs. His normal Argentine health insurance points to the trial consent form stating that Pfizer would cover his costs. He remains unwell and would appear to be unable get any medical assistance unless he lies about the origins of his problems. But if he lies he risks not getting the right medical treatment for his residual cardiac and liver problems, which need an assessment of the likely cause.

What has happened to Mr. Roux is not an isolated incident. There is evidence from a US Qui Tam case of gross breaches of good clinical trial practice at other Pfizer sites in the United States [20]. There is evidence in Pfizer's children's trial that at least one subject, Maddie de Garay, was seriously injured but in the published article the company has eliminated any linkage between her injuries and the Pfizer vaccine [21].

As in Study 329, the doctor best placed to acknowledge a link between Mr Roux's injuries at the time of the trial, was the lead investigator, Dr Polack, in the centre Mr. Roux attended. Dr Polack, however, became a first author on the first article reporting results from the Pfizer trial in the New England Journal of Medicine [22]. This article recorded an efficacy of 95% based on 162 cases of COVID-19 in the placebo arm of the trial compared with 8 in the vaccinated arm – 0.47% of trial participants. The article reported a low incidence of adverse events. A later article (2) recorded 15 deaths on vaccine with 14 on placebo and a later analysis of the Pfizer and Moderna trials shows more hospitalizations on these vaccines than on placebo [23].

4. The AstraZeneca COVID-19 Vaccine Trial

The AstraZeneca COVID-19 vaccine trial ran in parallel with the BNT169b2/Comirnaty trial. It was interrupted by its Data Safety Monitoring Board (DSMB) in the summer of 2020 to review three serious events. When it resumed Brienne Dressen was one of the first American volunteers entered into the study.

She was seriously injured and her injuries were apparent hours after the first dose of the vaccine. Her injuries are covered in Injuries in Vaccine Trials [24]. Since this was written, she has been diagnosed by the National Institutes of Health with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Treatment with steroids and intravenous immunoglobulins provide temporary relief from inflammatory flares, but she is steadily getting worse.

The consent form for participants in this trial states [25]:

If there is an emergency, call 911 right away or go to the emergency room and contact your study doctor as soon as you can.

If you become ill or are injured while you are in this research study, you must tell your study doctor straight away. The study doctor will provide medical treatment or refer you for treatment.

Injuries that have been caused by the vaccine, tests or procedures are called 'research 'injuries'. Injuries caused by your usual medical care are not research injuries.

The Sponsor has an insurance policy to cover the costs of research injuries as long as you have followed your study doctor's instructions. Sponsor will pay the costs of medical treatment for research injuries, provided that the costs are reasonable, and you did not cause the injury yourself.

Brienne Dressen followed instructions to the letter. She contacted the clinic where she had the injection and proceeded to hospital for assessment. The company effectively admitted causality by immediately blocking her from taking a second dose. However, it later wrote her injuries out of their published clinical trial report in the New England Journal of Medicine [3]. She took this issue up publicly in correspondence

with the New England Journal of Medicine [26]. The correspondence makes clear that despite publishing a paper on this trial's results, the New England Journal have not seen and do not have access to the data from this trial. They are unwilling to correct the published record because they have no way, in their view, to do so, even though she has been a research subject in National Institute of Health studies which have confirmed a vaccine link to her injuries.

Astra-Zeneca have failed to cover Brianne Dressen's medical expenses, which have been over \$300,000, despite repeated efforts to get them to engage. Eighteen months later she remains seriously impaired and on expensive ongoing treatment.

Astra-Zeneca have also failed to follow-up on her injuries despite her signing a consent form in which she agreed to be followed up for two years after vaccination.

We have contacted the Chair of the Data Safety Monitoring Board (DSMB) for this study, who has said that owing to issues of confidentiality he cannot confirm if AstraZeneca informed him of Ms. Dressen's injuries. While similar injuries previously caused the DSMB to pause this trial, Ms. Dressen's injuries, which are of the same nature as those recorded previously, did not lead to a pause in the trial.

