Clinical Trial Transparency: A Key to Better and Safer Medicines

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Clinical Trials are the foundation of modern medicine, but regulators, doctors and patients often do not get to see the full picture about how safe and effective drugs and treatments are.

The results of around half of all clinical trials remain hidden. By now, it is widely accepted that this is a huge problem – a problem so massive that former US Vice President Joe Biden personally felt compelled to speak out about it, and the United Nations have called on governments to resolve it. However, few people realize that even government agencies often lack access to the information they need to decide whether treatments are safe and effective. As a result, the agencies we rely on to keep us safe from dangerous drugs and ensure that public health money is spent in the most effective manner are often forced to fly blind, and both patients and taxpayers are paying a heavy price.

The paper analyses **six case studies** in which opacity in medical research has directly harmed patients, taxpayers and/or investors, and illustrates how these harms could have been avoided through three simple solutions promoted by the AllTrials campaign: trial registration, results posting, and full disclosure of trial reports.

#	DRUG	SUMMARY OF CASE	SOLUTION		
			REG	POST	REP
1	**Lorcainide (Remivox)**	American doctors inadvertently killed over 100,000 people over the course of a decade because the results of a single clinical trial remained hidden.	**X**	**X**	
2	**Avandia (rosiglitazone)**	Regulators were unable to safeguard patient safety because heart attacks and strokes by trial participants were not accurately reported.	**X**	**X**	**X**
3	**Vioxx (Rofecoxib)**	Thousands of people died because the harms of the drug took years to become public knowledge. Shareholders lost $37 billion when it was withdrawn.		**X**	**X**
4	**Reboxetine (Edronax)**	Selective publication of clinical trials seems to have exaggerated the drug's benefits and understated its harms.	**X**	**X**	
5	**Antidepressants (SSRIs)**	Data on suicides by teenagers remained hidden from independent medical researchers and regulators, leaving other underage patients exposed to danger.			**X**
6	**Tamiflu (oseltamivir)**	Based on evidence that was partial and fragmented, governments and individuals spent $18 billion on a drug of questionable effectiveness.	**X**		**X**

The theoretical framework is based on the AllTrials campaign's three key solutions:

> **1. Trial registration.** All clinical trials should be registered, with a full trial protocol, before the first participant is recruited.
> **2. Results posting.** A summary of results, including information on the primary and any secondary outcomes measured and statistical analysis, should be posted where a trial was registered within one year of completion of a trial.
> **3. Trial reports.** All trial reports (Clinical Study Reports or their equivalent in non-commercial settings) should be posted online in full, with only minimal redactions.

However, this study was completed and published independently and should not be taken to reflect the views of AllTrials. All contents are the responsibility of the authors alone.

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Disclaimer:

This study was written by Till Bruckner and Beth Ellis, based on research conducted by Beth Ellis during 2016. The authors would like to thank the AllTrials campaign for support provided during the research phase. However, this study was completed and published independently and should not be taken to reflect the views of AllTrials. All contents are the responsibility of the authors alone.

CASE STUDY 1: LORCAINIDE

American doctors prescribing the drug Lorcainide to patients who had suffered heart attacks inadvertently killed over 100,000 people over the course of the 1980s. Back then, the results of clinical trials only became known when their results were published in academic journals; non-publication meant that potentially life-saving research was lost. Today, trial registries enable medical researchers and doctors to see what research has been conducted on a drug and what results have been found – but only if those conducting trials register them and report their results. The story of Lorcainide shows why it is vital that researchers, including those working at universities, register and report all clinical trials, even those that at first glance do not appear to show 'interesting' results.

How could this case have been prevented?

Trial registration	**X**
Results posting	**X**
Trial reports	

After a heart attack, many patients develop a dangerous disturbance in the normal rhythm of the heart, known as arrhythmia, which can lead to death. In the 1980s, doctors logically assumed that giving drugs to people who had suffered heart attacks to reduce irregularities in their heartbeats would prevent early deaths, and prescribed a range of antiarrhythmic pills to their patients. There was only one problem with this assumption: it was wrong – in reality, antiarrhythmics killed more people than they saved. According to an article published in the Journal of the American Medical Association

> *"[T]here are estimates that 20,000 to 75,000 lives were lost each year in the 1980s in the United States alone from inappropriate administration of antiarrhythmic drugs for secondary prevention of myocardial infarctions."*

How could this happen? Why did doctors not realize how dangerous these pills were?

During the early 1980s, when several new antiarrhythmic drugs came onto the market, doctors started routinely prescribing them to patients recovering from heart attacks. One of these drugs was Lorcainide (brand name Remivox; the literature commonly references the generic name), which was approved for use in the United States by the Food and Drug Administration in 1980 after having been shown to be effective against experimentally induced arrhythmias in animals, and against some arrhythmias in patients.

> In the same year, a group of British researchers decided to conduct a clinical trial to gauge the effect of Lorcainide on arrhythmias in patients who had suffered a heart attack. The team had expected a death rate of around 10% overall, and indeed, 10 out of the 95 trial participants died during the course of their research. The researchers noted that nine times as many patients died in the Lorcainide group than died in the control group – 9 out of 49 patients, as opposed to 1 out of 46 – but did not consider this finding particularly remarkable in light of the expected overall 10% rate. Meanwhile, also as expected, the trial data showed that Lorcainide did significantly reduce the occurrence of arrhythmia, so the group's findings did not appear to be particularly exciting.

