

An Astute Guinea Pig in a First-in-Human Clinical Trial: Lessons for IRBs and the Disenfranchisement Social Science Literature

Martin Tolich*

Department of Sociology, University of Otago, New Zealand

*Corresponding author: Martin Tolich, Department of Sociology, University of Otago, New Zealand, Tel: 6434798755; E-mail: martin.tolich@otago.ac.nz

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Abstract

Objective: This sociological article sits outside the dominant social science research paradigm of those researching subjects recruited into first-in-human clinical trials; they routinely characterise “guinea pigs” as powerless, exploited persons who present themselves both “ready to recruit and ready to consent”. This article highlights an exception to this paradigm documenting an instance where a first-in-human clinical subject deciphers a clinical trial regime and allows for a rational decision to maximise personal safety.

Methods: This report of an ethically approved ethnographic study of clinical trialists (N=24) in either bioequivalency or first-in-human clinical trials focuses on one participant. Zach, a 25-year-old first-in-human trialist shared his secret and proudly agreed for its public airing.

Results: Zach recounts a moment during the recruitment phase of a first-in-human clinical trial where he calculated the risk quotient of participating in the study during given trial dates. Zach was able to identify one trial date (of eight dates) that he saw was less risky than the other seven trial dates. The interactive article gives the reader sufficient information for them to also attempt to decipher what is essentially a cryptic crossword.

Conclusion: If Zach’s claim is valid, and clinical trials safety or risk within a (sequential date) clinical trial is unequal, IRBs should insist this asymmetrical risk be made explicit in consent forms. Equally, future social science scholars researching clinical trial participants should be critically aware of human agency rather than blinded by their maximization of guinea pigs’ diminished autonomy.

Keywords: Autonomy/agency; First-in-human clinical trials; Sociology; Guinea pigs; Disenfranchisement

Background

What if a participant in a first-in-human clinical trial believed he or she could decipher risk variance within the experiment and enhance his or her own safety? What are the ramifications for IRBs? Should they require researchers to disclose that not all risk assumed as a participant in a first-in-human clinical trial is equal? And what of those social scientists who research participants in the first-in-human drug trials? [1–7]. Their research paradigm focuses exclusively on the alienation and exploitation of disenfranchised populations who feature most prominently in clinical trial recruitment. Few social scientists provide an account for the type of human agency outlined in this article, focusing solely on the disempowered subject. The first part of this article situates Zach among the twenty-four clinical trial subjects interviewed for this project [8] and recounts how he identified unequal risks in the trial’s schedule maximising his personal safety. Part Two situates Zach’s human agency within a broad social science literature that is routinely blinded by acts of human agency.

Aim of the study

The twenty-four persons interviewed in this qualitative study [8] of two clinical trial companies (first company and second company) are a different demographic to these other disenfranchisement studies who

feature poor disadvantaged minorities. The collective sentiment of these mostly university students (N=18) was “I want the money, I don’t need the money”; they participated in clinical trials not to earn a subsistence wage but to purchase extras—a motorbike, a surfboard, a holiday to Nepal or a rugby trip to Ireland. Money was, however, a major inducement to their participation. The other first-in-human trialists (N=6) were older persons, aged from 40 to 60, but they too were motivated by earning spending money, not subsistence money. They wanted extra money for an expensive camera, a new patio deck or Christmas presents for grandchildren. They were not disenfranchised persons.

The twenty-four persons interviewed participated in one of four separate clinical trials [8]. One trial was a bioequivalency trial in first company (N=7) and three trials were in second company including one bioequivalency trial (N=6) and two first-in-human trials (N=10). This article focuses on one of the twenty-four persons that I refer to as Zach. He was one of the ten first-in-human trialists interviewed at second company. Zach had been involved in two previous first-in-human trials and it was there he educated himself and could see through what he conceptualised as a puzzle. For Zach the puzzle was common sense, and like any cryptic crossword, if any two pieces of information are disclosed the conundrum was potentially solvable. The reader is invited below to unravel the puzzle similar to that routinely given to subjects in first-in-human clinical trials in second company when recruited to a trial. Other clinical trial companies’ recruitment procedures may differ.

