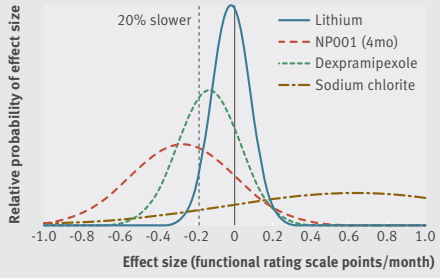
CLINICAL TRIALS **Paul Wicks, Timothy Vaughan, James Heywood**

Subjects no more: what happens when trial participants realise they hold the power?

Patients will hold us all accountable in new and necessary ways



Estimates of effect size for selected ALS treatments. Each line represents the probability distribution of the effect size; a high, narrow peak indicates that the effect size is more precisely estimated (generally because of larger sample size). More effective treatments will be centred towards the left[14]

The social contract of the randomised controlled trial is imbalanced: patients adhere to arduous protocols, are randomised to placebo, and are blinded to their health status. Although most participants (>90%) would like a lay summary of results,[1] only a minority (<10%) receive one,[2] with the remainder left with the option of paying around $30 (£18; €22) to read the results once the study is published in a peer reviewed journal.[3] Such imbalances may have contributed to an emerging movement, enabled online by "patient powered research networks,"[4] in which participants have begun systematically to unblind themselves, pool their data, parse literature, conduct statistical analyses, and post their findings online.

In 2007, patients with amyotrophic lateral sclerosis (ALS) used Google to translate an Italian conference abstract suggesting that lithium carbonate might slow their illness.[5] In a publication titled "Lithium delays progression of ALS" 16 patients treated with lithium (all of whom survived 15 months) were compared with 28 control patients (a third of whom did not survive the trial).[6] Within six months of the abstract's publication 160 patients reported obtaining lithium off-label and tracked their progression using Google Spreadsheets and the validated ALS functional rating scale (ALSFRS-R).[7] A patient in Brazil and a caregiver in the United States initiated this patient led study, raising the question of where ethical oversight lay.[8 9]

Our patient network, PatientsLikeMe, already allowed entry of ALSFRS-R scores but added tracking of lithium blood concentrations, data entry reminders, and monitoring by nurses to curate reported side effects. We presented data indicating that lithium was ineffective within nine months of the randomised controlled trial[10] then published longer term follow-up data with more sophisticated analyses in an open access *Nature Biotechnology* paper, which included the entire de-identified dataset as supplementary material.[11] Four randomised controlled trials subsequently replicated our negative findings.[12]

Shortly thereafter randomised controlled trials of two new drugs were under way: of NP001, manufactured by Neuraltus (in a phase II trial) and Biogen's dexpramipexole (phase III). Participants in these trials shared data while formally enrolled under protocols in which they were meant to be blinded and unaware of their ALSFRS-R score. They charted their own progress, seized on known side effects such as neutropenia in an attempt to unblind themselves, and used rudimentary statistics to analyse the efficacy of both drugs. Around a third of the total NP001 group and 10% of US dexpramipexole patients recorded data online. A third experimental group was formed when some patients read the patents on NP001 and inferred that the industrial cleaner sodium chlorite might be the active ingredient. Some patients who could not enroll in the trial started ingesting industrial sodium chlorite orally or intravenously.[13]

Although we had data on fewer participants than for the lithium trial, we shared our analysis of all three groups through Figshare on the eve of the unblinding of the dexpramipexole trial.[14] With important caveats, we estimated that dexpramipexole was below the cusp of providing a clinically significant benefit[15] and NP001 just above it, but with confidence intervals that were too wide to draw a reliable conclusion (figure). Alarmingly, patients ingesting off-label sodium chlorite progressed worse than expected (figure). Biogen's dexpramipexole trial reported no effect,[16] and funding is awaited for a phase III trial of NP001. When ALSUntangled used our data to warn against the potential dangers of sodium chlorite, its off-label use diminished.[17]

The concept of "scientific altruism" may be being trumped by "maximise your chance of survival." For better or worse, digital tools enable greater self knowledge and rapid dissemination. The consequence is that scientific design, informed consent, and ethical oversight can be short circuited by patient led "disobedience." Some drug companies will choose to share their clinical trial data (as AllTrials suggests), but even if they don't the data can become available if participants choose to share their data themselves, something that will only be enhanced by patient access to electronic medical records. Today members of PatientsLikeMe report tracking their outcomes in over 400 randomised trials. Patients increasingly realize that they are both statistically and literally the "power" in trials and we need to build systems that redress the imbalance. If we collectively do nothing, a phase III study might be rendered scientifically null by a critical mass of participants making intentional protocol violations on PatientsLikeMe, Facebook, or Twitter.