Upon completing the trial in 1980, the researchers submitted their results to numerous journals, but were rejected time and again. According to Professor John Hampton, lead author of the paper:

> *"On completing our study we tried to publish our results. Full of enthusiasm we started with The Lancet and then tried two or three cardiology journals. The result was always the same – immediate rejection."*

In 1980, the manufacturer stopped production of Lorcainide due to unrelated concerns. John Hampton eventually stopped sending out his paper to journals, making it impossible for other researchers to learn about its results.

Meanwhile, other antiarrhythmic drugs remained on the market and continued to be regularly prescribed until, in 1988, a meta-analysis of 14 trials found that patients on Lorcainide were 30% more likely to die than those on alternative treatments. A separate 1989 meta-analysis of eight trials also showed a significant increase in mortality rates among patients on Lorcainide.

Meanwhile, John Hampton's study, which contained the earliest indication that antiarrhythmic drugs might do more harm than good, remained unpublished. He later recalled that

> *"At a coffee break in 1993, someone remembered our old Lorcainide study and we realised that it was a perfect example of many of the failings of clinical trials. I suppose we had always felt that we had a moral duty to publish it…so we tried again, [and] again, the high-impact factor journals were not interested… At the time, the term 'publication bias' was beginning to appear in the journals, suggesting that the clinical research community was serving up for publication a biased sample of their research."*

Professor Hampton and his colleagues decided to renew their efforts at publication, and their paper finally came out in 1993, 13 years after their initial attempts. By then, doctors had already stopped prescribing anti-arrhythmics, and pharmaceutical companies had withdrawn them from the market. A study that might have saved tens of thousands of lives had instead become a sad cautionary tale.

Today, researchers no longer need to rely on academic journals to make their clinical trial results publicly available. They can easily and rapidly post their findings on one of several clinical trial registries. However, many individual researchers, companies and universities still fail to post results – despite clear ethical and legal obligations to do.

CASE STUDY 2: AVANDIA

According to an expert working for the US Food and Drug Administration, around 100,000 Americans suffered heart attacks, strokes or heart failure due to negative side effects of the diabetes drug Avandia that only became known once it was already on the market. While this claim remains disputed, the case of Avandia clearly shows that comprehensive clinical trial registration and results reporting is vital to progress in medical science, sound regulatory decision-making, and patient safety. Without access to the full range of medical evidence on a drug, independent researchers can neither systematically assess its effectiveness and harms, nor double-check the accuracy of claims made in academic journals. Furthermore, the extended debate and unresolved controversy about one single trial of Avandia illustrates that methodological flaws may undermine the validity of reported results, so independent researchers need access not only to the results of a trial, but also have to be able to review the details about how data was collected and analysed. (These details are usually contained in Clinical Study Reports, lengthy documents that pharmaceutical companies submit to regulators when seeking licenses to market new drugs.)

How could this case have been prevented?

Trial registration	**X**
Results posting	**X**
Trial reports	**X**

When the newly developed drug Avandia (generic name: rosiglitazone) first came to the attention of medical circles, it was hailed as a much needed alternative treatment for Type 2 diabetes; despite only limited evidence of its effectiveness, it was approved by the US Food and Drug Administration in 1999. The European Medicines Agency initially rejected Avandia in October 1999, but granted market authorisation in July 2000 after commissioning the pharmaceutical company GlaxoSmithKline to carry out further clinical trials to determine its safety.

The drug grew rapidly in popularity and soon became one of the company's top earners. By 2006, GlaxoSmithKline (GSK) was earning $3 billion a year from sales of Avandia.

In 2007, the summary results of clinical trials conducted by GSK since December 2000 became accessible when the company posted information on past drug research online in the wake of a legal dispute over GSK's non-disclosure of data on an unrelated antidepressant drug. The first summaries posted on the company's website, a few weeks after the settlement of the legal case, covered 65 tests of Avandia, with information on study design, population, statistical methods, confidence intervals, and adverse events. The company later created a clinical trials register – an innovation at the time – that allowed independent researchers to request access to research data.

In June 2007, Dr Steven Nissen and Kathy Wolski published a meta-analysis of 42 trials to assess the effect of Avandia on cardiovascular outcomes. Their analysis was largely based on data extracted from GSK's new trial register; of the 35 trials inclusion listed there that met their inclusion criteria, only 9 had been published in academic journals, while 26 had remained unpublished. The authors also included data contained in documents that had been posted online by the Food and Drug Administration, plus data on two additional trials. Their meta-analysis found that Avandia increased the risk of heart attack by more than 40% in people with Type 2 diabetes.

After the meta-analysis was published, the US Food and Drug Administration decided that Avandia could stay on the market, but made the manufacturer include a black box warning about increased

heart risk. In response, GSK in July 2007 published an interim report on its RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes) trial, commissioned by the European Medicines Agency when it approved the drug in 2000 in order to determine its safety, which concluded that Avandia did not increase mortality from cardiovascular events.

