

IS THE GENIE OUT OF THE BOTTLE? DIGITAL PLATFORMS AND THE FUTURE OF CLINICAL TRIALS

Niccolò Tempini & David Teira

This is the accepted author manuscript of the article published in *Economy and Society*. Please cite as follows: Tempini, N. & Teira, D. (2018). Is the Genie Out of the Bottle? Digital Platforms and the Future of Clinical Trials, *Economy and Society*, in press.

Abstract

Is it possible to conduct impartial clinical trials in a world full of digital networking tools that patients can use to coordinate themselves and act against research protocols? This paper builds on an ethnography of *PatientsLikeMe*, a company running an Internet social media network where patients with different conditions share their clinical data with standardised questionnaires. The company faced a serious dilemma in 2011 when some ALS patients, members of the site, started sharing data about a phase II clinical trial of an experimental drug (NP001) in which some of them were participating, to anticipate the experiment's outcomes and understand each one's allocation over trial arms. In parallel, some other patients were using the site and other web tools to coordinate and run their own replication of the trial with homebrew mixes of industrial grade chemicals. *PatientsLikeMe* researchers reflected on their position as networks managers and eventually decided to use the collected data to develop their own analysis of the efficacy of the original compound, and of the homebrewers' compound. They presented the NP001 events as a case in point for articulating a new social contract for clinical research. This paper analyses these events, first, by understanding the clinical trial as an experiment organisation form that can succeed only as long as its protocol can be enforced; second, we observe how web networks make it dramatically easier for the trial protocol to be violated; finally, we point out how a potentially dangerous confluence of interests over web networks could incubate developments that disrupt the status quo without creating a robust and safe alternative for experimentation. We conclude by warning about the interests of the pharmaceutical industry in exploiting patients' methodological requests to its own advantage.

Keywords

Social media; digital networks; patient activism; patient-led research; clinical trial; blinding

Niccolò Tempini*, *Department of Sociology, Philosophy and Anthropology & Exeter Centre for the Study of the Life Sciences (Egenis), University of Exeter, Byrne House, St Germans Road, EX4 6TJ Exeter, UK, n.tempini@exeter.ac.uk*

David Teira, *Department of Logic, History and Philosophy of science, UNED, Paseo de Senda del rey 7, 28040 Madrid, Spain, dteira@fsof.uned.es*

**corresponding author*

Acknowledgments

We wish to acknowledge the openness of the staff at PLM in welcoming one of us for fieldwork and engaging in a long exchange of ideas. We are also thankful for several opportunities to present developing versions of this work. We thank for their feedback the participants to our presentations in occasion of the workshop “Critical Studies of Citizen Science in Biomedical Research” at King’s College of London in March 2017 (esp. Barbara Prainsack, Sabina Leonelli, Alena Buyx and Tamar Sharon); the seminar at the Instituto de Salud Carlos III, Escuela Nacional de Sanidad, Madrid in April 2017; the “Boundaries of Truth” series seminar at the Institute for Science, Innovation and Society, University of Oxford, in February 2018 (esp. Javier Lezaun and Christopher Goldsworthy); the “Health and Big Data” series seminar at the École des Hautes Études en Sciences Sociales (and the Center for the Sociology of Innovation at Mines ParisTech) in May 2018 (esp. Madeleine Akrich and Emmanuel Didier). Many protracted discussions were very insightful. Finally, we thank María Jiménez-Buedo and Bennett Holman for helpful comments on early drafts of the manuscript, and the editorial team at E&S for invaluable feedback and support. Teira’s contribution has been funded by the the research grant FFI2014-57258-P.

Biography

Niccolò Tempini is Research Fellow in Data Studies at Egenis, University of Exeter. He researches big data medical research and digital infrastructures, investigating the specific knowledge production economies, organization forms and data management innovations that these projects engender with an interest in their social and epistemic consequences. His research has been published in international journals across science and technology studies, information systems and the philosophy of science. More information at www.tempini.info.

David Teira teaches philosophy of science at the Spanish Open University (UNED, Madrid). He has worked on the uses of statistical methods in economics and medicine. In particular, he has studied how the different stakeholders in a clinical trial can agree on an experimental outcome, despite their conflicts of interests. <http://www.uned.es/personal/dteira>.

1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a very rare, lethal and debilitating neurological disease for which no cure has yet been discovered. While prognosis is two to five years life expectancy from the date of diagnosis, research is slow, as with most orphan diseases: there are not enough patients to consistently attract research programme funding or to run clinical trials with enough statistical power to detect the real effects of potential treatments (Sinha, 2013). While patients are progressively paralysed as a result of the damage to their nerves, their cognitive capacities are unaffected. The experience, for patients and their friends and families, is excruciating. The dramatic condition created by the disease means that the ALS community is well known for a high level of activism and empathy, as is the ingenuity of grassroots organisations in promoting awareness and fundraising. Despite being relatively small, the ALS community has been able to occasionally push its plight into the mainstream – for instance, through the viral ‘ice bucket challenge’ (Wikipedia, 2018). By the same token, self-experimentation with a range of safe and unsafe treatments is endemic.

Since 2008, Eric Valor has lived paralysed in bed and depends on life-sustaining technological supports. And yet, like many other ALS patients, he has been incredibly socially active thanks to sophisticated computing interfaces and the Internet. Valor took ALS patient activism one step further when he launched the ALS Chlorite Project (ACP) in 2011. This was a collective self-experiment in which patients tried a homemade compound with (purportedly) the same active principle of NP001, an experimental treatment that was being developed and tested by a small Californian biotech company, Neuraltus.¹ The ACP website intended to gather patients interested in testing sodium chlorite (an industrial pesticide and cleaner) in an oral solution and sharing information about the effects.² The ACP provided its participants with a library of relevant scientific literature and a study protocol, including a dosage calculator and a sheet to be filled in with the treatment outcomes (ACP, 2011a). In parallel, Neuraltus was testing NP001 in a conventional (phase II) randomised clinical trial (RCT), scheduled from February 2011 to September 2012.

Another accomplishment of ALS activism is *PatientsLikeMe* (PLM). Started in 2005 by activists with a family history in ALS and a background in not-for-profit organisations (the ALS Therapy Development Institute), PLM is a website and “patient-powered research network” that gathers patients suffering from thousands of different conditions. Patients can track their own health (recording information about symptoms, conditions, hospitalisations, treatment evaluations and other dimensions of patient health and experience), see their progress via visualisations and analytics, and connect and socialise with other patients. No advertisement is present on the website, but PLM is owned by a for-profit organisation, PatientsLikeMe Inc., which generates revenue with the sale of pseudonymised data and custom research services, mainly to pharmaceutical corporations.

¹ Valor had reviewed scientific papers on an antecedent compound, WP10, and patents registered by lead developers of the drug. He also personally corresponded with one lead developer. And he was right to think that the drug was based on sodium chlorite, as it was later confirmed (among other sources) by the research articles reporting on the outcomes of the NP001 clinical trials (Miller et al., 2014, 2015). NP001 is, however, based on a highly purified, pH-adjusted secret formulation, and was delivered intravenously in the trial.

² Sodium chlorite, often used in water treatment plants as a cleaner, is inexpensive and easy to source in an industrial grade form.

This study examines what happened when some of the participants in the ACP and in the Neuraltus trial used the PLM platform to coordinate with other patients and share their outcomes. This initiative took patient-led experimentation to a new level of complexity (cfr. Vayena, 2014). Patients were sharing data from an ongoing RCT of a new drug, NP001, and from self-organised experiments with different homemade proxies for the same drug at the same time. These data were analysed not just by patients, but also by PLM researchers, and they were eventually published in various forms.

All this may be praised as a feat of patient-led research, although more for its organisational achievements than for the scientific value of the (inconclusive) outcome it yielded, as we will explain. Yet, all this activity and the disclosure of data from the Neuraltus trial on PLM put at stake the trial's own scientific reliability. RCTs are comparative experiments in which participants receive either the new or the conventional treatment, so that their effects can be compared. In standard RCTs, the participants are blinded about the treatments they receive so that the trial outcome remains uncontaminated by their expectations (e.g., placebo effects). In the Neuraltus trial, those participants who compared their outcomes on PLM had a bigger chance of guessing correctly which treatment they were receiving.

Drawing on both fieldwork conducted at PLM at the time of the disclosure of the Neuraltus trial data on the platform and on secondary reporting, we want to reflect on how patient activity coordinated over digital platforms can challenge current drug testing standards and regimes of medical experimentation. Current drug development and testing practice is vulnerable to many biases in trials originating in pharmaceutical interests and dysfunctional regulation (Gøtzsche et al., 2013; Abraham & Davis, 2013) but industry-sponsored tests are usually well blinded (Hrobjartsson et al., 2014) and are often run by third-party contract research organisations that have an interest in not meddling with the execution of the protocol. The manipulation of experimental knowledge production is mostly concentrated on the ways in which studies are designed (Dumit, 2012), approved and their results communicated (or better, are not – see Goldacre, 2013). With the emergence of digital platforms and powerful online communication and coordination tools, patients have the means to easily share information that might break any blinding device. For all the controversies of the current testing regime, is there any experimental design that can provide reliable outcomes about the safety and efficacy of drugs with unblinded participants?