This would be a tragic outcome. To prevent that, we propose forging a new social contract that maximises both scientific discovery and patient autonomy, setting the stage for better trials with more engaged participants. Together we can develop rigorous new methods to include patients in selecting therapies, protocol design, recruitment, feedback, lay summaries, publications, and assessment of value. We are encouraged by the development of an online "open research exchange" that allows researchers rapid access to patients for concept elicitation and psychometric validation during the development of patient reported outcome measures,[18] which are now required by the FDA.[19] We believe that patients may surprise many of us with their ability to identify obstacles to trial enrolment, prioritise the outcomes they truly value, and help us learn what works in the real world, not just in trials. With the new tools at their disposal patients will hold us all accountable in new and necessary ways. Patients themselves have already laid much of the groundwork; let's ask them to continue building on these new systems together as equals.

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TOBACCO CONTROL **Simon Chapman**

When will the tobacco industry apologise for its harms?

It agrees to corrective advertising after 15 years of legal kicking and screaming

Last week four tobacco companies finally reached agreement with the US Department of Justice to fund large scale corrective advertising about five areas of tobacco control.[1] Each advertisement will include the statement that these companies "deliberately deceived the American public."

The case against the companies began in 1999 and involved a 2006 judgment by a US District Court judge, Gladys Kessler, that the companies had misled the public for decades. Kessler's judgment came in a Department of Justice lawsuit alleging that the four companies had violated the Racketeer Influenced and Corrupt Organizations Act, an anti-racketeering statute. The companies dragged out the case for nearly 15 years, and further appeals are still possible on the wording of the correctives that they will have to pay for. These will appear in newspapers and on prime time television for a year.

Since the public release of some 80 million pages of previously internal and often highly explicit documents after the 1998 Master Settlement Agreement, the general view is that the tobacco industry has been forced to take a public truth serum. Because of the revelations in the documents, many thought that the industry could no longer engage in its standard denials of health effects and addiction; that it would try to hide its intense interest in ensuring that as many children as possible were beguiled by smoking. On the companies' websites, unctuous, weasel worded statements followed the agreement, advising smokers that medical scientists had found smoking to be a serious health hazard. Earnest requests intensified for cigarette makers to be seen as "stakeholders" in public health efforts. Watch us reduce the harms from smoking through product innovation, they promised, just as they had for decades previously.

But just as snakes shed their skins only to replace them with more of the same, the global tobacco industry continues its business as usual. A friend teaching in Myanmar (Burma) emailed me last week describing sales promotion staff for foreign brands openly handing out free cigarettes to children. Indonesia, the world's fourth largest nation—where smoking among men is almost compulsory and tobacco control policies are almost non-existent—is a paradise for the transnational tobacco industry wallpapered with tobacco advertising by British American Tobacco, Philip Morris, and local companies. The industry has claimed at length that it supports "effective" tobacco control while continuing to lobby, as if its economic life depended on it, against any law or policy that threatens its bottom line, such as plain packaging.

Tobacco companies are widely regarded as corporate pariahs whose conduct over many decades has set the lowest ethical benchmark. An online search for the phrase "just like the tobacco industry" brings up thousands of hits: writers reaching for an analogy use the tobacco trade as a way to calibrate the deceitful, duplicitous, irresponsible venality of a large variety of industries. It is not hard to explain why such a reputation is justified.

The obvious starting point is the industry's peerless record in sending its best customers to early graves: one hundred million last century, and a forecast one billion this century. Stalin's observation that "one death is a tragedy, a million deaths is a statistic" tends to inure people from the realities of these early deaths and the suffering that often precedes them.

My wife is a primary school teacher with 35 years' experience. She has often described incidents where 5-9 year olds with poorly developed moral compasses have been caught red handed while bullying, stealing, cheating, or lying but have unblinkingly denied their wrongdoing regardless of the evidence before them. More than once she's suggested that such a child might one day make an ideal applicant for a job in a tobacco company.

Writers reaching for an analogy use the tobacco trade as a way to calibrate the deceitful, duplicitous, irresponsible venality of a large variety of industries

Different legal, moral, and religious codes worldwide tend to share basic principles on how to deal with those who have done serious wrong. Sentencing often notes any evidence of contrition, and civilised societies and judiciaries tend to look for five broad preconditions when considering punishment:

- Full public acknowledgment of the misdeeds and the harms caused
- Apologising for these harms
- Promising never to repeat them
- Making good the damage done, and
- Undertaking some form of public penance to symbolise a changed moral status.

Like many caught-out 5 year olds and recidivist adult sociopaths, the tobacco industry has done none of those things. It is reluctantly implementing corrective advertising after 15 years of legal kicking and screaming, while schmoozing with the global corporate social responsibility movement, publicising its donations to carefully selected charities—and still trying to sell as much tobacco as possible, regardless of the misery it causes.

It has all the ethics of a cash register.

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