> *"[While the] interim analysis is restricted to a limited amount of information…There is no evidence of any increased mortality, either from any cause or from cardiovascular causes"*

In 2008, acting upon the concerns raised by the meta-analysis by Dr Steven Nissen and Kathy Wolski, the Finance Committee of the US Senate commissioned an investigation into the risks of Avandia. The committee produced a 342 page report that was highly critical of GSK. The report claimed that the company had suspected that Avandia caused heart attacks as early as 2005, but had withheld this information from physicians and patients:

> *"The totality of evidence suggests that GSK was aware of the possible cardiac risks associated with Avandia years before such evidence became public."*

The Food and Drug Administration (FDA) responded to the findings by commissioning a review into the safely of Avandia. FDA scientist Dr Thomas Marciniak conducted a review of a June 2009 academic paper based on the RECORD clinical trial. That journal article had concluded that

> *"Although the data are inconclusive about any possible effect on myocardial infarction, rosiglitazone [Avandia] does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs."*

Dr Marciniaks review challenged this claim. It identified numerous instances of under-reporting. Dr Marciniak, reviewed the case report forms from the RECORD trial that GSK had submitted to the FDA. His analysis identified several instances in which heart attacks and strokes suffered by trial participants had not been recorded as adverse events. In one case, a patient suffered a severe stroke and was hospitalized for 67 days, but the incident was not recorded as a cardiovascular event in the trial's adverse event records or in the related academic paper. Similarly, another participant died after experiencing cardiovascular problems, but the death was listed as arising from an unknown cause and not as heart-related.

Dr Marciniak also had reservations about the design of the RECORD study, commenting that it was not adequate to properly investigating the risks of Avandia on cardiovascular events. The findings of review were included in a public FDA briefing document, written for an internal advisory meeting about Avandia, and stated that:

> *"We judge that there are sufficient issues with the study design that introduce biases, particularly towards the null, that we cannot rely upon RECORD to provide reassurances regarding the effects of rosiglitazone [Avandia] upon CV [cardiovascular] risk."*

The FDA briefing document also included an observation study, led by FDA scientist Dr David Graham, which looked at patients over the age of 65 who had been prescribed Avandia. The study, which was subsequently published in the Journal of American Medical Association, found that the diabetes drug increased the risk of heart attack or stroke in patients over 65.

> *"Compared with prescription of pioglitazone [an alternative drug], prescription of rosiglitazone [Avandia] was associated with an increased risk of stroke, heart failure, and all-*

> *cause mortality and an increased risk of the composite of AMI (*acute myocardial infarction*) stroke, heart failure, or all-cause mortality in patients 65 years or older."*

Dr Graham told the media that around 100,000 Americans had suffered heart attacks, strokes or heart failure due to Avandia since the drug had come on the market in 1999. GSK contested the findings of the report, insisting that the RECORD trial had showed Avandia to be safe.

In 2010, the FDA reviewed the evidence yet again and decided to severely restrict access to Avandia due to concerns about its safety, explaining in a press release that:

> *"The FDA is taking this action today to protect patients, after a careful effort to weigh benefits and risks."*

In the same year, the European Medicines Agency decided to withdraw Avandia from the European market.

Soon after the US Senate committee published its report, patients who had suffered heart attacks or strokes after taking Avandia began filing lawsuits. According to media reports, back in 2001 a pharmaceutical executive had written an email recommending that the results of a clinical trial comparing Avendia to a rival drug should remain hidden:

> *"This was done for the U.S. business, way under the radar. Per Sr. Mgmt request, these data should not see the light of day to anyone outside of GSK."*

In 2012, the Department of Justice and GSK reached a $3 billion settlement related to a range of federal charges related to several drugs, including Avandia, constituting the largest healthcare fraud settlement in US history. As part of the criminal plea agreement, GSK pleaded guilty to failing to report safety data to the FDA:

> *"The United States alleges that, between 2001 and 2007, GSK failed to include certain safety data about Avandia, a diabetes drug, in reports to the FDA that are meant to allow the FDA to determine if a drug continues to be safe for its approved indications and to spot drug safety trends. The missing information included data regarding certain post-marketing studies, as well as data regarding two studies undertaken in response to European regulators' concerns about the cardiovascular safety of Avandia… GSK has agreed to plead guilty to failing to report data to the FDA and has agreed to pay a criminal fine in the amount of $242,612,800 for its unlawful conduct concerning Avandia."*

As part of the civil settlement agreement, GSK also agreed to pay over half a billion dollars in connection with charges of having misrepresented Avandia's benefits:

> *"[T]he United States alleges that GSK promoted Avandia to physicians and other health care providers with false and misleading representations about Avandia's safety profile, causing false claims to be submitted to federal health care programs. Specifically, the United States alleges that GSK stated that Avandia had a positive cholesterol profile despite having no well-controlled studies to support that message. The United States also alleges that the company sponsored programs suggesting cardiovascular benefits from Avandia therapy despite warnings on the FDA-approved label regarding cardiovascular risks. GSK has agreed to pay $657 million relating to false claims arising from misrepresentations about Avandia."*

In 2013, GSK persuaded the FDA to take yet another look at the RECORD trial's data, and in 2015, an FDA advisory panel concluded that this data did not indicate an increased risk of heart attack in patients taking Avandia, compared to patients taking other commonly used diabetes drugs. The panel voted to remove virtually all restrictions it had previously put into place. In a press release, Janet Woodcock, director of the FDA's Centre for Drug Evaluation and Research, stated that "our level of concern is considerably reduced".