Patient participation in RCTs has been usually studied, in science and technology studies, from the standpoint of the legitimacy of patients' concerns, and how these concerns are neglected or constrained by the scientific or financial interests that articulate trials (e.g. Epstein, 2007; Petryna, 2009). Citizen science (including patient-led research – cfr. Tempini & Del Savio, 2018) is often vindicated as an alternative and more democratic model for the integration of all these perspectives (Bonney et al., 2009; Follett & Strezov, 2015). Our case study on PLM will allow us to introduce a note of caution about this approach. As we will argue in the conclusion, the pharmaceutical industry has exploited all opportunities in the past, including patients' initiatives, to weaken the methodological constraints on drug testing. Without a new drug-testing standard that accommodates patients' preferences without bias, the eventual proliferation of patient online initiatives may weaken even further the reliability of the RCT regime but without a clear long-term benefit for the patients involved. And, worryingly, initiatives organised on digital platforms could be vulnerable to the new types of manipulation and interferences in public

interest that have recently attracted much concern (Sismondo, 2017).

In the next section, we will review the rationale for controlling the participants' preferences in trials, and the reasons why patients are not always fully aligned with the prescriptions of the protocol. In section 3, we reconstruct how on PLM gathered an online group of ALS patients who developed a series of out-of-protocol initiatives around the NP001 trial. We also review how PLM managed its position with respect to these controversial initiatives. They chose not to discourage these patients or take an early position in favour of protecting the NP001 trial. Free to coordinate on the platform, the initiatives of the ALS patients around the Neuraltus trial yielded an unusual amount of publicly accessible data for a phase II experimental drug, including other data for related compounds that patients experimented with. Yet, the scientific value of these data could not be vindicated by the subsequent analyses undertaken both by patients and PLM researchers. In the fourth and final section, we discuss the ethical self-justification of both PLM and the patients involved in the data-sharing process, pitting it against our current understanding of RCT biases and warning about the ability of the pharmaceutical industry to exploit patients' methodological requests to its own advantage. We conclude our warning by pointing at the bigger picture in which it should be framed, highlighting the links between this scenario and other recent examples where Internet networks were weaponised to orchestrate, manipulate and capture the initiatives of active citizens, and undermine the construction of facts.

2. PREFERENCES IN CLINICAL TRIAL DESIGNS

RCTs are comparative experiments that pharmaceutical authorities all over the world use to assess the safety and efficacy of medical treatments (Hackshaw, 2009). Established as the regulatory yardstick with the 1962 amendments to the Federal Food, Drugs and Cosmetics Act, RCTs are designed to test the hypothesis that there is no difference between the standard intervention and an experimental treatment, randomly allocated to at least two groups of patients. The size of the key phase III trial sample is calculated to reliably assess the effects of both treatments and is usually big (hundreds or thousands of patients). But phase III RCTs are just the third phase of a larger experiment. In phase I, researchers find the appropriate dosage in a small group of healthy subjects, investigating the toxicity and other pharmacological properties of the drug. Phase II is a pilot for the RCT, with a small number of patients that rarely allow the detection of statistically significant effects. Phase IV begins once the treatment is approved for use, after two successful phase III RCTs; the market is monitored for adverse effects that might not have been detected at the previous stages.

RCTs, in phases I-III, are experimental designs with a central locus of control: whoever plans the experiment creates a research protocol that all the participants (physicians and patients alike) must meticulously follow. The protocol constrains the enactment of preferences that participants may hold regarding the experiment. The treatment should be the only relevant difference between the RCT's arms. If we allow the preferences of participants to play a role in the experiment, they will introduce a confounding factor in the comparison (a bias). Physicians, for instance, usually have their own clinical judgement about which patients could benefit more from each of the treatments under trial. If they were to allocate treatments according to their views, the comparison would be biased. This is why treatments are randomised in RCTs.

A trial is a "scientific experiment grounded in clinical design" (Brives, 2013). A trial participant

should not expect to derive any personal health benefit from the interventions under study, beyond that which s/he may reasonably expect to derive from healthcare outside the trial. Hence, no set of patient preferences will unambiguously lead to participation in RCTs and, indeed, 70% of clinical trials fail to recruit the desired number of participants. There is extensive literature on the factors affecting patients' preferences about trials; these factors are multidimensional and, often, context-dependent (see, e.g., Bell & Balneaves (2015) for a review focused on cancer trials). For instance, it seems a consensus in this literature that many features in the methodological design of the trial pose a barrier to patient participation; for instance, many patients do not like randomisation or placebos (see, e.g., Mills et al. (2006) for a review again on cancer RCTs). Most patients judge it better to receive a customised prescription from a physician than a blind treatment allocation – and to know which treatment they are receiving than to ignore it. Changing these preferences is crucial for increasing participation in the trial and there is an active line of research in decision aid methods to get patients to articulate their beliefs about trials in a way that does not hinder their participation (Gillies et al., 2015).

However, patients often enrol spontaneously in a way that suggests a degree of altruism: many patients are willing to suffer the inconveniences of a trial despite the standard of care available (and that they could receive) outside the experiment. This altruism has been broadly documented in the studies on patient participation. It usually coexists with a degree of self-interest, which is also extensively detected in the same studies. Following McCann et al. (2010), we may rather speak of *conditional altruism*:

[A]lthough people may initially have a tendency to participate in a trial based on a willingness to help others or contribute to a general good, this is unlikely to lead to trial participation in practice unless people can also recognise that trial participation can benefit (or at least not harm) themselves in ways that they regard as salient. (McCann et al., 2010)

Conditional altruism seems to be context-dependent. There is at least preliminary evidence that patients with poor prognosis (e.g., less than a 10% probability of 5-year cancer-free survival) report altruist motivations to enrol in trials less often than those with better prognosis (Truong et al., 2011).

When trial participants enrol in a trial seeking access to the experimental treatment and they come to believe, as the trial progresses, that they are not receiving it, they tend to abandon the trial, damaging its statistical design. In a review by Hrobjartsson et al. (2014), it was found that, for trials of more than two weeks, the risk of patient dropout was 79% higher in the non-blinded control group as compared to the blinded control group. Blinding patients about the treatment they receive (making the treatments under study as similar as possible at least in their presentation and delivery) is a way to control for behaviour motivated by this sort of conditionally altruistic preferences.³

³ In the previous paragraphs, we draw from quantitative and qualitative social research on trial participation. There are few STS studies that deal with patients' preferences regarding trial protocols but their diagnoses are sometimes more radical than what we characterise as "conditional altruism". For example, in Jill Fisher's ethnography of the companies conducting RCTs, we find that patients behave as "neoliberal subjects motivated by their social and economic positions to benefit the best they can from the system of drug development" – Fisher JA. (2009:178). And this is why they often deviate from the research protocols. At any rate, for successful *protocol compliance*, it is necessary that patients acquire an entirely

Blinding can only be partial though for both ethical and methodological reasons (Teira, 2013). In fields where deception was considered acceptable for a while (e.g., social psychology), it was observed that deception could trigger strategic interactions with the experimenter that may challenge the very possibility of a test (Ortmann & Hertwig, 2002). For instance, Taylor & Shepperd (1996) used deception to study the effectiveness of conventional debriefing procedures for detecting the suspicion of deception among research participants. In the experiment, the participants were told not to communicate if the experimenter left the room. They did and found out that they had been, at some point, deceived. Yet, the debriefing procedures did not make the participants reveal this fact. If the validity of the experiment's outcome depends on the, so to speak, innocence of the participants about the goals of the experiment, not being able to detect their suspicions of deception threatens the interpretation of the results.

In clinical trials, it is considered ethically unacceptable to deceive participants and, therefore, the informed consent form and enrolment interviews will alert patients about the different treatment options in a trial and the existence of blinding mechanisms. Blinding can only be partial then.

From the standpoint of protocol compliance, participant preferences may interfere with the conduct of a trial to three different degrees. Let us name them as follows: *mild*, *severe* and *fatal*. For a start, we should notice that blinding does not suppress these preferences: it just warrants, if successful, that they shall have no systematic correlation with the outcome. The preferences of the participants will put at stake the trial outcome if, knowing the former (preferences), it is possible to predict the latter (outcome). If blinding works properly, there will be a small correlation at most, and hence a mild degree of interference. The trial outcome will be reliable. If the blinding mechanism is not well implemented or partially broken, there might a higher correlation between preferences and outcome. If patients find out that they are receiving their favourite drug in a medical RCT, they may generate a placebo effect, making the drug look more effective than it actually is;⁴ if they find out the opposite, they may just drop out of the trial, diminishing its statistical power to detect the treatment effect reliably. In this severe degree of interference, the trial outcome will not be reliable but the experiment, as such, will be at least completed.

The fatal third degree of interference occurs when blinding cannot be enforced and the participants can subvert the protocol to the point of making the experiment unfeasible. Until very recently, the only documented case of such severe interference was the AZT trials subverted by gay activist groups such as ACT UP in the 1980s (Epstein, 1996). The AIDS patients taking part in the trials had preferences about the interventions: they wanted to receive the experimental treatment and not the placebo. They organised themselves to access the former; they swapped pills, took them to chemists for analysis, etc. At some point, the Food and Drug Administration (FDA) had to accept that the trial was unfeasible since there was no way to control for the participants' preferences and gave patients advanced access to AZT.

Severe interferences become fatal when a significant subset of the participants (or other actors involved in the trial) can coordinate themselves to break the blinding and act against the protocol.

new set of skills, practices and responsibilities as they "become actors in the experiment" (Brives, 2013:406) and participate in "their very construction as objects of biomedical research" (2013:410).

⁴ At least in terms of subjectively reported outcomes, such as pain. Hrobjartsson A and Gotzsche PC. (2010) Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*: Cd003974. The necessity of blinding for other trial outcomes may vary (Teira, 2013).