Findings

In second company, after a healthy volunteer has responded to an advertisement to take part in a first-in-human clinical trial (in Zach's case the advertisement was in a free University newspaper) and deemed to match the desired demographic (usually male, aged 18-65) and physical criteria, the volunteer is given a list of calendar dates. These dates indicate when the eight sequential small batch trials (comprising five to eight volunteers) will be held. Trialists are then required to notify the recruiter as to which two dates best fit their schedules.

First company and second company used this system because eighteen of the twenty-four trialists interviewed [8] were university students meaning any trial dates had to fit around the students' mid-term or final examinations and University assignments.

Assuming that participation in any clinical trial is subject to risk, but choosing the right date could minimize that risk, the participant is presented with a puzzle (Figure 1).

1. March 1
2. March 6
3. March 10
4. March 14
5. March 20
6. March 25
7. March 29
8. April 5

Figure 1: Based on your availability choose a study date for a first-in-human clinical trial that would best maximise your safety.

The eight trial dates were identical in payment and format, however, on the first date, March 1, the lowest level of the trial drug is administered. In subsequent trial dates the amount of trial drug given to each subject increases sequentially. Thus the toxicity of the drug administered in the March 1 batch was significantly lower than the toxicity of the drug given on April 5.

Readers should also note that information on any first-in-human drug is severely restricted. Potential recruits cannot Google a first-in-human test drug like they might do with a bioequivalency study searching for the drug name bmB3Tx-2r. The only information available to trialists is either in the participant information sheet or is deciphered by the participant.

When presenting this conundrum to a social science conference audience, they too were invited to make their selection of dates. Many chose March 1, which was smart as they were responding to the knowledge that March 1 was the lowest dose of the drug. Others in the audience were more calculated, if not Machiavellian choosing April 5, the last date. This too is smart for reasons explained by Zach below. There were some, though not many, in the audience who critiqued the March 1 and April 5 dates and synthesised them. Hopefully the reader's choice is neither March 1 nor April 5; Zach chose another date.

Zach, like all twenty-four persons interviewed in this study, was also fully cognizant of the clinical trial disaster at Northwick Park in 2006 [9] where five of six healthy subjects required intensive care after their severe reaction to the first batch of a phase 1 trial. (Obviously the placebo trialist was not harmed). At Northwick Park there was no

follow up. In other words, in terms of this puzzle there was no March 6 to April 5 trial as the Northwick project was cancelled.

Zach evaluated the first trial date, March 1, as a potential TGN1412 event; to him it was the most risky date of all dates as it was on this date that the drug is given to a human being for the first time. The difference between March 1 and March 6 is complex; it was not just the increased level of the trial drug. For Zach, the key difference between March 1 and March 6 was that the March 6 trial would only proceed if there were no serious adverse events in the March 1 trial. Although Zach did not articulate further, he was essentially saying that he personally benefited from those persons taking part in the first wave of first-in-human trials on March 1. They were his guinea pigs.

Zach's decision to choose March 6 as his preferred date allowed him to minimize his exposure to risk in relation to other trialists enrolled for March 1, or the later trials, essentially allowing him to earn his \$3000 for less risk.

Ethical issues arise from Zach's disclosure for the author, social science and IRBs.

The first issue concerns the author's right to disclose Zach's trade secret. Should Zach's information be made public, will the disclosure here have repercussions for other trial subjects who may use this ploy to minimize harm? Will trial administrators tweak their trial design by creating a non-existent dummy trial, in this case offering a trial on February 25 and declaring the trial date fully subscribed?

As the author, I am not obligated to conceal this information as Zach shared the information with me without any restriction. He was genuinely surprised at my astonishment and delighted to have put one across my professorial role. To Zach, his puzzle solving was common sense derived from observations made during his two previous trials. Moreover, of the 10 first-in-human trialists interviewed only Zach used the ploy. Two other trialists in Zach's March 6 cohort mentioned in hindsight they were glad not to have been recruited into the first or later trials, but they had not deciphered risk to select their dates.

The second ethical issue is for social scientist working in this area. Zach's cautionary tale serves as a warning that if researchers are not open to contrary perspectives they may dismiss glimpses of human agency. The fact that Zach could mastermind some control over his involvement in the trials, enhancing his safety, is testimony to guinea pigs' resilience.