Dr Steven Nissen disagreed with this verdict and criticised the FDA's new review of RECORD. He argued that the flaws in the both the conduct and design of the trial itself noted in the earlier review of RECORD by Dr Marciniak rendered any re-analysis worthless. Dr Nissen further argued that multiple conflicts of interests undermined the credibility of the FDA's new review. He claimed that the independence of the process was questionable because GSK itself had prepared the materials for the re-analysis. He also noted that out of the eight named authors of the RECORD study, seven were paid consultants to GSK, and the eighth was a GSK employee. Dr Nissen charged that

"The current effort is intended to 'whitewash' the Avandia scandal and re-write history."

In response, GSK insisted that RECORD remained the "only randomized trial of cardiovascular outcomes for Avandia," thus constituting the best available evidence as to its safety, and that the trial's initial conclusions had been supported by independent researchers and thus remained valid and relevant.

Avandia was never allowed back onto the market in the European Union. In the US, Avandia is still available; while it carries a black box label warning about cardiovascular side effects, it is no longer subject to strict prescribing or dispensing restrictions.

CASE STUDY 3: VIOXX

The case of Vioxx illustrates that clinical trial transparency is vital not only to doctors and patients, but also to private investors. The design of a clinical trial run by the company developing Vioxx resulted in the under-counting of deaths that occurred among trial participants taking the drug. A high profile academic paper presenting the trial's results to a wider audience omitted important safety data. Important additional safety data that was provided to a regulator by the manufacturer after drug had been approved was not detected by independent researchers for several years.
According to a Food and Drug Administration scientist, in the United States alone, between 26,000 and 56,000 people died as a direct consequence of taking Vioxx. When the drug was finally withdrawn from the market, private investors holding shares in the company marketing saw $37 billion wiped off its value within a single month.
Vioxx remained on the market for over five years before it was withdrawn. An independent expert concluded that if all data on the safety of Vioxx had been accessible from the outset, the drug could have been withdrawn from the market after less than two years, saving thousands of lives.

How could this case have been prevented?

Trial registration	
Results posting	**X**
Trial reports	**X**

Between 26,000 and 56,000 Americans died as a result of taking the prescription painkiller Vioxx because data from clinical trials showing that the drug could cause heart attacks and strokes remained inaccessible to independent researchers, doctors and patients for several years.

Vioxx (generic name: rofecoxib) is a non-steroidal anti-inflammatory drug (NSAID) and prescription painkiller that was licensed in the US and UK in 1999 to treat pain such as arthritis and menstrual-related symptoms. Compared to other painkillers, Vioxx seemed to cause fewer harmful side effects, in particular fewer gastrointestinal symptoms. It offered an alternative for treating musculoskeletal pain, and was welcomed the musculoskeletal community as a major advance for patients with osteoarthritis.

Vioxx was instantly a popular prescription painkiller, with 80 million people taking the drug worldwide between 1999 and 2004. Vioxx was marketed in more than 80 countries, and generated $2.5 billion in sales in 2003 alone. By the time Vioxx was removed from the market, in 2004, two million Americans were taking the drug, up to 139,000 had suffered heart attacks or strokes.

Shortly before approval by the US Food and Drug Agency (FDA), manufacturer Merck launched the VIGOR clinical trial, which compared Vioxx against a competitor drug, naproxen, to build on existing evidence suggesting that Vioxx caused fewer gastrointestinal side effects. The trial began in 1999 and ran until 2000, involving over 8,000 participants at 301 centres in 22 countries. It found that Vioxx was as effective as similar painkillers, with significantly fewer gastrointestinal side effects, but also showed a four-fold increased risk of heart attacks and stroke.

The trial results were published in a 2000 paper in the New England Journal of Medicine (NEJM), but underreported the risk of heart problems. The academic paper did not report the absolute number of cardiovascular events, only percentages; it proposed that the higher incidence of cardiovascular events observed among trial participants taking Vioxx was due to the alternative painkiller having a protective effect.

> *"The overall mortality rate was similar in the two groups, as were the rates of death from gastrointestinal events and from cardiovascular causes. The rate of myocardial infarction was significantly lower in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent)… Our results are consistent with the theory that naproxen [the control group painkiller] has a coronary protective effect and highlight the fact that rofecoxib [Vioxx] does not provide this type of protection… The finding that naproxen therapy was associated with a lower rate of myocardial infarction needs further confirmation in larger studies."*

These findings were first questioned in 2001, when independent researchers took a second look at the VIGOR data and published a paper warning that "[t]he available data raise a cautionary flag about the risk of cardiovascular events" associated with Vioxx. According to Forbes, Merck in the same year "said it would to conduct a big study testing Vioxx's heart safety, but the clinical trial never materialized."

Then, in October 2004, an internal Merck memorandum became public in the course a New Jersey class action lawsuit. It indicated that during the VIGOR trial, 47 serious cardiovascular events had been recorded in the Vioxx group, compared to only 20 in the naxopren group, suggesting that Vioxx carried a significantly higher risk of cardiovascular side effects. Merck's memorandum also revealed that three heart attacks had not been included in the published paper, calling into the question the integrity of the rest of the data.