The AZT trials illustrate how rare coordination was in the pre-digital age; unlike most other trials, many of the participants in the AZT trials had been gay right activists in the previous decade. Before entering the trial, they were already part of a network operating to defend their mutual interests and they just adapted it to serve their purposes as trial participants. The case illustrates an important point about research protocols: they rely on the assumption that non-compliant patients will not reach a degree of group coordination that allows them to breach the blinding mechanisms and other specific features of a trial protocol (e.g., constraints on treatment regime, enrolment in other trials) (Zizzo, 2010). If, for instance, patients coordinate their investigation about the treatment arms in which they are, they may bias the outcome independently of the correctness of their guess; if a big enough number of patients in a trial arm form the same belief about the treatment they are receiving (e.g., “we are all receiving the placebo”), even if false, it might bias the outcome of the experiment in a predictable direction. There is evidence that if patients think they are receiving their preferred treatment, its effect rises – and the opposite. Of course, without a certain degree of coordination between patients, the formation of such beliefs will be entirely due to chance (to the best of our knowledge).

Group coordination was unlikely in the pre-digital era. For most trial subjects, it was too costly to get to know a significant number of their fellow participants, least of all interact with them. Even in cases in which there has been a degree of coordination, as those documented by Akrich et al. (2015), patients tend to “accept the language of ‘dominant’ actors” and play by their rules (2015:85). For instance, the French Muscular Dystrophy Association, as well as other French organisations for patients with rare diseases, gather funds and orient the research process without interfering in actual RCTs (see also Rabeharisoa & Callon, 2002). The Alzheimer Society of Ireland has succeeded at including the patients’ perspective in evaluative studies of care technologies, previously only aimed at carers. More critical with standard medical approaches to childbirth, the French network Collectif Interassociatif Autour de la Naissance (CIANE) has succeeded at funding a research project on some of their hypotheses on postpartum haemorrhage that was published in the *British Medical Journal* in 2011 (Akrich et al., 2015).

All these patients’ groups have successfully introduced new perspectives on their conditions in an open exchange with biomedical researchers, often challenging the received scientific wisdom. This is why, according to Akrich et al. (2015:86), their activism cannot be considered *soft*. As we are going to see in the following section, the activity ensuing around the NP001 trial was perhaps even ‘harder’: patients largely adopted the dominant language of the RCTs (they promoted official RCT enrolment) and their methodological apparatus (they organised a parallel experiment) while they broke the rules of the official experiment, ‘hijacking’ it to their immediate advantage (cfr. Epstein 1996). One may perhaps interpret this form of radicalisation as a form of *individualism*.⁵

Previous examples of ‘hard’ patient activism were built through institutional networks and practices and long-developing “epistemic communities” (Akrich, 2009). Both ACT UP and the four cases discussed in Akrich et al. (2015) were organised as patients’ associations, often legally incorporated. The advent of web platforms greatly reduces friction in distributed coordination and communication, making it possible for ‘splinter’ groups to ephemerally emerge around an individual interest that the members share.⁶ In RCTs, this means that it can be enough for patients

⁵ We are indebted to an anonymous reviewer for suggesting this interpretative key.

⁶ In this regard, as another reviewer suggests, these patients would be more like the self-interested paid participants that nowadays proliferate in industry-sponsored trials (Monahan & Fisher, 2015).

to be conditionally altruistic, in the sense defined above, to generate the sort of situation at the centre of this paper. *Once digital coordination is possible, the feasibility of trials entirely depends on the preferences of the participants.* If a significant number of them choose to play against the protocol, as we are going to see next, fatal biases might be simply impossible to prevent or correct.

The existing social contract in medical experimentation is not changing because the scientific consensus has shifted to support different epistemic standards, but because of lack of *enforcement*. Whereas coordination was too costly for most trial participants before the digital age, nowadays it is within everybody's reach with dedicated Internet platforms where patients can meet. Breaking the clauses of any experimental protocol is now easier than ever before, and different social actors can use this power to force their own priorities and epistemic standards onto the negotiating table. One thing that will make the integration of their demands difficult, we observe, is the absence of stable issue owners and reference organisations. The challengers that can eventually emerge and throw a trial off the rails might remain undetermined until the event.

3. NP001 AND THE WEB OF UNBLINDING

3.1 METHODOLOGY AND STAGE SETTING

This article draws on an embedded organisational ethnography of PLM. In September 2011, one of the authors (Tempini) arrived in Cambridge (Mass.) to spend more than six months at the headquarters of PLM. The purpose was to participate in research and development activities, offering help both on pilot projects of potential future architectures and designs and on PLM's current research projects, while simultaneously conducting the study. The researcher acted as an independently resourced collaborator. No financial exchange took place; he collaborated in exchange for access and freedom to document the life of the company. The general focus of the study was on the development of a 'universal' infrastructure, to get myriad different patients to produce data that could be used in multiple and unspecified ways. What kinds of patient knowledge, experience and meanings were represented, for what uses and outputs? What were the interests of the patients, and of other users, in the data? And what was the role of data in organising this relationship? Documenting the different kinds of practices around data that different parties, including PLM researchers and patients, were undertaking at the same time was a primary operative principle of data collection.⁷

As a member of the R&D and Health Data Integrity teams, regular discussion with PLM staff (from all teams) on the challenges the company was facing (both from a systems design and

Nonetheless, we believe that there is a crucial difference: whereas 'professional' participants can be punished if they are detected breaking the trial protocol (by banning them from future enrolment in paid trials), patients coordinating on PLM could not be deterred so simply: the threat of not being enrolled again might not seem very intimidating to them, as it will soon become clear.

⁷ For 26 weeks, full time, between September 2011 and April 2012, the ethnographer took notes on a daily basis about events and episodes of significance for the ethnography *and* also for the kinds of questions he was helping with. He sat in 128 meetings ranging from Software Development to R&D, Health Data Integrity, and Community team meetings, as well as project task-force and company-wide meetings. He collaborated with most of the employees on site, and corroborated the observational and documental material with focused interviews for a total of 30 hours of recording. Some of this ethnographic research has been published as peer-reviewed articles before, but these works did not deal with the issues this article is concerned with (Kallinikos & Tempini, 2014; Tempini, 2015; Tempini, 2017).

development point of view) often led to a more general commentary about the place of PLM in the broader landscape of actors, movements, institutions and regulations. In particular, the staff often talked about what sort of research could be carried out with the data contributed by the patients and how the PLM website could be engineered in order to improve patient involvement and data gathering. The tone of these exchanges was often revolutionary; just as many other digital companies had been disruptive in their fields, PLM staff hoped to transform clinical research to make it faster, more transparent and more participative. The company shared a strong sense, steeped in personal experiences of activism and family histories of chronic and life-changing conditions, of the necessity of taking into account the initiatives of the patients on their site, learning from them and eventually supporting them.

The landmark event in this regard had been a “virtual trial” of lithium carbonate (Wicks et al., 2011) that eventually gave the network much publicity. Using the communication and tracking tools of PLM, some ALS users on the site had organised a coordinated study in which they self-administered lithium carbonate and kept a public record of self-reports about its effects, in order to test whether it slowed the progression of ALS. PLM staff had joined efforts to help and standardise data collection and co-authored with the two patient-initiative leaders a short interim report in *Amyotrophic Lateral Sclerosis* (Wicks et al., 2008), arguing for PLM’s potential to improve quality, safety of self-experimentation, and time and cost efficiency over placebo-controlled trials. Later, PLM staff developed an original method for analysing the data and published the results of the data in *Nature Biotechnology* (Wicks et al., 2011). The analysis disconfirmed an earlier randomised study of the compound published on *Proceedings of the National Academy of Sciences* (Fornai et al., 2008). Eric Valor, the leader of ACP whom we mentioned in the introduction, had been participating in the lithium carbonate self-experimentation.

But the staff was also clearly aware that not all patient initiatives were equally defensible on ethical, legal and scientific grounds, and they often discussed the potential liabilities for PLM. A case in point had emerged soon before the Tempini’s arrival, in September 2011, at a time of growing public interest in PLM as a potentially revolutionary model of medical research that was bottom-up and participatory. On the Tempini’s first day at the company headquarters, he was introduced to the situation at the heart of this paper, presented by an R&D staff member as an example of the sort of interactions between patients that the site could incubate, and an intricate puzzle to solve for the company. Since then, the researcher took part in several meetings and discussions related to these events due to PLM’s respect for both his research interest in data practices and organising and epistemic cultures, and the ongoing collaboration with the organisation.

The Neuraltus phase II trial of NP001 (from now on, simply the Neuraltus trial), which was mentioned in the introduction, had started in February 2011. It was a two-arm double-blinded trial in which ALS patients were randomly allocated either NP001 or a placebo. What eventually made this trial unusual was that some of the participating patients were registered users of PLM. Through the forums and the pages where patients record first-person evaluations of treatments, some of the trial participants organised themselves to try to find out which treatment they were receiving, whether it was NP001 or a placebo. In other words, they were explicitly breaching the trial protocol with a concerted attempt at breaking its blinding.

Through fall 2011 to spring 2012, the development was closely observed and discussed within

the company. As we show in what follows, the issue was brought up in several meetings and also shared with visiting collaborators as a problem directly linked to current trial designs. Patient leaders were keen to directly involve PLM staff in a repeat of the lithium carbonate study collaboration, but the staff was wary of the unclear implications of interfering with an external trial (as opposed to supporting the bottom-up organisation of a self-organised one). The issue of the company's own positioning with respect to the NP001 initiatives was a sensitive concern until the end of the researcher's fieldwork period, and PLM took an official position only with the release on *Figshare* of their analysis (discussed later) in October 2012. This was then followed by other publications.

