

Bad Pharma

when it lands heads-up, I can convince you that this is a two-headed coin. But that doesn't mean I really do have a two-headed coin: it means I'm misleading you, and you're a fool for letting me get away with it. This is exactly the situation we tolerate in medicine, and always have. Researchers are free to do as many trials as they wish, and then choose which ones to publish.

The repercussions of this go way beyond simply misleading doctors about the benefits and harms of interventions for patients, and way beyond trials. Medical research isn't an abstract academic pursuit: it's about people, so every time we fail to publish a piece of research we expose real, living people to unnecessary, avoidable suffering.

TGN1412

In March 2006, six volunteers arrived at a London hospital to take place in a trial. It was the first time a new drug called TGN1412 had ever been given to humans, and they were paid £2,000 each.⁷ Within an hour these six men developed headaches, muscle aches, and a feeling of unease. Then things got worse: high temperatures, restlessness, periods of forgetting who and where they were. Soon they were shivering, flushed, their pulses racing, their blood pressure falling. Then, a cliff: one went into respiratory failure, the oxygen levels in his blood falling rapidly as his lungs filled with fluid. Nobody knew why. Another dropped his blood pressure to just 65/40, stopped breathing properly, and was rushed to an intensive care unit, knocked out, intubated, mechanically ventilated. Within a day all six were disastrously unwell: fluid on their lungs, struggling to breathe, their kidneys failing, their blood clotting uncontrollably throughout their bodies, and their white blood cells disappearing. Doctors threw everything they could at them: steroids, anti-histamines, immune-system receptor blockers. All six were ventilated on intensive care. They stopped producing urine; they

Missing Data

were all put on dialysis; their blood was replaced, first slowly, then rapidly; they needed plasma, red cells, platelets. The fevers continued. One developed pneumonia. And then the blood stopped getting to their peripheries. Their fingers and toes went flushed, then brown, then black, and then began to rot and die. With heroic effort, all escaped, at least, with their lives.

The Department of Health convened an Expert Scientific Group to try to understand what had happened, and from this two concerns were raised.⁸ Firstly: can we stop things like this from happening again? It's plainly foolish, for example, to give a new experimental treatment to all six participants in a 'first-in-man' trial at the same time, if that treatment is a completely unknown quantity. New drugs should be given to participants in a staggered process, slowly, over a day. This idea received considerable attention from regulators and the media.

Less noted was a second concern: could we have foreseen this disaster? TGN1412 is a molecule that attaches to a receptor called CD28 on the white blood cells of the immune system. It was a new and experimental treatment, and it interfered with the immune system in ways that are poorly understood, and hard to model in animals (unlike, say, blood pressure, because immune systems are very variable between different species). But as the final report found, there was experience with a similar intervention: it had simply not been published. One researcher presented the inquiry with unpublished data on a study he had conducted in a single human subject a full ten years earlier, using an antibody that attached to the CD3, CD2 and CD28 receptors. The effects of this antibody had parallels with those of TGN1412, and the subject on whom it was tested had become unwell. But nobody could possibly have known that, because these results were never shared with the scientific community. They sat unpublished, unknown, when they could have helped save six men from a terrifying, destructive, avoidable ordeal.

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That original researcher could not foresee the specific harm he contributed to, and it's hard to blame him as an individual, because he operated in an academic culture where leaving data unpublished was regarded as completely normal. The same culture exists today. The final report on TGN1412 concluded that sharing the results of all first-in-man studies was essential: they should be published, every last one, as a matter of routine. But phase 1 trial results weren't published then, and they're still not published now. In 2009, for the first time, a study was published looking specifically at how many of these first-in-man trials get published, and how many remain hidden.⁹ They took all such trials approved by one ethics committee over a year. After four years, nine out of ten remained published; after eight years, four out of five were still unpublished.

In medicine, as we shall see time and again, research is not abstract: it relates directly to life, death, suffering and pain. With every one of these unpublished studies we are potentially exposed, quite unnecessarily, to another TGN1412. Even a huge international news story, with horrific images of young men brandishing blackened feet and hands from hospital beds, wasn't enough to get movement, because the issue of missing data is too complicated to fit in one sentence.

When we don't share the results of basic research, such as a small first-in-man study, we expose people to unnecessary risks in the future. Was this an extreme case? Is the problem limited to early, experimental, new drugs, in small groups of trial participants? No.

In the 1980s, doctors began giving anti-arrhythmic drugs to all patients who'd had a heart attack. This practice made perfect sense on paper: we knew that anti-arrhythmic drugs helped prevent abnormal heart rhythms; we also knew that people who've had a heart attack are quite likely to have abnormal heart rhythms; we also knew that often these went unnoticed, undiagnosed and untreated. Giving anti-arrhythmic drugs to