After having learned of the Merck memorandum, NEJM editors publicly voiced their concern in December 2005. They noted that:

> *"Three myocardial infarctions, all in the rofecoxib group, were not included in the data submitted to the Journal. The editors first became aware of the additional myocardial infarctions in 2001 when updated data were made public by the Food and Drug Administration. Until the end of November 2005, we believed that these were late events that were not known to the authors in time to be included in the article published in the Journal... It now appears, however, from a memorandum dated July 5, 2000… that at least two of the authors knew about the three additional myocardial infarctions… before publication of the article.*
> *In addition, the memorandum… contained other data on cardiovascular adverse events that we believe would have been relevant to the article. We determined from a computer diskette that some of these data were deleted from the VIGOR manuscript two days before it was initially submitted to the Journal on May 18, 2000.*
> *Taken together, these inaccuracies and deletions call into question the integrity of the data on adverse cardiovascular events in this article."*

The journal editors later added that heart attacks seemed to have been systematically underreported during the trial due to an "untenable" feature of its data collection methodology:

> *"[T]hree myocardial infarctions in the rofecoxib group were not included in the data submitted to the Journal. The authors state that these events did occur during the trial but did not qualify for inclusion in the article because they were reported after a 'prespecified cutoff date' for the reporting of cardiovascular events. This date, which the sponsor selected shortly before the trial ended, was one month earlier than the cutoff date for the reporting of adverse gastrointestinal events. This untenable feature of trial design, which inevitably skewed the results, was not disclosed to the editors or the academic authors of the study… [T]he VIGOR article, because it did not contain relevant safety data available to the authors*

> *more than four months before publication, did not accurately reflect the potential for serious cardiovascular toxicity with rofecoxib."*

While the information in the internal Merck memorandum had only come to public attention in 2004 following a lawsuit, years earlier it had already been reported by Merck to the FDA. At the time, an FDA researcher analysed the additional VIGOR data and concluded that:

> *"[T]here is an increased risk of cardiovascular thrombotic events, particularly myocardial infarction, in the rofecoxib group compared with the naproxen group."*

In fact, the analysis containing this warning had been written in in February 2001 and posted on the FDA website. As a new label warning of the elevated risk of heart attacks and strokes was only added in April 2002, doctors remained unaware of the drug's risks, and continued prescribing Vioxx widely to their patients.

Even in retrospect, it is unclear why the FDA had not acted on the early warning raised by one of its own scientists. A hearing by the US Senate's Finance Committee in November 2004, just after Vioxx had been withdrawn from the market, suggested an inappropriately close relationship between the pharmaceutical company and the regulator. Testimony given to the committee indicated that the FDA seemed to have colluded with Merck in underplaying the side effects of Vioxx. Senator Charles Grassley, Chairman of the Committee on Finance, claimed that the FDA's relationship with drug companies was "far too cozy".

Meanwhile, a new clinical trial involving Vioxx was underway. Originally launched by Merck in 2000, it involved 2,600 patients. By 2004, early results showed an even greater risk of cardtrial iovascular events than those that had surfaced during the earlier VIGOR trial. Merck quickly stopped the new trial, and voluntarily withdrew Vioxx from the market in late September 2004. At that time, two million people worldwide were taking the drug. In total, 84 million people had taken Vioxx while it was on the market.

After Vioxx was withdrawn, numerous lawsuits were filed against Merck. In November 2007, the company agreed to pay $4.45 billion to settle 27,000 lawsuits in US courts over claims that taking Vioxx had led to heart attacks and strokes; the company did not admit liability.

In addition, Merck agreed in 2011 to pay $950 million to settle claims by the U.S. Justice Department and state governments that the company deceived the government about the safety of Vioxx, and marketed it for off-label uses. Merck agreed to pay a $321 million criminal fine and plead guilty to one misdemeanor count of illegally introducing a drug into interstate commerce, plus $426 million to the federal government and $202 million to state Medicaid agencies. The latter two payments settled civil claims that its illegal marketing caused doctors to prescribe and bill the government for Vioxx they otherwise would not have prescribed. No individual executive was held liable for Merck's conduct.

Merck had recorded more than $11 billion in Vioxx sales during the drug's years on the market from mid-1999 to September 2004. Within a day of announcing the withdrawal, more than £14bn had been wiped from the company's stock market value, equivalent to a quarter of its worth. Merck's market capitalization plunged more than $37 billion in the month after the company stopped selling Vioxx.

A class-action lawsuit subsequently brought by investors against Merck claimed that stocks "were artificially inflated [between 1999 and 2004] as a result of allegedly false statements and non-

disclosures concerning Vioxx" by the company and senior executives. In January 2016, over a decade after it had withdrawn the drug from the market, Merck agreed to pay $830 million to settle the shareholder lawsuit without an admission of liability or wrongdoing by the company or individual executives. According to the Wall Street Journal, this brought Merck's "total payouts to settle Vioxx-safety-related litigation to at least $6 billion".

