A QUESTION OF CONTROL

Clinical-trial participants and their carers are gaining influence over how experiments are run. As they take to social media, that could make things messy for the science.

BY HEIDI LEDFORD

Amber Sapp was browsing the Internet late one night in August when she happened to find out that her 12-year-old son's clinical trial had failed.

Every four weeks for two-and-a-half years, she had shuttled Garrett to a hospital nearly six hours away. There, he was prodded and pricked with needles in the hope that the antibody treatment being tested would reverse a devastating genetic disease called Duchenne muscular dystrophy. But an early data analysis, Sapp learnt, had shown that the treatment wasn't working.

The thought of wasting Garrett's limited time with a failed trial was hard enough. The news was all the more disturbing because it didn't come from the trial organizers, but through a Facebook post from another parent. "It was upsetting that we found out that way," says Amber. "It sent everybody on Facebook into a tizzy." Even Garrett's local clinical-trial coordinator, someone who should have had intimate knowledge of what was happening with the research, hadn't yet heard the news.

Some members of the Facebook group had regularly discussed how their children were faring in the trial, even speculating as to who was in the control arm of the study, receiving a placebo instead of the experimental treatment. Social-media interactions can empower those living with disease, and their families, to make informed choices about their health care and clinical trials. Some people have even united on social media to launch trials of their own.

It's part of a major shift in clinical research. A 2016 survey found that three out of every four major pharmaceutical companies had used a patient-advisory board to gather feedback on clinical-trial designs (S. Stergiopoulos *et al. Ther. Innov. Regul. Sci.*, in the press). And several scientific journals, including *The BMJ*, have included patients as peer reviewers of submitted manuscripts.

But Amber's experience also shows how trial participants are disrupting the usual flow of information in clinical studies. As participants become more empowered, the natural tensions between their goals and those of the researchers become more pronounced. Online discussions threaten to compromise trial integrity when participants join forces to work out who is receiving a placebo. Discussing potential side effects can also influence results, particularly when the symptoms are subjective. Drug companies have yet to report any cases of such actions causing irrevocable damage to a trial, but some researchers worry that information-sharing by participants could sink trials or weaken their findings.

Now, scientists are grappling with how best to work with — and for — the people they are trying to study. "The fallback for most researchers is, 'I have to get these patients to change,'" says Craig Lipset, head of clinical innovation at Pfizer, a pharmaceutical company based in New York City. "But I think there are other things we'll have to take more seriously in the design of studies."

TRIALS AND TRIBULATIONS

By the time Garrett turned three, Amber, who works as a physical therapist in Nashville, Tennessee, noticed that something was off. When he tried to jump, he couldn't get his feet off the ground, and he looked unstable climbing stairs. Amber asked Garrett's paediatrician for answers, but was told that, in time, he would probably catch up with his peers.

One day, she watched Garrett stand up from sitting on the floor, and the answer came to her. The way that he used his arms to help raise his body was not just a quirk: it was a hallmark of muscular dystrophy that she had studied in school. "It just took me out of the blue," she says. "I thought, 'Oh my God, that's what it is.'"

Duchenne muscular dystrophy (DMD) is a genetic disorder that affects mainly boys, and is caused by mutations in a gene called *DMD*. The dystrophin protein that it encodes is important for maintaining healthy muscle cells; without it, muscles gradually deteriorate. Many people with the disorder need a wheelchair by the time they are 12, and will have difficulty breathing by their late teens.

Amber and her husband spent the next four years consumed by grief. "We refer to them as the dark days," she says. "We couldn't do anything: couldn't function, couldn't talk to other parents, couldn't reach out for resources."

When Garrett was about seven, Amber began to open up. She ventured online and met other carers, chatting to parents of older boys who were grappling with later stages of the disease. "Watching them go through that process of clinical trials and the difficulties — I guess maybe that's where we learned about clinical trials," she says.

Medical centres and pharmaceutical companies have noticed the power of social media to draw in patients. Some have launched efforts to advertise trials, for example to targeted Facebook groups. The hope is that it could help trial recruiters to tackle a growing problem: a shortage of participants that has been stretching the time required to do clinical research.

As companies increasingly focus on rare diseases and precision medicine tailored to a specific subset of patients, it has become more difficult to find willing volunteers who meet the necessary criteria. Recruitment and retention rates are the worst that they've been since the Tufts Center for the Study of Drug Development started tracking them 20 years ago, says Kenneth Getz, who studies clinical trials at the centre in Boston, Massachusetts.

"Industry-wide, everybody recognizes this as a huge problem," says James Nolan, chief executive at InClinica, a contract-research organization in Wayne, Pennsylvania, that conducts clinical trials. "It's not going away — it's going to get much worse."

The recruiting problem has given potential participants leverage and altered their relationship with clinical researchers: a trial that is too burdensome, or forces many participants into a control group, could be doomed to failure from the start. "Many of the companies understand that we can't do this now without patients being equal partners," says Sohini Chowdhury, deputy chief executive of the Michael J. Fox Foundation for Parkinson's Research in New York City.

