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FEATURE

OPEN DATA

# Tug of war for antiviral drugs data

**Julia Belluz** hears from both sides in the lengthy battle between the drug giants and researchers that led to the release of full clinical trial data on neuraminidase inhibitors. Does the release of these files herald a more transparent era?

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Tom Jefferson can recite the details of every published study on the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza): date of publication, authors' names, journal title, research question, methods, funder, and findings. But what has occupied the mind of the physician-academic from Cochrane's Acute Respiratory Infections Group for the better part of five years is another detail about the science behind the influenza antivirals: that much of it has been missing or unpublished.

Before he knew better, in 2006, Jefferson waded into the evidence and released a Cochrane systematic review about the neuraminidase inhibitors based on published research findings. He and his coauthors found that the drugs decreased the risk of influenza complications and hospital admissions in adults.

By 2009, however, Jefferson's opinion had started to shift. Europe was in the clutches of the influenza A/H1N1 panic, and he and his peers were asked to update their analysis of the flu drugs. Just as he was stepping into the research again, a letter arrived from a Japanese paediatrician, Keiji Hayashi. He was concerned that he could not verify the data that supported some of Jefferson's conclusions about oseltamivir. In particular, he pointed out that the claims that the drug reduced secondary complications and hospital admissions were based on a 2003 analysis coauthored by Roche employees. Hayashi also noted that eight out of the 10 trials included in that analysis were never published in peer reviewed journals. In other words, Cochrane's previous studies on the influenza treatments were based on an incomplete and possibly biased picture of the evidence.

The Cochrane team didn't have an answer for Hayashi. They didn't even know about the existence of the unpublished research. "This is when I started thinking there is something wrong," Jefferson now recalls. He felt duped and worried that his previous work was misleading physicians, patients, and public health authorities. "I don't like being made a fool," the former British military physician, told the *BMJ*. "I trusted literature. I trusted people who were doctors and researchers. I trusted the archive. I trusted Roche."

That trust evaporated. In December 2009, Jefferson and the Cochrane group published an updated review on neuraminidase inhibitors in the *BMJ*.[1] This time, the researchers asked Roche for raw data from the unpublished trials. Roche, in exchange, asked them to sign a confidentiality agreement with a secrecy clause. The academics refused and went ahead with their review, noting the inconsistencies in the evidence and omitting the studies based on unpublished trials. Without the raw data about oseltamivir, they wrote that the drug may work no better than aspirin. They also could not say whether it truly reduced the risk of serious complications and hospital admissions.

## Data promises

On 8 December 2009, the same day the review was released, Roche announced that it would give the Cochrane team full clinical study reports about oseltamivir "within the coming days." (These documents are usually prepared by industry for regulators and include far more detailed reporting of trials than appears in published articles.) But the dialogue between Roche and Cochrane didn't end with that promise. Instead, it marked the beginning of a lengthy tug of war over data. By mid-2010, GlaxoSmithKline entered the fray, promising to hand over its unpublished research about their influenza antiviral, zanamivir.

According to the Cochrane researchers, accessing all the evidence necessary to answer the question of whether neuraminidase inhibitors did what the drug giants claimed took four fraught years, dozens of letters and emails to key stakeholders within the drug companies and outside, regulatory changes, and public and political pressure through open data campaigns by the *BMJ* and the AllTrials advocacy group. "We were met with refusal," says Jefferson. The drug companies stalled and stonewalled, releasing their data only in incomplete pieces and breaking promises about transparency along the way.

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Suddenly, last year, the tug of war ended. Both GSK and Roche gave the Cochrane group what are believed to be complete sets of clinical study reports and regulator documents on their neuraminidase inhibitors with no strings attached. For the researchers, this seemed like an about face. "After all this worry and concern about data protection, they just couriered them over to me," said Carl Heneghan, director of the Centre of Evidence-Based Medicine at Oxford University, who was also working on the Cochrane reviews.

Early last year, five CDs arrived at his Oxford University office from GSK, and by September, six more were delivered from Roche. In total, the discs contained more than 160 000 pages of clinical trial information about zanamivir and oseltamivir. These data underpinned the two new reviews on the drugs, which have much less favourable conclusions—such as the new concerns about neuropsychiatric harms—than the early studies.[2 3] The researchers are grateful, but they wonder why the companies finally decided to relent and reveal unpublished data that had been hidden from public view for so long.