The analysis we present builds on primary data in the form of written notes from both spontaneous conversations and meetings that the researcher directly participated in, and a selection of interviews (semi-structured, customised for each interviewee and ranging across a number of topics). Due to the sensitive nature of the company's concerns at the time, the researcher felt it sensible to pose direct questions in an interview only in a limited number of occasions and only for management-level employees. This primary material is well poised to discuss concerns that staff members had in trying to formulate the company's position with respect to the initiatives, and their interpretations of the patients' actions.

The patient leaders' perspectives have instead been constructed from a wealth of secondary data, including published scientific reports and articles, and a variety of online resources, including: blogs written by the patient leaders themselves about the experimentation initiatives and their research on NP001; posts published on the PLM platform; newspaper articles featuring initiative leader interviews; and other Internet resources (some recovered with the Internet Archive's Wayback Machine, for correct temporal reconstruction of events or if otherwise unavailable). The perspective of the pharmaceutical company Neuraltus has not been directly documented but, where relevant, we refer to secondary resources that report about their interactions with the initiative leaders.

3.2 *PERSEVERING'S* INITIATIVE AT PLM

The patient leader in the unblinding initiative was known for his username: *Persevering* (his real name was Rob Tison). As opposed to Eric Valor, who was ineligible for the Neuraltus trial, *Persevering* was himself a participant. He started reporting on PLM in July 2011 (the NP001 phase II trial ran from February 2011 to September 2012), and then decided to organise the other participants registered on PLM so that they could find out which treatment they received. Like the patients in the early AZT trials in the 1980s, some of the PLM users who joined *Persevering* in breaking away from the Neuraltus research protocol had a track record of networked actions: they had taken part in the virtual trial of lithium carbonate and knew what they could jointly achieve.

These patients replicated the trial data collection both to discover the trial arm they belonged to, and to anticipate official results. For this, they would mainly use a standard Patient-Reported Outcome tool already available on the site, the ALSFRS-R questionnaire: this is a functional rating scale that provides a 0–48 score of disease progression based on the assessment of voluntary motion function. The ALSFRS-R is a widely used standard in ALS and was being used in the Neuraltus trial as a measure of clinical outcome, so two measurements were taken for each participant: one was filled in by the patient and was publicly accessible as soon as it was

completed through PLM, whereas the other one was deposited in the Neuraltus trial record, awaiting further analysis.

Importantly, both versions of the data on NP001 are proprietary. The monopoly of the trial data is controlled by the NP001 trial sponsor, Neuraltus. The PLM data monopoly is controlled by the sponsoring organisation (PatientsLikeMe Inc.), which exploits the data for the commercial and scientific research projects that fund the development of the platform. Simultaneously, it shares them with the patients in a controlled fashion and with the main aim of facilitating the satisfaction of their own health information needs and peer social interaction. The data that patients indeed access about themselves and other patients on PLM are consumed through webpages replete of visualisations, filters and counts, designed to satisfy the information needs that users may have to understand their own or others' health situation, and to structure and foster social interaction. Patients cannot access and research the 'source' data on their own. The research use of the data collected through the platform is limited by the terms and conditions that users accept upon signing up to authorised projects and partnerships.

Persevering collected and aggregated the ALSFRS-R scores as they became available on the website, plus any additional information shared through other treatment evaluation questionnaires that the participants filled out on the site, by manually 'scraping'⁸ the data from the webpages. Soon after the unblinding process started in the summer of 2011, *Persevering* contacted the staff at PLM to share his project with them. Unlike in the lithium carbonate virtual trial, here the PLM staff was concerned with the scientific rationale of the initiative. The patients' reasoning assumed that any effect they could register on the questionnaires was most likely caused by the active treatment (NP001), be it in the form of self-registered improvement or any other side effects. Consequently, they were trying to devise the composition of the treatment and the placebo arms of the trial by grouping together patients with normally uncommon, yet repeated side effects, and putatively attributing them to the treatment arm. What they were doing was *"like shooting an arrow at a blank wall and then drawing a target around it after the arrow has already landed"*, as one staff member put it to the ethnographer. Moreover, as Akst (2016) reports, *Persevering* had unblinded his own trial treatment once in the clinic where NP001 was administered, by smuggling his and other patients' empty treatment containers from the clinic (with some guesswork as to the attribution of each bag to each patient), then analysing them for pH, to conclude that he was on the treatment arm.

Importantly, *Persevering* and several others experienced dramatic reversals, temporarily recovering functional capacity soon after injection, though the positive effects became increasingly ephemeral and waned over time. The excitement was high but so were the doubts. The PLM staff was cautious; they knew that the progressive loss of function in ALS is S-shaped rather than linear, so apparent improvement can just be part of the normal course of disease progression. Still, as part of the evaluation of the situation, the staff undertook an informal, preliminary statistical analysis to assess the purported effects of NP001. At this early stage, a positive outcome seemed possible, albeit on unreliable grounds (a small sample and a fluctuating condition). The staff member who initially introduced the ethnographer to the situation highlighted uncertainty as to what PLM should do: *"You don't know what unintended consequences that could have in the scenario of a clinical trial. I'm not saying that's necessarily a bad thing but I'm*

⁸ Scraping is a technical term for the extraction of data from a raw html source, i.e. the information that makes up a webpage.

saying the medical world is not equipped to deal with that right now. So I think it's very different [to the previous study of lithium-carbonate]." In several conversations, staff shared the conviction that this situation could repeat itself on many other social media and web platforms other than PLM. PLM staff felt that they were witnessing a major development that was *facilitated by the PLM platform better than any other, yet not dependent on it*. Patients could have easily grouped and coordinated elsewhere. In a meeting with an external expert, focusing on the problem of including the patient perspective in better patient-reported outcome research, one member of staff put it this way: *"we have partially created the world that he needs to do that, but he doesn't need us, he can use the hashtag NP001 on Twitter."* As a matter of fact, the patients in Eric Valor's parallel ACP initiative were relying on an external Google site for sharing protocol, calculating dosage and coordinating data gathering.

It was difficult for PLM to evaluate this dilemma. Staff was aware that their site was being used for an initiative that could disrupt the Neuraltus trial, and for which the ethical and legal liabilities were unclear. There was concern about the potential damage to research that this initiative could cause. At the same time, other considerations sympathetic to the spirit of empowerment, group support and empathy of the initiative pointed at a potential conflict of interest: supporting patient communication, learning and empowerment is a main value proposition of the platform, and for PLM staff to conduct health research with patient data is important also for its reputation and future partnership prospects. And yet other potential conflicts of interests were highlighted to the ethnographer: if PLM had advanced access (even if limited) to the trial outcome, and decided to invest in Neuraltus, would this constitute some sort of insider trading?⁹ One can easily speculate further and imagine other potential beneficiaries of this potential future information asymmetry (patients, trial sponsor, any observing third party).

Persevering's initiative sparked a debate that reverberated all over the company in the fall of 2011. The issue was brought up in several meetings, so most staff members became aware of it. PLM staff kept in communication with the patient leaders, while they tried to understand if there could be some sort of compromise, allowing patients to gather information (and *"not leave them in the dark"*) without disrupting the Neuraltus trial. The issue was also discussed with relevant external collaborators who could help the company manage the situation. Two points stood out in all these exchanges.

First, PLM staff felt the necessity of articulating a general company position regarding this sort of initiative, and that they could not simply be banned. While patients could make use of any social network to revolt against a trial protocol, PLM made such disruption easier. The responses to ASFRS-R and other questionnaires were so easily accessible that any site user could, in principle, find them and harvest the data without any patient coordination or engagement. This level of accessibility of health information was crucial to the company's mission: to conduct health research with patient-reported data, on the basis of a policy of patient empowerment. PLM wanted patients to have shared access to the information they reported in order to best serve their perceived needs. In this regard, *Persevering's* initiative was an inevitable side effect of the core architecture of PLM. It could not be aborted without damaging the company's value proposition statement (and related market position). In addition to this, several patients participating in either one of the NP001 initiatives had been members of the lithium carbonate

⁹ In their final report (Wicks et al., 2012), the patient-researchers declared that they had no financial interest in the outcome.

study; at least in part, they were re-enacting a way to organise patient research that had been previously officially experimented with on PLM.

Second, the staff quickly grasped the potential epistemic conflict between *Persevering's* initiative and the Neuraltus trial: the more information the patients gathered about the latter, the more likely it was that the trial yielded a biased (unblinded) outcome. But the conflict was not a zero-sum situation. A shared understanding was that this initiative was not research for science's sake but a quest for patients to save their lives. Seen from this 'oblique' perspective, the conflict was more difficult to judge. One staff member shared this point of view in a meeting as: "[Persevering] *he's not trying to unblind it [...] they have a sense of urgency that we cannot understand.*" A colleague added: "*Also, they got to know each other, [...] they want to know how each other is doing.*" Many of these reflections drew from the staff member's own personal histories. The Heywood brothers, founders of the platform, had a background in patient activism (founding the ALS Therapy Development Institute, a non-profit) and what had once been called 'guerrilla science'. Through their painful family history, they were familiar with how patients were thinking about their own chances in leading this initiative.

Overall, PLM challenged a central assumption in the current bioethical consensus on clinical trials: the primary goal of participation in a trial is to study potential treatments, not to find a cure for the individual participants (the contrary is the so-called *therapeutic misconception*). For more than five decades after the 1962 Act, publicly and privately sponsored RCTs had been organised on this assumption, arguably against the preference of many trial participants. As far as we can tell, PLM became the first private company willing to take a stance on the attempt of patients to break free of research protocols and support the argument that the current research regime did not fit the needs of the patients (while also voicing concern about its risks for the regime of clinical research), which Eric Valor, among others, has vocally shared.