Additional unpublished data became public in the course of the investment court case. In 2009, Professor Harlan Krumholz used this new data, plus data from all published trials and internal company analyses and information provided by the Merck to the FDA, to conduct a cardiovascular harm meta-analysis. He concluded that if all this data had been available from the outset, the risk of cardiovascular harm could have been discovered soon after the drug first came onto the market:

> *"Cumulative pooled analysis of all randomized, placebo-controlled trials demonstrates… an increased cardiovascular risk associated with rofecoxib [Vioxx] compared with placebo as early as December 2000… nearly 3 and a half years before the manufacturer's voluntary market withdrawal."*

In his testimony to the US Senate Finance Committee, Dr David Graham, Associate Director for Science and Medicine at the FDA Office of Drug Safety, told Senators that

> *"If you apply the risk levels seen in the two Merck clinical trials, VIGOR and APPROVe, you obtain a more realistic and likely range of estimates for the number of excess cases. This estimate ranges from 88,000 to 139,000 Americans. Of these, 30 to 40 percent probably died."*

This FDA expert estimate implies that between 26,000 and 56,000 people died as a direct consequence of taking Vioxx in the US alone.

CASE STUDY 4: REBOXETINE

A German government agency's struggle to determine whether an expensive new drug could help patients shows why comprehensive trial registration and results reporting are so important. Experts working for the agency discovered that many clinical trials conducted on reboxetine, an antidepressant, had remained hidden because the pharmaceutical company marketing the drug had not registered them. The results of these hidden trials had also not been posted on any trial register or published in any journals. When the agency's experts finally managed to get the hidden results off the company and looked at all of the evidence available, they found indications that the company had selectively released evidence that reflected positively on the drug while keeping the bad news hidden from independent researchers, doctors and patients.

How could this case have been prevented?

Trial registration	**X**
Results posting	**X**
Trial reports	

The confusion surrounding reboxetine, an antidepressant drug, is a case in point. European regulators approved reboxetine – sold in most countries under the trade name Edronax – for marketing in 1997. Doctors started prescribing the drug, and in a single year, German patients alone swallowed 6.7 million doses of the drug. Its key selling point was that unlike other anti-depressants such as Prozac, it has no effect on serotonin, and thus was assumed to have lower side effects. So even though reboxetine cost four times as much as alternative treatments, many health agencies concluded it was worth the additional expenditure.

But exactly how effective at treating depression was this new drug? Could its advantages justify the additional expenditure? When reboxetine was first released, all published data pointed to it being as effective as other anti-depressants, which – in combination with its lower side effects – made it seem an attractive treatment option. However, doubts quickly emerged. In 2001 America's Food and Drug Agency, which had provisionally approved the drug in 1999, revoked its approval, citing a "lack of compelling evidence of efficacy" based on new evidence that had emerged in the wake of additional trials.

Over the following years, systematic reviews raised further doubts about reboxetine's effectiveness. This led the German Institute for Quality and Efficiency in Health Care (IQWIG) to decide to take a fresh look at the evidence to decide whether to continue recommending use of the drug. Its researchers approached Pfizer, the pharmaceutical company selling reboxetine, and asked for access to the results of all clinical trials it had conducted. Pfizer refused to share the data.

In response, the German institute issued a preliminary version of its report in June 2009, stating that reboxetine was not effective as a treatment for depression, citing the volume of unpublished studies. In a journal article published in 2010, IQWIG staff remembered that

> *"The retrieval of previously unpublished trials was hampered by the fact that during preparation of the preliminary health technology assessment report, the manufacturer of reboxetine did not provide a complete list of unpublished trials as requested by IQWiG. Secondary publications clearly indicated that further potentially relevant unpublished trials existed. As the preliminary report showed that reboxetine had been tested in at least 16 trials including about 4600 patients, but data on almost two thirds of these patients were not*

> *accessible, the institute initially concluded that no meaningful assessment of reboxetine was possible."*

Pfizer then did provide all the data to the German institute, but only on an exclusive basis; the company refused to make it publicly available. The German researchers reviewed the trove of evidence and discovered that Pfizer had not published the results of many clinical trials it had conducted on the antidepressant. Including this previously hidden data – which other regulators and researchers still had no access to – in its analysis, the review team found that the company had exaggerated the effectiveness of reboxetine. In fact, after looking at the entire body of evidence, the independent researchers concluded that reboxetine may be no more effective than a placebo.

Even worse, they found indications that the negative side effects of the drug may more serious than previously thought. Many patients participating in the trials had stopped taking reboxetine due to adverse side effects such as headache, feeling sick, palpitations, low sex drive and erectile dysfunction.

When the German institute's researchers published their findings in the British Medical Journal, they found indications that Pfizer had electively released evidence that reflected positively on the drug while keeping the bad news hidden from independent researchers, doctors and patients:

> *"Data on 74% of the patients included in our analysis was unpublished, indicating that the published evidence on reboxetine so far has been severely affected by publication bias… underlining the urgent need for mandatory publication of trial data."*

In an accompanying editorial, the British Medical Journal warned that hidden data was undermining the entire evidence base of modern medicine:

> *"The reboxetine story and similar episodes must call into question the entire evidence synthesis enterprise. Meta-analyses are generally considered the best form of evidence, but is that a plausible world view any longer when so many of them are likely to be missing relevant information?"*

Concerns about the effectiveness and safety of reboxetine were so great that in 2011, the European Pharmacovigilance Working Party and the UK's Medicines and Healthcare Regulatory Agency jointly decided to conduct yet another review of all available data on of reboxetine, which widened the data pool by including three studies that the Germans had chosen not to include due to methodological concerns.

The conclusions of this European review contradicted the earlier German findings. Though the review only found a small positive effect, it did conclude that reboxetine was statistically more effective than a placebo.

