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

Patients will hold us all accountable in new and necessary ways

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The social contract of the randomized controlled trial is imbalanced: patients adhere to arduous protocols, are randomized to placebo, and are blinded to their health status. Although most participants (>90%) would like a lay summary of results, only a minority (<10%) receive one, 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. Such imbalances may have contributed to an emerging movement, enabled online by "patient powered research networks," 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. 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). 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 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 analyze 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.

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. With important caveats, we estimated that dexpramipexole was below the cusp of providing a clinically significant benefit 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 chloride progressed worse than expected (figure). Biogen’s dexpramipexole trial reported no effect, 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.
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 centered toward the left.

The concept of “scientific altruism” may be being trumped by “maximize 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 randomized 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 maximizes both scientific discovery and patient autonomy, setting the stage for better ways. Patients themselves have already laid much of the groundwork; let’s ask them to continue building on these new systems together as equals.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare PW, TV, and JH are employees of PatientsLikeMe and own stock or stock options in the company. The PatientsLikeMe research and development team has received research support from pharmaceutical companies and private foundations.

Provenance and peer review: Not commissioned; not externally peer reviewed.

Cite this as: BMJ 2014;348:g368

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