In the meanwhile, patients were not standing by and looking. As journalist Akst reports in detail in a short self-published e-book (Akst, 2016), among the forum discussions that patients were having in relation to NP001, a conversation ensued about an antecedent drug also based on sodium chlorite, WF10, about its links and similarity with NP001, and about how to source it. Patients were concerned about securing their continued access to the drug after the trial end, and Neuraltus was reportedly aware of these forum threads. Patients lobbied the company and led a petition, signed by 18k supporters, for an expanded access programme. Neuraltus refused, on grounds of the financial cost and the delay in the approval process that an extended access would have caused.

WF10 was available from Thailand, but patients had to coordinate to help and fend off quacks and fraudsters. A few were able to face the steep costs (in the region of 10–20k for a year's worth of provision), others resorted to industrial grade sodium chlorite – following Valor who, as we anticipated in the beginning of this article, had devised a way to intake the chemical orally and was interested in enrolling others to experiment and share outcomes as well. Akst (2016) explains how *Persevering* was able to procure himself WF10, thanks to the generosity of Ben Harris (aka *Happy Physicist*), fellow participant in NP001 and another leading figure of the NP001 patient initiative, who shared his stock. Hope had been wearing thinner, as already during the trial the reversals that patients had initially experienced had started to have smaller effect and shorter duration. Some patients, including Ben Harris, broke the trial protocol again and did not wait for the three months of after-treatment observation to end. After consuming the WF10 orally

to little avail, *Persevering* became disillusioned. In September 2012, he stopped eating and drinking and let himself die. Ben Harris, who had devised a way to take sodium chlorite intravenously, consumed WF10 in this way and continued to inject himself with industrial grade sodium chlorite to stay closer to the trial drug's delivery mechanism and bypass concerns about the absorption of the chemical through the digestive system. When he surrendered, in August 2013, he chose to die in the same way as his friend (Akst, 2016). The excruciating experience that patients with ALS go through can lead them to bravely (if dangerously) pursue a hopeful vision with seemingly inexhaustible energy for many years, but can also exhaust them, beneath the surface, until they lose all will to continue.¹⁰

3.3 ONE TRIAL, MANY ANALYSES

Access to the raw data generated in a clinical trial is a source of endless controversy. Pharmaceutical companies should submit their data sets to the regulatory agencies for the approval of new treatments, on the basis of treatment safety and efficacy. Other than for regulatory approval, pharmaceutical companies rarely release the data of the RCTs they sponsor, despite their potential scientific interest.¹¹ In the Neuraltus trial, we find patients, instead of researchers, organising to access the data and find out about the efficacy of a treatment in a trial through two highly unusual paths.

On the one hand, *Persevering's* initiative disclosed through PLM a self-reported sample of the Neuraltus trial data. On the other hand, Valor's ACP organised a virtual trial of a substance the patients considered a proxy for NP001, an oral solution of sodium chlorite. At the end of both the real trial (Neuraltus) and the virtual trial (ACP), there were three competing data sets on at least three preparations or drugs (see Fig. 1): 1) the Neuraltus complete data on a) NP001; 2) PLM's data on a) NP001 (partially disclosed through *Persevering's* initiative) and sodium chlorite homebrews in both b) oral and c) intravenous solutions; 3) the ACP data on the b) sodium chlorite oral solution. The Neuraltus trial data were only accessible for the company's scientists; the latter two data sets were publicly accessible online.

Three main analyses of these three data sets were eventually conducted. 1) *Persevering* presented his own statistical discussion of the data he had collected through PLM (Persevering, 2012). 2) Researchers at PLM published their own independent report, which included an analysis of both the sodium chlorite oral solution homebrew and NP001, together with a re-analysis of the previous lithium carbonate study and an analysis of data about another recent ALS trial (dexpramipexole) that were also available through PLM (Wicks et al., 2012). Finally, 3) Neuraltus published a standard statistical analysis of its own trial outcome (Miller et al., 2015). The ACP did not release a formal analysis of its own data.

¹⁰ As important as it is to recognise the heartbreaking and dramatic personal stories behind the events at the heart of this paper, regrettably, we cannot discuss them any further. The dilemmas of caring for terminally ill patients with experimental treatments have been extensively analysed in bioethics. For the latest episode in this debate, see, for instance Carrieri et al. (2018).

¹¹ In the EU, it is now mandatory to release these data sets. See the European Medicines Agency policy on publication of clinical data for medicinal products for human use (EMA/240810/2013, 2 October 2014).

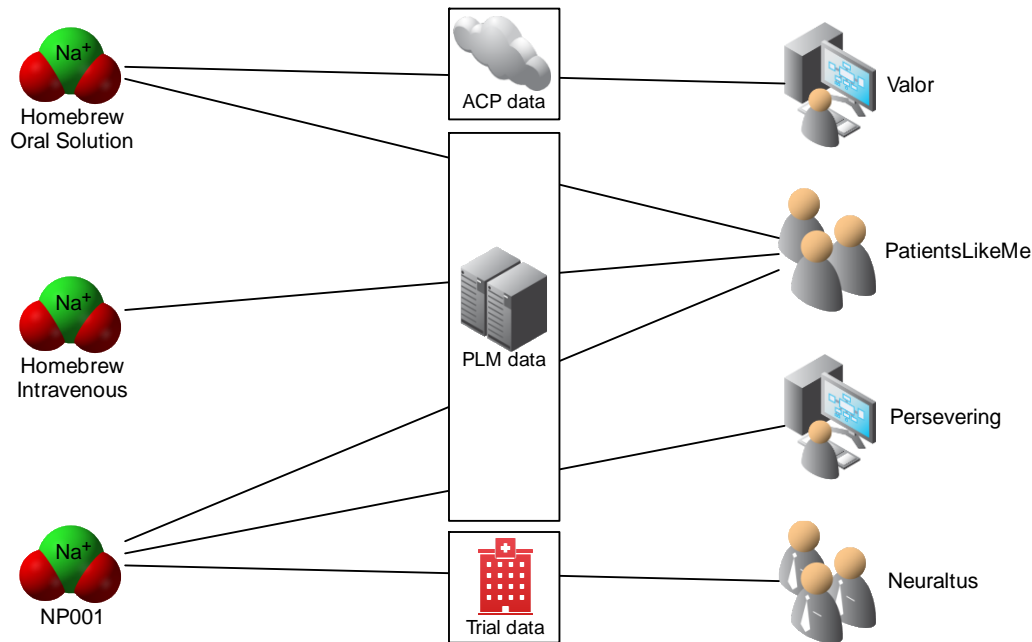


Figure 1 – A visual summary of the many initiatives around the NP001 trial

The ACP was a mixture of phase I and phase II trials. As in a phase I trial, patients had been experimenting with composition and dosage. They kept a record of their homebrew solutions, trying increasingly higher doses to test their own tolerance to the side effects – which were sometimes taxing. They also kept a rich, detailed record of their perceived clinical effects, as if it were a phase II trial. They shared visual data in the form of photographs and videos (via YouTube) as evidence of speech and limb movement functions. Arguably, the lack of homogeneity in treatment regimes, duration, and data collection, as well as the overall low number of participants, would have made the data difficult to analyse with standard statistical techniques.

Three months after the completion date of the Neuraltus trial, on the 8th January 2012, *Persevering* published a guest post on Eric Valor’s blog (Persevering, 2012). He had gathered data from 34 PLM users on the NP001 trial, which amounted to about one third of the official trial’s sample. *Persevering* assigned his patients to the two arms of the NP001 trial depending on their self-reported side effects, under the assumption that some of these would signal the administration of the active treatment. He then found a statistically significant difference between the means of the outcome variable ALSFRS-R in the two groups, showing that NP001 apparently brought about a self-reported improvement, stopping the progression of the disease. However, a self-selected sample of that size does not allow for a reliable statistical estimation of the treatment effect; such an improvement may also be due to the natural progression of the disease.¹²

Despite their awareness of such methodological pitfalls, the PLM researchers also contributed their analysis of both the ACP and *Persevering’s* data (after the end of the Neuraltus trial). The report, they argued, highlighted a void around the ethics of patient and corporate initiatives outside trial:

¹² Recall that the patients had registered with PLM and had chosen to share their data through the site’s questionnaires and communication tools.

Should our analysis of this data on unproven therapies be provided to the patients and clinicians treating them or should it remain in our servers until it reaches the significance or scientific rigor required for submission to a peer-reviewed journal? What questions should guide our decision about sharing our conclusions? (Wicks et al., 2012:5)

The data alone certainly did not justify it. Their analysis was, in both cases, inconclusive. The mean difference between the inferred trial groups suggested that NP001 somewhat slowed the progression of ALS, but it was not statistically significant. Only a complete analysis of the Neuraltus trial, they warned, could settle the matter. As for the sodium chlorite oral solution homebrew data, the PLM analysis showed that it was actually worsening the disease progression and causing harm to patients. The quality of the evidence grounding this conclusion was poor, since the data had been generated with a scarcely controlled research protocol and very few patients.