So, is reboxetine effective or not? Well, unfortunately the picture is not very clear. The small difference in results between the two studies is due to the inclusion of trials in the European study that were excluded from the German study. The German researchers found that patients who took reboxetine in a hospital were significantly more likely to show a positive response than those who took it at home. They surmised that the setting rather than the drug were causing these positive effects, so they excluded three studies involving hospital patients from their review.

This raises the possibility that the European study only found a positive effect of the drug because the trial data from hospital patients distorted the overall picture. However, the European review

team insists that their review is more accurate as it involved all available data. The European Medicines Agency has accepted this conclusion and has not revoked its approval of reboxetine for the treatment of depression, allowing the drug to remain on the market.

The ongoing debate surrounding reboxetine's effectiveness illustrates how complex modern medicine is. Medical progress can only thrive when the evidence base is complete and universally accessible, allowing researchers to build on, challenge and refine the findings of their peers.

CASE STUDY 5: ANTIDEPRESSANTS (SSRIs)

The ongoing debate about the effectiveness and safety of a class of antidepressants called SSRIs illustrates the importance of giving independent researchers access to unabridged and only minimally redacted Clinical Study Reports. When independent experts looked in great detail at Clinical Study Reports, they discovered that some data on drug harms generated by clinical trials had not been reported in academic journals or even inside the voluminous Clinical Study Reports that pharmaceutical companies had submitted to regulators. Instead, some data on harms had been buried in appendices that these regulators had never reviewed. This case clearly shows that giving independent researchers access to unabridged Clinical Study Reports – which usually remain locked away from public view – can further medical progress and help to improve regulators' efforts to keep patients safe.

How could this case have been prevented?

Trial registration	
Results posting	
Trial reports	**X**

One in ten Americans are taking antidepressants, making them the nation's second most widely prescribed type of drugs, right after drugs for lowering cholesterol. Antidepressants' popularity soared following the 1988 introduction into the US of Prozac, the first of a new class of drugs called Selective Serotonin Reuptake Inhibitors (SSRIs). Within a few years, doctors were prescribing not only Prozac, but also a host of rival SSRIs including Celexa, Lexapro, Luvox, Paxil and Zoloft. Between 2004 and 2008, there was a four-fold increase in the prescription of antidepressants in the US. In Britain, the number of people taking SSRIs has quadrupled over the past two decades.

While many doctors and patients found SSRIs a useful tool to combat depression, others noted unexpected negative side effects. In 1990, a series of published case reports suggested a link between taking SSRIs and suicidal thoughts and behaviours. This lead to an hearing at the Food and Drug Administration in 1991, after which the agency concluded that there was no evidence of an increased risk of suicidal acts.

During the 1990s, while SSRIs remained approved only for use in adults, SmithKline Beecham conducted a clinical trial with 275 teenagers suffering from depression to study the effects of paroxetine (trade names Paxil and Seroxat) on that population, with the aim of extending the drug's licensing approval to adolescents. The first academic paper based on Study 329, as the now-famous trial was called, was published in 2001. It concluded that paroxetine was effective and that its side effect rates were similar to those of placebo pills.

> *"Paroxetine is generally well tolerated and effective for major depression in adolescents… [SSRIs] have a safer side-effect profile than other antidepressants, particularly in overdose."*

In 2004, a UK review compared published data on SSRIs with unpublished data that had been included in an earlier review by the Committee on Safety of Medicines. The new review found a noticeable discrepancy between published and unpublished trials and increased suicidal behaviour in children and adolescents. In response, the European Medicines Agency (EMA) mandated warnings about potential side effects on the packaging of SSRIs.

In the wake of the British review, numerous lawsuits were launched against manufacturers of SSRIs. In 2012, the US Department of Justice took GSK to court, claiming that it had

> *"unlawfully promoted Paxil for treating depression in patients under age 18… [and] participated in preparing, publishing and distributing a misleading medical journal article that misreported that a clinical trial of Paxil demonstrated efficacy in the treatment of depression in patients under age 18, when the study failed to demonstrate efficacy..."*

as well as not making available data from two other studies in which Paxil had also failed to demonstrate efficacy. In 2012, GSK pleaded guilty to criminal charges and agreed to pay $3 billion as part of a wider settlement involving multiple charges related to several drugs, including Paxil.

In 2015, a group of academic researchers decided to reanalyse the data from Study 329. They examined 6,000 pages of Clinical Study Reports which had been made publicly available by GSK on its website as part of the 2004 settlement of a lawsuit brought by the New York Attorney General over the alleged suppression of data from paroxetine trials. However, these CSRs were incomplete, missing an unknown number of pages, so the researchers contacted GSK to request access to the de-identified case report forms. GSK eventually agreed to make 77,000 pages of de-identified individual forms available through the SAS Solutions OnDemand website, accessible only to users approved by GSK.

The independent research group found 15 instances of suicidal behaviour among teenagers taking paroxetine, compared with only four in the similarly sized placebo group. They concluded that the risk of suicide had been understated in both the published literature and the Clinical Study Reports, and that if the full trial data from Study 329 been available from the beginning, the risks of suicidal behaviour associated with SSRIs could have been discovered years earlier.