## Unavoidable delay

Representatives of the drug companies tell a different story. They describe feeling bullied and misunderstood by the researchers. Instead of stalling, pharmaceutical executives on the oseltamivir and zanamivir files say that they were scrambling behind the scenes to figure out how to respond to a new kind of request for more granular clinical trial data. They argued that privacy and legal concerns, logistical challenges, and miscommunications between the two camps halted progress. The companies didn't crack under pressure last year; instead they describe a slow and gradual learning curve that culminated in the landmark release of their data trove. "It seems [the data have] been dragged out of the company with everyone kicking and screaming not to let it go," said GSK's president of pharmaceuticals research and development, Patrick Vallance. "That was not my perception at all."

From Vallance's vantage point, GSK was keen to give the Cochrane group the data they wanted all along—but it first had to find it. Doing so was a herculean task. "These are studies going back a long way, stored in all sorts of different parts, in all sorts of different places. People don't expect to have to go and pull out everything again." GSK estimates 15 to 20 people worked on the file part time over three years. "Because these workers were doing the tracking down in addition to their day jobs," said Vallance, "There may have been an element in sometimes not feeling this was the top of their priority list."

When GSK found all the information the Cochrane group requested, the drug company offered the batch of files to the researchers if they would sign a confidentiality agreement. "Cochrane weren't willing to sign something that said they'd keep it to themselves," said Vallance. The academics wanted to be able to publish the data so that others could replicate their findings. They argued this would be a giant step towards open data about public health medicine that had been stockpiled to the tune of billions globally.

For the drug makers, this presented a challenge: they now had to figure out how to conceal patient information in the clinical study reports, which are usually written for regulators and not the public. Jeffrey Helterbrand, the global head of biometrics at Roche, says, "Our main conversations were around, 'How do we balance protecting patient privacy versus meeting the altruistic desires of patients and society to have greater access to this kind of information?'"

Similarly, Vallance says, "There was an issue about—not whether to do it—but how to do it in a way to protect confidentiality." GSK hired a third party to redact the zanamivir trials. "That had to be done form by form," he explains, and it was a learning process. At first, he says, the people hired to do the job overinterpreted privacy laws and blacked out more pages than was necessary. "That fuelled suspicion on the other side that something was deliberately being hidden," he says. "I could sense that that was leading to a log jam of communications."

Vallance says that the Cochrane group interpreted the mistake in another way: "The next thing that we saw was the [comment] in the *BMJ* saying they were appalled by the degree of the redaction. Frankly, as a lifelong academic researcher, I would have thought that the right thing to do was to write to us and say, 'This is over-redacted.'"

Instead of prompting swift action, the letters had the opposite of the desired effect internally. "Put yourself in the position of a scientist within GSK trying to do this because we have said we're going to do it —and we're absolutely clear we want to do it—and being treated as though somehow your intent was bad, which is how they felt." He adds: "It's not easy to motivate a group of people who are being beaten."

These miscommunications slowed things down, says Vallance. "What was interesting to me was the degree of mutual misunderstanding as to what was actually required. At one stage, I saw a very formal email exchange with long gaps between emails rather than what seemed to me was the obvious way to get to the real issue: to pick up the phone and talk to each other and say what is it that you haven't got that you now need."

Even without communications mishaps, Roche representatives say that until very recently the conditions for data sharing weren't quite ripe. "Looking back to 2009, bear in mind how different the environment that we operated in then was compared to how it is now," said Barry Clinch, UK clinical lead for oseltamivir at Roche. Back then, few outside of industry and the regulators had even heard of a clinical study report, and there was no critical mass regarding open data in the pharmaceutical sector. "We are now in a situation where governments, health regulatory agencies, patients, and the industry at large all have a way of looking at data sharing now that is completely different to how it was in 2009. At that point, we were used to a very simple relationship with our regulatory bodies."

Clinch called the Cochrane researchers' request for clinical study reports unprecedented. "We didn't have an equivalent way to respond to a request that the Cochrane group was giving to us." He claims that the company had, before this, little experience sharing large amounts of patient level information with non-statutory bodies. Other similar requests—such as those from global collaborative research initiatives—were typically signed under confidentiality agreements.

There was also the ever present but little mentioned problem of competition among the pharmaceutical giants. Roche did not want to be seen to be moving out of step with the rest of industry, Clinch says. "When it was sufficiently mature, when we were clear about the direction we wanted to take, the direction that society could be comfortable with us taking, we started to share the CSRs."