At the same time, PLM researchers were keenly aware of the risks entailed in *Persevering's* initiative. They pointed out that the release of a defective preliminary data analysis might be damaging for actual and future trials; the participants may stop their treatments if they believe them ineffective or not enrol in any subsequent trial. And the intake of homebrew solutions can harm and introduce bias in the trial if it happens during the study period. Why then did PLM decide not to take an early position against *Persevering's* unblinding initiative, and instead contribute their own analysis of his data after the trial's end? The PLM researchers instead used the report to open up a more general debate about considering whether patient-powered digital platforms are contributing to the public good or not:

Open data architectures, the Internet, education, empowerment of patients, and what appears to be a frustratingly slow pace of clinical innovation have all combined to bring us to where we are today. It is important to determine whether models such as ours can hasten this process or be deployed to investigate the "real world" efficacy of treatments that have already been approved. Or, as may be the case, whether such contributions merely add confusion to the mix. (Wicks et al., 2012:12)

PLM researchers defended the potential value of learning from self-reported information alongside clinical trials. They made a distinction between publishing about a trial before the official results were released (i.e. publishing about NP001), and publishing about the patient self-experimentation that was happening because of the trial (i.e. publishing about the sodium chlorite homebrew). Acknowledging that the first could be seen as an outright disruption, they defended their own publication of the second for the opportunity to reduce harm.

It was only a few years later that the official outcome of the Neuraltus NP001 trials became available, in September 2014 through *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* for the phase I trial, and April 2015 through *Neurology – Neuroimmunology Neuroinflammation* for the phase II trial that the patient initiatives paralleled. No statistically significant difference was found between the NP001 and the placebo group, regarding the primary outcome variable (the ASFRS decline slope) and the secondary variables. A subgroup analysis revealed that NP001 seemed to have some positive effects on patients with higher cytokine inflammation who were testing the higher dose (Miller et al., 2015). Neuraltus organised a second phase II trial, currently in progress, to find out more about the efficacy of NP001 on this particular class of patients.

4. THE FUTURE OF CLINICAL TRIALS

The preferences of the pharmaceutical industry are the source of many different biases in the trials it sponsors. Dumit's work (2012) shows how much of the focus of the industry is on the construction of conditions for the management of which drugs can be tested and then marketed. Trials can be biased, not so much for the statistical mechanisms with which evidence is evaluated, but in the way they define target populations, conditions and interventions, and how samples are consequently constructed so as to maximise the chances of success. And indeed, it is more likely that experimental treatments test positive in an industry-sponsored (published) RCT than in publicly sponsored trials (Lundh et al., 2012). In addition, the sponsor may decide to report only positive findings (focusing only on a sample of the trial data) or just submit successful trials, neglecting failures. In any case, the financial incentive for the bias is clear: new treatments come with fresh patents for the sponsor to exploit. However, the same sort of meta-analyses that detect sponsor biases argue that industry-sponsored trials are conducted with strong methodological precautions (e.g., patients are regularly blinded in order to prevent biases originating in their preferences – Savovic, 2012). There is a clear incentive for the industry to be this careful: if positive, the experiment should persuade the regulator that the new compound is safe and effective. Hence, so far, the pharmaceutical industry has found itself in a position to not have any reason to accommodate the participants' preferences when they conflict with the trial blinding requirements. Even if it was an early stage trial, Neuraltus probably would have wanted the NP001 trial blind, lest any positive results be turned down as spurious by the regulator.

4.1 DIGITAL TECHNOLOGY AND CONTRACT RESEARCH ORGANISATION

Our case study illustrates a different understanding of industry biases. Whereas the interests of the trial participants and the pharmaceutical companies, as far as blinding is concerned, are often not aligned, a different convergence ensues between the business model of platforms such as PLM and the preferences about blinding of some of the participants in the NP001 trial. Digital communication and socialisation platforms such as PLM depend on the sharing of data by their users, and the ability to support their interaction and coordination needs. As we saw, PLM found itself in a peculiar position, hosting *Persevering's* initiative even if it created a conflict between the goals of PLM and Neuraltus.¹³ PLM could not take a stance against *Persevering's* initiative without risking damage to its main business asset: an active community of patients willing to share data about their health life. These initiatives can make leader users influential, and alienating them can be particularly risky in this respect. If unblinding a trial is a potential source of bias, we may see in *Persevering's* initiative the grounds for a different *industry-powered bias*: the interested industry in this case is not the pharmaceutical but technology, or rather, that blurry space that social media companies occupy.¹⁴ Interestingly, PLM does not make money through

¹³ As we saw, it is not simply the breach of the trial's blinding: *Persevering's* initiative through PLM disclosed preliminary data about the prospects of NP001 as a treatment. Trial data could be of potential financial value for investing (or disinvesting) in the drug developer.

¹⁴ In widely publicised appearances before US and UK legislators, Facebook has been resisting concerns about its accountability over the content that is shared on its network, by claiming to be a technology company not a media company (hence trying to shift the legislators' choice of the framework through which it would be regulated). The endless controversy caused by Facebook's standards and choices on content moderation highlights the unavoidable clash between the principle of neutrality over users' use of the media for communication, and protecting diverse principles of legality and cultural norms.

the sale of ads (unlike Facebook) but through research services, primarily to the pharmaceutical industry. In a research landscape where RCTs have been increasingly organised and managed by third-party contract research organisations such as IQVIA (formerly Quintiles), the potential damage to the stability of the RCT as a testing regime, consequence of the emergence of digital platforms for self-reported observational studies, pitches the financial interests of one kind of research services firm against another rather starkly. Since, *PatientsLikeMe* has indeed made early moves towards the provision of clinical trial support, by collaborating and providing research infrastructure on a trial of a diet supplement, Lunasin, organised in collaboration with Duke University's ALS Clinic (Bedlack, 2015).

As we mentioned, there were a number of other reasons shaping PLM's view not to undermine the initiative. On the one hand, a widespread belief in the managers' powerlessness to block the initiative reduced the possibilities for dissent to public positioning. Staff believed they lacked the means to fully enforce any such action, as patients could move the initiative to other digital tools such as the ones employed by Valor's own ACP: Google Sites, Google Spreadsheets and general-purpose broadcasting and coordination tools such as forums, Twitter or Facebook. On the other hand, PLM was tied with ALS activism since its founding, and the network had actively collaborated with the patient community in the previous lithium carbonate study. While they did not collaborate in the NP001 initiative, they sympathised with the human struggle for life motivating the mission as they observed *Persevering* coordinate his action. In a letter to the *British Medical Journal*, compellingly titled "*Subjects no more: What happens when trial participants realise they hold the power?*" and published two years after the NP001 events, PLM researchers discussed the NP001 events further and asked to "*forge a new social contract that maximizes both scientific discovery and patient autonomy, setting the stage for better trials with more engaged participants*" (Wicks et al., 2014). This will be necessary to reduce the risk of revolt against the protocol – "*patient-led 'disobedience'*" (Wicks et al., 2014). The solution PLM suggested is to involve patients in trial design and organisation, and make them active collaborators in clinical research. *Persevering* and *Happy Physicist* saw themselves as supporters, not saboteurs, of the NP001 programme: they actively helped the organisers to enrol patients, spreading the news of a promising trial (Akst, 2016). Even though their own initiative depended on successful enrolment (to run the trial, and to achieve good sample size), they were not scheming against Neuraltus. They hoped to live long enough to access the drug once approved. Valor, of his own, saw no direct conflict between his self-experimentation initiative and standard trials: "[W]e have no delusion that anything we are doing is intended to replace clinical trials. Rather, we intend to augment and push forward the actual science" (Valor, 2012).

4.2 DIGITAL TECHNOLOGY AND INFORMAL ACTIVISM

In a digital world of fluid, distributed communications, where small initiatives can emerge and coordinate at the fringes of bigger, better-resourced enterprises such as a clinical trial, trial participants can feel like research collaborators and yet breach the trial protocol. It might be tempting to dismiss this story as a unique case, but we believe that the repeat of this experience is not an unlikely scenario. In the 1980s, very few trial participants could reach the degree of coordination in their actions exhibited by the ACT UP activists, who relied on the pre-existing political networks of gay activists (Epstein, 1996). As far as we can tell, after the AZT trial, there was no other organised attempt to breach a trial protocol on the same scale. Nowadays, digital platforms allow almost every group of patients to meet and organise, if they wish, to coordinate

action in trials. Platforms greatly reduce friction in distributed coordination and communication, making it possible for ‘splinter’ groups of individuals facing an extreme challenge to *ephemerally*¹⁵ emerge and disappear; users can quickly find each other, coordinate as long as they share the same individual interests, and disband.

These groups do not need to be affiliated to formal organisations. On the contrary, if their purposes are controversial, they might better not be like a formal group or organisation; rather, to work as understated individuals contingently helping each other might be more convenient. It has been well observed how digital environments allow ‘pro-ana’ groups (support and self-construction in favour of anorexia) to grow on the Internet against all adversities (Shirky, 2008; cfr. Vellar, 2018). The plight of the patient initiatives we discuss is much less controversial and at least in part legitimised by discourses of self-empowerment and challenge to power. What is most controversial is that the methodological consequences of their actions (potential *lethal interference* with an RCT protocol; generation of worse-quality alternative evidence; probable harm to homebrew testers) were so counterproductive. These web-based initiatives can arise in the absence of a mandate (or pretence thereof) of an activist organisation, evolve very quickly, multiply (*Persevering’s* NP001 data collection, Valor’s ACP project, *Happy Physicist’s* intravenous solution experiment), crossover (e.g., *Persevering* switching to oral solution homebrew after NP001), and generate self-experimentation activity that does not always leave a conclusive data trail.