5. Breaching the Blind

Augusto Roux's and Brianne Dressen's cases raise another ethical issue. In 2020, whether he or she had an active vaccine was central to their proper medical treatment.

He asked whether he had been on the active vaccine, but the research team refused to break the blind. He took his case to the Argentine regulator (ANMAT), as well as to Pfizer and others. It was agreed the blind should be broken in his case, but his efforts to establish this were described by the research team as paranoid, and this was written into his medical record by Pfizer operatives not qualified to make this diagnosis.

Bri Dressen was led to believe she was on active treatment and NIH subsequently enrolled her as a research subject in efforts to pinpoint what injuries these vaccines might cause and how they might produce injuries.

Breaking the blind in an individual case does not invalidate that person's data. Prior randomization is more important than blinding, especially in the Pfizer trial, where practices around keeping staff blind appear to have been impossible owing to storage issues [18]. If for whatever reason a company wants to maintain the blind, there would appear to be an even greater onus on them to provide the maximum possible support for volunteers with health problems afterwards, especially in the case of injuries for which there are no established treatment protocols.

Acknowledging the injuries subjects have is a way to learn more through science. Not acknowledging injuries is a business matter that appears incompatible with scientific research.

The International Council for Harmonization Guidelines [27] at 4.3.2, state:

During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

6. Conclusion

Mr. Roux's and Ms. Dressen's cases illustrate what now appears to be an established company approach that applies to all company vaccine and drug trials. It seems possible that this approach underpins a final result in the Pfizer trial where apparent protocol deviations on active treatment outnumber those on placebo by five to one (311 v 61) [30].

In the case of vaccines, especially where these have been mandated, company concealment of injuries risks causing a consequent wider public health injury.

In the case of drugs, as pointed out over twenty years ago, a sequestration of clinical trial data, especially data on harms, and the ghostwriting of trial reports which further conceals harms, puts everyone who later takes the drug in a state of legal jeopardy [28,29]. If participants in a trial have their injuries concealed, anyone else similarly injured, who seeks a legal or other redress, will face company claims that there is no evidence from their trials of a link between this injury and their medicine.

Paying Mr. Roux's or Ms. Dressen's medical costs risks being portrayed as an admission a company vaccine or drug has caused problems. Such an admission risks being at odds with submissions to FDA, with latter FDA representations to the public [15,30], and at odds with the published medical reports of this trial [2]. This mismatch risks opening a company up to a fraud charge, as happened to GlaxoSmithKline with Study 329, but it would seem possible to manage this risk with judicious wording.

Everything hinges on an approach companies have taken for two decades, which, as noted above, champions the idea that unless an effect happens to a statistically significant extent in a trial, then there is no evidence that this effect has been caused by the drug or vaccine. This is particularly problematic in that adverse events are never the primary outcome in licensing trials and events are unlikely to be detected and if detected testing for statistical significance is strictly speaking inappropriate. Adhering to this approach, companies can offer a consent form like the ones outlined here knowing that nobody injured in their trial is ever likely to be able to establish the therapeutic agent has caused an injury.

This position stands at odds with common sense and normal judicial process as embodied by NIH in Ms. Dressen's case and by the doctors in Hospital Aleman in which Mr. Roux sought treatment. In these cases, doctors practicing in accordance with standard medical practice have said both she and he have vaccine induced injuries.

Company statements regarding prospective support for injuries incurred seem likely to predispose to consent to participate in the trials outlined here. This information, however, appears misleading, and likely applies to many company consent forms. This is a matter of concern, but it is not clear how to reconcile the business, scientific and ethical issues involved.

Facing a novel, unexpected problem, in company trials, allied business and time pressures do not make it easy for investigators to determine causality. It is not clear how feasible it would be to offer all trial participants an independent review of causality for harms in real time, but this would be good medical and scientific practice.

Conflict of interest

Two of the authors are contributing from a position of lived experience.

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