## New era of openness

Though the drug companies and the researchers view the road to open data very differently, they agree that the release of the oseltamivir and zanamivir files heralds a more transparent era.

The Roche and GSK executives say that the experience has helped them shape systems for making their science more freely available. As Helterbrand puts it, "I'm optimistic this is a big step forward, not just for industry but for researchers in general who deal with clinical trial data."

In 2012, GSK announced a web portal for sharing anonymised patient level data, which inspired the recent launch of the joint website ClinicalStudyDataRequest.com, where independent researchers can request patient level data from clinical studies by GSK, Roche, Boehringer Ingelheim, Novartis, Sanofi, and ViiV Healthcare. (To date, 13 requests for GSK data have been approved and there are 16 making their way through the system. None has been turned down. Roche has received four requests and all are currently being considered.)

Third party researchers can also now request clinical study reports from Roche, while GSK has committed to post documents automatically alongside their online trial registration. GSK also leads a steering committee—including representatives from academia and other drug companies—which is working on getting an independent, third party such as the Wellcome Trust to govern access to data.

Still, not all drug companies are on side with the transparency push. Last year, AbbVie sued the European Medicines Agency to block the agency's plan to release clinical trials data from drug companies. Representatives from GSK and Roche would not comment on the case but said that they believe the trend among drug companies is moving in the opposite direction. Vallance observed a pack effect among industry leaders. Everyone is going to be sharing data, he said. "The fact we've managed to do it shows it's possible; it shows it's not this great risk that people have sometimes claimed it is."

Looking forward, he is optimistic that these gestures will lead to warmer relations with academia. "I hope as we get to the new era, that suspicion will break down and will allow a peer scientist to peer scientist interaction."

The academics also acknowledge progress, but they say any thawing of relations may take some time. "I would wish for warmer relations and less scepticism as well, which will hopefully occur naturally as trust grows," says Peter Doshi, assistant professor at the University of Maryland School of Pharmacy and associate editor at the *BMJ*. "But the track record is that of fundamental problems in transparency, with serious ramifications to patient safety, which have led to dramatic declines in trust." For these reasons, and because the Cochrane group was so geographically dispersed, Doshi says it was important to get all negotiations with industry in writing—even if it slowed down the process.

Others remain sceptical about the drug companies' supposed difficulties with redacting study reports and establishing methods for data sharing. Iain Chalmers, one of the founders of the Cochrane Collaboration and an advocate of open data, says that the so called challenges were just diversions from core issues about the effectiveness of flu drugs. "The key thing is that only two out of 10 studies on Tamiflu were ever published. That's not to do with individual patient data." (Roche responded by saying that, unlike today, 10 years ago it was not standard policy within industry or Roche to publish all its clinical trial data.)

Over the years Jefferson counted at least 12 reasons from Roche why it couldn't hand over its data. These include everything from patient confidentiality to the Cochrane group's failure to sign a confidentiality agreement to Roche's belief that the researchers had all the data they desired. "This is a smokescreen," Jefferson says. "How many more stories are we going to hear?"

If anything, Jefferson says his involvement in the battle for the oseltamivir and zanamivir data has made him more sceptical. "I do not trust fellow researchers. I don't trust journals. I don't trust the literature. Everything for me is marketing and publicity, unless proven otherwise."

Even with the latest transparency initiatives, industry still controls the data it produces. It decides who gets access, Jefferson says, and who doesn't. If clinical study reports are released to third party researchers, and companies have varying policies about redactions, vital data points—such as those about harms—might remain hidden. As Doshi wrote in a recent *BMJ* analysis, despite the widespread practice of off-label prescribing, all companies share trials only of approved indications and not those examining off-label uses.[4]

These individual failures to share data, says Jefferson, belie systemic information inequities at the core of medicine. Though the battle for data left him exhausted, and "cost my family and me a lot," he wouldn't give up because of what the Cochrane reviews of oseltamivir reveal: a gulf between conclusions based on syntheses of published research findings and those based on raw data. And he won't rest until that gap is closed.

"Tamiflu involves everyone," he says. "It involves public health bodies worldwide. It involves journals . . . the research community . . . the pharmaceutical industry. All these actors are responsible. The system is broken. It can't be fixed. It has to be redesigned."

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