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“WE COULDN’T DO ANYTHING: COULDN’T FUNCTION, COULDN’T TALK TO OTHER PARENTS, COULDN’T REACH OUT FOR RESOURCES.”

Amber Sapp looks to many places for guidance on experimental treatments for her son, Garrett, who has Duchenne muscular dystrophy.

So drug firms and medical centres have enlisted the aid of patient advisory boards to evaluate clinical trials. Participants are getting the opportunity to demand trials with fewer procedures, or more comfortable conditions. Lipset recalls a protocol for a trial in atopic dermatitis, a form of eczema, that would have required participants to stop using all their usual medications for six weeks to clear their system of drugs. A panel of people with dermatitis was shocked: going that long without relief was unfathomable. "The washout period made perfect sense scientifically," Lipset says. "But to the humans involved it was completely intolerable."

The team adjusted the protocol, rather than risk launching a trial that was destined to fail. An evaluation of 30 patient advisory boards found that many were making recommendations about the convenience and feasibility of study visits, and the schedule of procedures performed (A. Anderson and K. A. Getz *Ther. Innov. Regul. Sci.* **52**, 469–473; 2018). The advisory boards have good cause to push back. Getz says that as many as one-third of procedures — such as blood tests or biopsies — performed during clinical trials are not crucial to the applications for drug approval.

"Part of the balance is recognizing that although good science is great, it also has to be feasible and convenient," says Getz. "That's where patient engagement has completely changed the philosophy."

In some cases, patients and their advocates band together to launch clinical studies of their own. When Katherine Leon had a heart attack in 2003, soon after the birth of her second child, she was told that it was just something that can happen after having a baby. But Leon eventually learnt that she had spontaneous coronary artery dissection (SCAD), a rare condition that few community physicians are familiar with.

Leon says that she was "randomly googling around" one night when she stumbled on a message board for women with heart disease. Over time, a community of people with SCAD emerged. Then she started keeping a record of their symptoms and disease course: at what age were they diagnosed, which artery was affected and whether it might have been related to pregnancy. She took her data to a physician and convinced her to launch a research project to catalogue features of SCAD. "It was huge, because we felt as patients that we had definitely initiated it," Leon says. "When I compare what they've discovered so far with the anecdotal data in my little proposal, it jibes pretty well — and that's all just from people having conversations."

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A PLACEBO EFFECT

Garrett's first clinical trial was designed to test whether a drug called tadalafil (Cialis) would help to keep boys with DMD walking. The protocol was relatively simple: just a few pills in the morning with a spoonful of apple sauce.

But Garrett's ability to walk continued to decline. Faced with a degenerative disease and a ticking clock, the family wrestled with worries that he should move on to another trial. Eventually, Amber called the coordinator and said it was time to consider leaving the trial and to look ahead to the next one.

Online, Amber could see carers facing the same decision in various clinical studies. Some parents posted videos of their children walking or climbing stairs, and speculated as to whether they were receiving the active drug. If they suspected that their child was taking the placebo, a number of parents openly talked about their plans to withdraw from a study. "Nobody wants to be in the control," says Amber. "We don't have a lot of time with our boys. Nobody has time to waste."

Trial participants have long sought to avoid being in the placebo group; they would rather have the chance to benefit from an experimental drug. The advent of social media has made it much easier to 'unblind' a study, says Pat Furlong, founding president and chief executive of Parent Project Muscular Dystrophy, an advocacy group based in Hackensack, New Jersey. "Before social media, you wouldn't know the other people in that trial," says Furlong, whose two sons had DMD.

Bioethicist Lindsay McNair first became aware of the phenomenon while working for Vertex Pharmaceuticals, which is now in Boston. The company was running a clinical trial of a potential treatment for the hepatitis C virus in 2007 when a researcher reported activity from its participants on MedHelp.org, a health-related social-media site. Some participants said that they were having their blood tested by an outside laboratory to find out their levels of virus, to guess who was receiving the active drug and who the placebo.

McNair, who is now the chief medical officer at WIRB-Copernicus Group in Boston, a company that performs ethical reviews of clinical trials, decided to take a closer look with her colleagues. They read publicly available online health discussions over the course of about a year, noting any that might affect a study's outcome. They found that participants were comparing the appearance and taste of their pills, even crushing them up to get a better look (S. W. Glickman *et al. J. Empir. Res. Hum. Res. Ethics* **7**, 71–80; 2012). Some of the activity, McNair recalls, was on Yahoo Finance company message boards — and at least one financial analyst cited data from these boards in his or her predictions about the trial and in recommendations about Vertex stock.

There is no evidence that online unblinding affected any of these trials. But anecdotes such as these are troubling drug-makers. "We have largely turned a blind eye to the use of social media," says Lipset. "It's only a matter of time before Facebook jeopardizes the scientific integrity of a study."