Web-based collaborative tools not only offer networking and coordination capabilities (finding alike people, coordinating with them), but they also allow easy generation, computation and analysis of new kinds of data (e.g., Google Forms, Google Spreadsheets, etc.), the standards of which (what is data about, how it needs to be produced, what can it be evidence for) have been agreed extemporaneously. These initiatives mobilise statistics knowledge, techniques and discourses in ways similar to those observed in studies of data activism in domains other than science (Bruno et al., 2014; Milan & van der Velden, 2016), although, in our case, patients are not mainly involved in resistance to the state or corporates, nor in making an issue visible and relevant, despite elements of these drivers being clearly at play. They are about curing oneself. Generating new knowledge (does homebrew work?) or uncovering other knowledge (does NP001 work?) are means to that end. Activists abandon the task once they have answered these questions.

And again, without being absorbed into the structure of formal organisations, patients are able to operationalise these questions over and over again, to pursue new hypotheses. The material legacy of previous experiences is distributed over a number of digital platforms interconnected by the web, and their organisation and leadership skills – along with scientific expertise – allow them to move from one self-organised experiment to another. The NP001 initiatives were led by patients who had previously participated in the lithium carbonate experiment; simultaneously to the NP001 experiments, the data of another trial were also shared on the platform (Wicks et al., 2012) and Valor has taken part in patient-led experiments on two other (not patented) compounds, before and after ACP: ursodeoxycholic acid and fisetin (ALSFisetin, 2013; ALSURSO, 2010). This hybrid repertoire of political and scientific practices can be re-deployed informally

¹⁵ This vocabulary is inspired by Lanzara’s seminal organisation studies paper, “*Ephemeral organisations in extreme environments*” (1983).

and repeated several times without coalescing into a formal organisational structure.

Might the genie be out of the bottle? The development of a culture and expertise where patients are free to generate epistemic evidence about compounds, regardless of whether they are currently being tested in trials or freely available, is here. But crucially, epistemic conflicts, such as the one we have documented, risk generating a situation where no reliable evidence is available. The more information patients gathered about the trial, the more likely it was that the trial would yield a biased outcome. In the end, patient-led analyses were inconclusive, while the trial was potentially biased, its statistical power weakened, and led to a phase IIb only several years after the first.

4.3 DIGITAL TECHNOLOGY AND PHARMACEUTICAL REGULATION

A pressure seems to be mounting in the online world to make the social contract of blinding increasingly unpalatable, as it becomes easier to break it. Here, the crux of the matter becomes the trial methodology: the consensus among trialists today requires participants' blinding in most tests as a necessary condition for an unbiased outcome. If a testing method was found, as reliable as the RCT, in which the patients could express their preferences without biasing the results, there would be no problem in patients sharing their data however they wished. Short of this, NP001-like scenarios may undermine the reliability of many RCTs.

An obvious rejoinder is to challenge the reliability of RCTs as a testing standard. Many philosophers of science have questioned, during the last decade, the superiority of RCTs to grasp causal connections; STS scholars have argued against a method that pharmaceutical interests bend so easily (e.g., Bell, 2017). Maybe it is time for change and, indeed, there are clear signs that it is about to happen. On 13th December 2016, the 21st Century Cures Act was signed into law, an ambitious bill aimed at reforming biomedical research in the US with the goal of bringing new treatments faster to patients. It quite radically changes the regulatory standards adopted in the 1962 Act, inviting the FDA to use "*alternative statistical methods*" (section 2061) and "*evidence from clinical experience (in place of evidence from clinical trials)*" (section 2062) in order to support approval of a drug for new medical use (indication).¹⁶ Just as the 1962 Act created the clinical trial industry by requesting two positive RCTs in every new drug application, we may expect that the implementation of the 21st Century Cures Act will create new testing standards where the participants' preferences will be better accommodated. On the basis of these new standards, the FDA will authorise new treatments in pharmaceutical markets.

Perhaps new reliable standards will emerge but, in negotiating any new social contract for clinical trials, all the stakeholders (and patients, in particular) should bear in mind the fate of the FDA *advanced access* programme. In response to ACT UP's demands, the FDA inaugurated an *advanced access* system for certain drugs (Carpenter, 2010), which were approved on the basis of shorter RCTs. Trials were shortened using *surrogate outcomes* (González-Moreno, Saborido, & Teira, 2015): if the variable indicating the success of a treatment took many years to track, the trial would target instead another variable whose value at an earlier date should predict the treatment outcome. Even if the original intention of this methodological shift might have been to accommodate the patients' legitimate preferences, the pharmaceutical industry has exploited it for its own purposes with a self-serving choice of surrogate outcomes. Positive trials based on

¹⁶ These new regulatory developments are still controversial and we think there are reasons to fear this new testing flexibility. For our own analysis, see Tempini and Teira (forthcoming).

these early end points have served to obtain regulatory approval and bring into the pharmaceutical market treatments of inferior quality.

No wonder then a former ACT UP activist reacted so early against the 21st Century Cures Act, in an early opinion piece published in the *New York Times*. Gregg Gonsalves and co-authors warned that the Act “*could substantially lower the standards for approval of many medical products, potentially placing patients at unnecessary risk of injury or death*” (Gonsalves et al., 2015; see also Gonsalves et al., 2016). Just after the approval, scientists and FDA officers alike have warned about the potential regulatory mistakes that might follow from using evidence where sources of bias are not properly controlled for (Sherman et al., 2016).

In a connected yet distributed world, spontaneous coordination over digital platforms such as PLM is the norm and NP001-like scenarios may become common, where patients share live information about all forms of medical experimentation. Perhaps worrying is that, while it might seem that the possibility of breaking the clauses of any experimental protocol can allow different social actors to use this power to force their own priorities and epistemic standards onto the negotiating table, these initiatives by themselves do not leave behind stable issue owners and reference organisations capable of articulating and advocating patients’ methodological preferences – if the door was left open to them. There is a possibility that new challengers that can eventually emerge and throw a trial off the rails might remain undetermined until the event.

4.4 CODA

We do not know yet if a new epistemic regime is emerging where digital platforms will feature as a source of personal health data and of logistical support for observational research, alongside electronic health records and other databases, at the expenses of traditional (blinded) RCTs. Notably, the problems that we singled out in this paper are problems that emerge as people share information, not hide it (as in RCTs’ reporting bias). And yet, late developments in the digital public sphere offer further grounds for worry about the proliferation of digital noise and the ways in which industries and heterogeneous interests can exploit it. Just recently, Internet platforms have been repeatedly weaponised to orchestrate, influence and capture the initiatives of active citizens, undermining the practices by which facts are constructed, shared and become the bedrock of a healthy democracy (Sismondo, 2017). The world of self-organised and spontaneous digital interaction is now questioned for being dangerously, and inadvertently, open to the influence of organisations with well-defined agendas. What would happen if the strategies of social media influence, with their celebrity dynamics, polarising bots, and fake news farms were to be introduced in the world of digital patient groups? This might sound like far-fetched speculation, but reports on the 2016 votes (American elections and the Brexit referendum) suggest that a relatively small number of targeted interventions might multiply many times in online echo chambers. In the world of patient participation and pharmaceutical innovation, the specific forms these influencing strategies might take are undefined as much as their outcomes, but it is not difficult to imagine they could allow their perpetrators to sabotage a competitor’s trial, or to gain insight on their industrial trade secrets. Seeing whether a drug shows early signs of efficacy before they are made public may also allow privy investors to buy shares of the manufacturing company at a better price.

The disappointment of groups that feel left behind can be genuine and very well justified. But it can still be manipulated and seized upon, even in ways that can ultimately harm the very

protesters and that could be difficult to defeat. Paradoxically, in the world of medical research, it might be that those communities that could have the most to gain, the orphan diseases' communities, risk losing the most. If noise were to proliferate further along the lines we have indicated, the availability of new life-saving therapies might be further delayed. Where this imaginative scenario leaves us is difficult to tell, but we hope to generate a stimulating discussion.

REFERENCES

- Abraham, J., & Davis, C.** (2013). *Unhealthy pharmaceutical regulation: Innovation, politics and promissory science*, Basingstoke: Palgrave Macmillan.
- ACP.** (2011a). ALS Chlorite Project. *ALS Chlorite Project*. Retrieved from: <http://sites.google.com/site/alschlorite/> (accessed 25 May 2017).
- ACP.** (2011b). Reality Check - ALS Chlorite Project. *ALS Chlorite Project*. Retrieved from: <http://sites.google.com/site/alschlorite/updates/realitycheck> (accessed 25 May 2017).
- ALSFisetin.** (2013). *ALSFisetin project website*. Retrieved from: <http://sites.google.com/site/alsfisetin/>
- ALSURSO.** (2010). *ALSURSO project website*. Retrieved from: <http://alsurso.atspace.com/index.html>
- Akrich, M.** (2009). From Communities of Practice to Epistemic Communities: Health Mobilizations on the Internet. *Sociological Research Online*, 15(2), 10.
- Akrich, M., O'Donovan, O., Rabeharisoa, V.** (2015). The entanglement of scientific and political claims. Towards a new form of patients' activism. In Wehling, P., Viehöver, W., & Koenen, S., (eds.), *The Public Shaping of medical Research. Patient associations, health movements and biomedicine*, London and New York, Routledge, 72-88.
- Akst, J.** (2016). *Personal Trials: How Terminally Ill ALS Patients Took Medical Treatment Into Their Own Hands*. CreateSpace Independent Publishing Platform.
- Bedlack, R.** (2015). *An open-label, single-center, 12-month trial of a Lunasin regimen for patients with Amyotrophic Lateral Sclerosis (ALS)*. Clinical Trial Protocol, Duke University, Version 11; IND Number: 128306; Duke IRB Protocol Number: Pro00063754.
- Bell, J. A. & Balneaves, L. G.** (2015). Cancer patient decision making related to clinical trial participation: an integrative review with implications for patients' relational autonomy. *Support Care Cancer*, 23, 1169-1196.
- Bell, K.** (2017). *Health and other unassailable values: Reconfigurations of health, evidence and ethics*, New York, NY: Routledge.
- Bonney, R., Cooper, C. B., Dickinson, J., et al.** (2009). Citizen Science: A Developing Tool for Expanding Science Knowledge and Scientific Literacy. *BioScience*, 59, 977-984.
- Brives, C.** (2013). Identifying ontologies in a clinical trial. *Social Studies of Science*, 43, 397-416.
- Bruno, I., Didier, E., & Vitale, T.** (2014). Statactivism: Forms of Action between Disclosure and Affirmation. *Partecipazione e Conflitto*, 7(2), 198-220.
- Carpenter, D. P.** (2010). *Reputation and power: organizational image and pharmaceutical regulation at the FDA*, Princeton: Princeton University Press.
- Carrieri, D., Peccatori, F. A., & Boniolo, G.** (2018). The Ethical Plausibility of the 'Right To Try' Laws. *Critical Reviews in Oncology/Hematology*, 122(February), 64-71.
- Dumit, J.** (2012). *Drugs for life: How pharmaceutical companies define our health*, Durham: Duke University Press.
- Epstein, S.** (1996). *Impure Science. Aids and the Politics of Knowledge*, Berkeley-Los Angeles: University of California Press.
- Epstein, S.** (2007) *Inclusion: The politics of difference in medical research*, Chicago: University of Chicago Press.
- Fisher, J. A.** (2009). *Medical research for hire: The political economy of pharmaceutical clinical*