This resilient moment does not square with the current paradigm of those framing clinical trials as disempowerment. Numerous researchers present clinical trialists as powerless and an exploited disenfranchised minority [2,10-12] but in First and Second Company they are not. They do not need the money they want the money for discretionary income.

The literature's consensus claims research subjects enrolled in first-in-human clinical trials are disproportionately poor [1,4,6] – their deprived circumstances diminishing their autonomy [7] to the point that some characterise first-in-human trialists as an exploited underclass, operating within a shadow economy that bears the burden of the safety testing of new drugs [3].

Money plays an important role in the recruitment of healthy volunteers into phase one trials as money is often linked with motivating less well-off persons [4]. For example, Abadie [12] claims trialists treat their bodies as "an ATM machine", earning a living "renting their body and their bodily fluids" for money. Typically, these

poor volunteers are male, unemployed, self-employed, or working in contract jobs for finite periods, and are not primary caregivers of family members [2]. Fisher classifies these men as exploited, without options, and taken advantage of by clinical trial companies. "Everyone pretends that guinea pigging is not really a job" but there is no doubt that first-in-human clinical research is a business [3].

Glimpses of human agency are recorded in this social science literature but they are trivial. Stealing food in the middle of the night from a locked pantry is one example [11] and Abadie's claim that trialists have agency as professional guinea pigs [12]. Yet Abadie overstates trialists' agency: to the pharmaceutical industry these indentured men represent a reserve army of labour. They are assembled electronically, not by themselves, but on clinical trial databases making these individuals on-call, available at the whim of the clinical trial organisation, both ready to recruit and ready to consent.

The third ethical issue involves IRB responsibilities. If Zach's claim is valid, and clinical trials safety or risk within a single, sequential date clinical trial is not equal, should IRBs insist information that asymmetrical risk be made explicit in consent forms? Potential first-in-human trialist should be alerted that if there were an adverse reaction to the trial drug in the first batch, the trial would be postponed or cancelled.

What makes Zach's ploy unusual is that the information was not part of the rich folklore that pervaded the pre-recruitment dialogue between experienced and novice trialists. In all other trials the ex-trialists freely shared information with their friends about how to get access to these lucrative trials and how to survive the bloods [8] i.e. the use of a cannula rather than repeated blood extractions.

A friend said, "You want some quick cash? Easiest way." I think that's what everybody says. You know, so yeah, he said apply, but just read what you're doing first. They're very good. They give you everything you need to know, and so you read about it and it's pretty simple.

The in crowd-those students privy to knowledge of the lucrative trials – were complicit in the recruitment of new trialists. As labour market insiders, they let their friends in, not wanting to broadcast the trials openly for fear a huge influx of new volunteers would restrict their future access.

I've got to stop giving out information on it, 'cause there'll be too many people trying, yeah, everybody seems quite keen to.

In the UK, clinical trial companies offer between ninety to three hundred and fifty pounds <http://www.trials4us.co.uk/> for any incumbent trialist to recommend a friend to the clinical trials company. In New Zealand this referral is gratis, although it may have non-financial repercussions.

If trialists are informed by friends about the remuneration and the trial procedures, the informed consent process can become a ceremonial exchange rather than a robust process. Human agency may be nullified. This is similar to Fisher's claim that the disenfranchised are both ready to recruit and ready to consent. Fisher (2007), a

sociologist, dismisses the assumption that individual autonomy is present in the informed consent process [13]. She says informed consent should not be seen as a panacea and claims economic disenfranchisement robs these men of the genuine autonomy needed to take an active role in consent. Disenfranchisement means these men are indiscriminate with risk, "not concerned about the details of particular trials in which they enrol" [2]. They are ready to consent [13] and are likely to have decided to take part in the trial before participating in any informed consent process.

The students and the five older trialists in this study were not disenfranchised, they did not need the money, they wanted it buy extras.

Conclusion

If Zach's claim is valid, and clinical trials safety or risk within a single, sequential date clinical trial is unequal, IRBs should insist this asymmetrical risk be made explicit in consent forms. Equally, future social science scholars researching clinical trial participants should be aware of human agency rather than blinded by their maximization of guinea pigs' disenfranchisement.

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