Sharon Terry, president and chief executive of the advocacy group Genetic Alliance in Washington DC, recalls working on a 2013 trial testing high doses of magnesium in 44 people with a rare genetic disease, pseudoxanthoma elasticum, which affects elastic fibres in connective tissue. "The group of individuals all got on Facebook and figured out pretty fast which were in the control," she says.

In some online conversations that Furlong and McNair have seen, parents discussed leaving a trial if they didn't see any improvement. "Dropouts are super frustrating," says Brian Loew, founder and chief executive of Inspire, a social-media site that caters to people with medical conditions and their carers. This can delay the completion of a trial and raise warning flags to reviewers at regulatory agencies.

And when participants share details about which side effects they might be experiencing, they can induce others to wonder about — and then perhaps report — similar symptoms. The same could be true of a key clinical endpoint of the trial, particularly if that endpoint is somewhat subjective, such as a ranking on a pain scale. And, sometimes, participants swap information about entry criteria, such as the score on a cognitive test that might be required to join an Alzheimer's disease study, says Lipset. Armed with that knowledge, those who want to join the study can prepare accordingly.

Amber says that she generally stayed quiet during such online discussions, but it was still painful to see other families talking about possible improvements in their sons' ability to walk or climb stairs. Garrett had experienced no such progress.

After the first clinical trial, the family began shuttling Garrett to Cincinnati, Ohio, for the antibody trial. The drive, the needles and the time spent in the hospital all took their toll. "Clinical trials are exciting, frustrating and frightening," says Furlong. "There is certainly some altruism. But I can say to you — especially in rare disease, especially when so many people with rare disease are children — what you want, as a caregiver, is benefit."

When Garrett turned 11, Amber held her breath. At that age, he would have to give his own assent to remain in the antibody trial. Garrett agreed, but Amber suspects he bowed to his parents' wishes.

Garrett Sapp (right), a 12-year-old who has Duchenne muscular dystrophy, might be eligible for gene-therapy trials. But the decision to enrol is a complex one.

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Furlong recognizes that anxiety. "There's a moment when your son looks at you and says, 'I don't think I want to do this. I miss my friends. I don't want them to stick me another time.'" she says. "As a parent, you are second-guessing: 'Is this the right thing?'" Often, parents of children with DMD will share information online because they are desperate to hear someone, anyone, tell them that their child is improving, she says.

Researchers are still grappling with how best to handle such online discussions. Inspire, which displays targeted advertisements for clinical trials to some of its 1.5 million members, expressly prohibits discussions that could affect clinical-trial results, such as comparing possible side effects or discussing ways to game eligibility criteria to gain entry to a trial. The site employs moderators to check posts after they go live.

"We had a lot of internal debate about it," says Loew of the policy. "On the one hand, people should be able to talk about whatever they want. But we decided that you can actually do harm to the science." Other sites, however, such as Twitter and Facebook, have no such policies.

Some companies running trials have inserted guidance about such communications in the consent forms that study participants sign. But that can backfire and cause undue worry, or limit participants' ability to find support online, says Lipset. "You can see in online communities where participants are scared that they have just signed a confidentiality agreement and will be thrown in jail for posting."

Lipset says that investigators will have to become savvier about how they set up their trials. This could include firming up eligibility criteria for a study, he says, to make them less subjective — and harder for a potential participant to game.

Some firms are hiring outside companies that specialize in listening in on social media, to report back when conversations veer towards unblinding a trial. Others are looking to facilitate the groups. Bristol-Myers Squibb, headquartered in New York City, partnered with Inspire to launch a moderated online community in April, in which patients in a given trial can support one another and discuss their condition, says Loew. This idea is catching on, says Lipset. "We're maturing to a place where people have to take seriously even the potential to create online communities for your research participants, so that people can have a safe place to share. Because they want to share."

THE TOUGH DECISIONS

When Amber learnt that Garrett's second trial had ended, it was time to weigh options for the next one. But Garrett's choices are narrowing. He stopped walking this summer, and few trials will take boys who are no longer able to walk.

The family then considered a gene-therapy trial. It was a difficult decision. "Gene therapy is huge and promising and terrifying at the same time," Amber says.

It comes with a slew of new challenges, and risks. The virus that is used to deliver genes could raise an immune response that would make Garrett ineligible for future gene-therapy trials. And if he's in the placebo arm, he won't know whether he's eligible to receive the actual treatment until a year has passed. Added to these tensions would be three muscle biopsies performed under general anaesthesia, procedures that are particularly unnerving for people whose muscle is wasting away. "If the trial we had just come out of was, to us, pretty invasive, this is ten times that discomfort," Amber says.

It's a gamble. In October, Amber and her family opted to hold off from joining the gene-therapy trial. While they were weighing their options, Amber decided not to rely on other parents on social media to help with the decision. Instead, she stuck to her "board of directors", a few trusted medical professionals. "Social media has such a wide pool of people that you don't always know that the answers you're going to get are on the level," she says. "It's hard," Amber adds. "Time is limited." ■ SEE EDITORIAL P.293

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