- trials*, New Brunswick, N.J.: Rutgers University Press.
- Follett, R., & Strezov, V.** (2015). An Analysis of Citizen Science Based Research: Usage and Publication Patterns. *PLOS ONE*, *10*, e0143687.
- Fornai, F., Longone, P., Cafaro, L., et al.** (2008). Lithium delays progression of amyotrophic lateral sclerosis. *Proceedings of the National Academy of Sciences*, *105*(6), 2052–2057.
- Gillies, K., Cotton, S. C., Brehaut, J. C., et al.** (2015). Decision aids for people considering taking part in clinical trials. *Cochrane Database Syst Rev*, Cd009736.
- Goldacre, B.** (2013). *Bad pharma : how drug companies mislead doctors and harm patients*, New York: Faber.
- Gonsalves, G., Carpenter, D. P. and Ross, J. S.** (2016). Lawmakers must ask tough questions about the 21st Century Cures Act. *The Hill*. Retrieved from <http://thehill.com/blogs/congress-blog/healthcare/307020-lawmakers-must-ask-tough-questions-about-the-21st-century>
- Gonsalves, G., Harrington, M., & Kessler, D.** (2015). Don't Weaken the F.D.A.'s Drug Approval Process. *New York Times*.
- González-Moreno, M., Saborido, C., & Teira, D. (2015). Disease-mongering through clinical trials. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, *51*, 11–18.
- Gøtzsche, P.C., Smith, R. & Rennie, D.** (2013). *Deadly medicines and organised crime: How big pharma has corrupted healthcare*, London: Radcliffe Publishing.
- Hackshaw, A.K.** (2009). *A concise guide to clinical trials*, Oxford: Wiley-Blackwell.
- Hrobjartsson, A., Emanuelsson, F., Skou Thomsen A. S., et al.** (2014). Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *Int J Epidemiol*, *43*, 1272-1283.
- Hrobjartsson, A. & Gotzsche, P. C.** (2010). Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*, Cd003974.
- Kallinikos, J., & Tempini, N.** (2014). Patient Data as Medical Facts: Social Media Practices as a Foundation for Medical Knowledge Creation. *Information Systems Research*, *25*(4), 817–833.
- Lanzara, G. F.** (1983). "Ephemeral Organizations in Extreme Environments: Emergence, Strategy, Extinction [I]." *Journal of Management Studies*, *20*(1), 71–95.
- Lundh, A., Sismondo, S., Lexchin, J., et al.** (2012). Industry sponsorship and research outcome. *Cochrane Database Syst Rev*, *12*, Mr000033.
- McCann, S. K., Campbell, M. K., and Entwistle, V. A.** (2010). Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials*, *11*, 31.
- Milan, S., & van der Velden, L.** (2016). The Alternative Epistemologies of Data Activism. *Digital Culture & Society*, *2*(2).
- Mills, E. J., Seely, D., Rachlis, B., et al.** (2006). Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Oncol*, *7*, 141-148.
- Miller, R.G., Zhang, R., Block, G., et al.** (2014). NP001 regulation of macrophage activation markers in ALS: A phase I clinical and biomarker study. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *15*(7–8), 601–609.
- Miller, R. G., Block, G., Katz, J. S., et al.** (2015). Randomized phase 2 trial of NP001, a novel immune regulator safety and early efficacy in ALS. *Neurology - Neuroimmunology Neuroinflammation*, *2*(3), e100.
- Monahan, T. & Fisher, J. A.** (2015). 'I'm still a hustler': entrepreneurial responses to precarity by participants in phase I clinical trials. *Economy and Society*, *44*(4), 545-566.
- Ortmann, A. & Hertwig, R.** (2002). The Costs of Deception: Evidence from Psychology. *Experimental Economics*, *5*, 111-131.
- Persevering.** (2012). Guest: Persevering On NP001 – EricValor.org. *EricValor.org*. Retrieved

- from: <http://www.ericvalor.org/guest-persevering-on-np001/> (accessed 29 August 2016).
- Petryna, A.** (2009). *When experiments travel : clinical trials and the global search for human subjects*, Princeton: Princeton University Press.
- Rabeharisoa, V. & Callon, M.** (2002). The involvement of patients' associations in research. *International Social Science Journal*, 54, 57-63.
- Savovic, J., Jones, H. E., Altman, D. G., et al.** (2012). Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med*, 157(6), 429-38.
- Sherman, R. E., Anderson, S. A., Dal Pan, G. J., et al.** (2016). Real-World Evidence — What Is It and What Can It Tell Us? *New England Journal of Medicine*, 375, 2293-2297.
- Shirky, C.** (2008). *Here Comes Everybody: The Power of Organizing Without Organizations*. London: Penguin Press.
- Sinha, G.** (2013). Another blow for ALS. *Nature Biotechnology*, 31(3), 185–185.
- Sismondo, S.** (2017). Post-truth? *Social Studies of Science*, 47, 3-6.
- Teira, D.** (2013). Blinding and the Non-interference Assumption in Medical and Social Trials. *Philosophy of the Social Sciences*, 43, 358-372.
- Tempini, N.** (2015). Governing PatientsLikeMe: information production and research through an open, distributed and data-based social media network. *The Information Society*, 31(2), 193–211.
- Tempini, N.** (2017). Till data do us part: Understanding data-based value creation in data-intensive infrastructures. *Information and Organization*, 27(4), 191–210.
- Tempini, N., & Del Savio, L.** (2018). Digital Orphans: Data Closure and Openness in Patient-Powered Networks. *BioSocieties*, June. Retrieved from <https://doi.org/10.1057/s41292-018-0125-0>.
- Tempini, N. & Teira, D.** (forthcoming). The Babel of Drugs: Data Journeys and Evidential Pluralism in Pharmaceutical Regulation. In Leonelli, S., & Tempini, N., (eds.), *Varieties of Data Journeys: Data Processing and Movements Within and Across Practices*, forthcoming.
- Truong, T. H., Weeks, J. C., Cook, E.F., et al.** (2011). Altruism among participants in cancer clinical trials. *Clin Trials*, 8, 616-623.
- Valor, E.** (2012) Response-Able – EricValor.org. *EricValor.org*. Retrieved from: <http://www.ericvalor.org/response-able/> (accessed 29 August 2016).
- Vayena, E.** (2014). The next step in the patient revolution: patients initiating and leading research. *BMJ: British Medical Journal*, 349.
- Vellar, A.** (2018). “#anawarrior Identities and the Stigmatization Process: An Ethnography in Italian Networked Publics.” *First Monday*, 23(6). Retrieved from <http://firstmonday.org/ojs/index.php/fm/article/view/8412>.
- Wicks, P., Massagli, M., Frost, J., et al.** (2008). A patient-led trial of lithium in ALS using the internet. *Amyotrophic Lateral Sclerosis*, 9(sup1), 59–66.
- Wicks, P., Vaughan, T., Massagli, M., et al.** (2011). Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm. *Nature Biotechnology*, 29(5), 411–414.
- Wicks, P., Heywood, J., & Vaughan, T.** (2012). Waiting for p<0.05. *Figshare*. Available from: http://figshare.com/articles/Waiting_for_p<0.05/96802.
- Wicks, P., Vaughan, T., & Heywood, J.** (2014). Subjects no more: what happens when trial participants realize they hold the power? *BMJ* 348(jan28 9), g368–g368.
- Wikipedia.** (2016). “Sodium Chlorite.” In *Wikipedia, the Free Encyclopedia*. Retrieved from https://en.wikipedia.org/w/index.php?title=Sodium_chlorite&oldid=735247181.
- Wikipedia.** (2018). Ice Bucket Challenge. In *Wikipedia, the free encyclopedia*. Retrieved from https://en.wikipedia.org/wiki/Ice_Bucket_Challenge
- Zizzo, D.** (2010) Experimenter demand effects in economic experiments. *Experimental Economics* 13, 75-98.