> *"There were clinically significant increases in harms, including suicidal ideation and behaviour and other serious adverse events in the paroxetine group…The reanalysis of Study 329 illustrates the necessity of making primary trial data and protocols available to increase the rigour of the evidence base."*

A Cochrane review also published in 2015 also concluded that some types of antidepressants heightened the risks of suicidal behaviour in children and adolescents. The researchers had requested access to Clinical Study Reports on SSRIs that had been submitted to the EMA and Britain's Medicine and Healthcare Regulatory Agency, and were granted access to 198 Clinical Study Reports relating to trials for two common types of antidepressants, SSRIs and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs). Seventy trials were included in the analysis, which identified a doubling of the risk of suicide and aggression in adolescents taking either class of antidepressants.

Further scrutiny of the adverse events by a Cochrane team showed extensive evidence of under-reporting suicide and aggressive behaviour in the Clinical Study Reports which had been submitted to regulators prior to approval of the drugs. According to an article in Scientific American:

> *"They discovered that some of most the useful information was in individual patient listings buried in the appendices. For example, they uncovered suicide attempts that were passed off as 'emotional liability' or 'worsening depression' in the report itself. This information, however, was only available for 32 out of the 70 trials. 'We found that a lot of the appendices were often only available upon request to the authorities, and the authorities had never requested them,' says Tarang Sharma, a PhD student at Cochrane and lead author of the study. 'I'm actually kind of scared about how bad the actual situation would be if we had the complete data.'"*

Four suicides were misreported by an unnamed pharmaceutical company, which claimed that they had occurred after the patients had been administered the final dose; this data had been recorded in patient narratives but omitted from Clinical Study Reports. Another patient strangled himself after taking SSRIs but survived for five days, so the company claimed he was no longer a trial participant when he finally died in hospital. In total, over half of the suicide attempts and suicidal thoughts had been incorrectly recorded as emotional instability or worsening of depression.

An academic study published in the BMJ reported that:

> *"Of the remaining 62 suicide attempts... Four of these events were only listed in the individual patient listings and three others only noted in adverse events tables… and 27 events were coded as emotional liability or worsening depression, although in patient narratives or individual patient listings they were clearly suicide attempts… research in other areas has shown that misclassifying or omitting even one adverse event can mean the difference between a statistically significant and non-statistically significant association with a drug."*

This widespread exclusion of suicide and aggressive behaviour, not only from articles published in academic journals but also from the unpublished Clinical Study Reports that had been submitted to regulators, meant that even the regulatory agencies responsible for drug safety were unaware of how serious the risks of SSRIs were for adolescents – of course, patients, doctors and outside researchers also remained in the dark.

The lead author of the Cochrane review, Professor Peter Gøtzsche from The Nordic Cochrane Centre harshly criticized the pharmaceutical companies involved in trialling and marketing antidepressants, commenting that "It is absolutely horrendous that they have such disregard for human lives."
Pharmaceutical companies strongly disagree with this characterization. A spokesman for Eli Lilly said that "[n]o regulatory authority has ever determined that Lilly withheld or improperly disclosed any data related to these medications". GSK argued that that the relevant drug labels had reflected an increasing risk of suicide since 2004; "Product labels have, for more than a decade, carried clear warnings about the increased risk of suicidal behaviour in adolescents. As such, we don't believe this reanalysis affects patient safety."

According to the National Institute of Mental Health, Prozac is currently the only medication currently approved by the Food and Drug Administration for use in treating depression in children aged eight years and above; the agency recommended in 2003 that children and adolescents should not be given paroxetine (Paxil and Seroxat) against depression. The institute has concluded that:

> *"Fluoxetine [Prozac] can be helpful in treating childhood depression, and can lead to significant improvement of depression overall. However, it may increase the risk for suicidal behaviors in a small subset of adolescents. As with all medical decisions, doctors and families should weigh the risks and benefits of treatment for each individual patient." [italics in the original]*

Meanwhile, the effectiveness (as well as the risks) of SSRIs for different patient groups remains contested. A 2008 meta-analysis concluded that SSRIs are no more effective at treating depression than a placebo in patients of all ages with mild or moderate depression, adding that "[d]rug-placebo differences in antidepressant efficacy… are relatively small even for severely depressed patients." Other experts in the field have challenged this conclusion; the debate is ongoing.

CASE STUDY 6: TAMIFLU

The case of Tamiflu shows how fragmented and partial evidence on drug safety and effectiveness can undermine sound decision-making by regulatory agencies, cause billions of public health dollars to be spent on drugs of questionable effectiveness, and endanger patients' safety. It took independent researchers four years to get hold of all the evidence they needed to evaluate the effectiveness and safety of a drug that had been on the market for a decade, had generated more than $18 billion in sales, and had already been taken by hundreds of thousands of patients worldwide. Tamiflu's example also highlights the crucial importance of publishing Clinical Study Reports, detailed documents that enable outside experts to review and validate pharmaceutical companies' claims about the effectiveness and safety of the drugs they sell.

How could this case have been prevented?

Trial registration	**X**
Results posting	
Trial reports	**X**

Tamiflu (generic name: oseltamivir) is an anti-retroviral drug developed by the pharmaceutical company Roche to treat the symptoms and complications associated with influenza infections. Tamiflu was first approved in the United States in 1999 and in Europe in 2002.

In 2006, amid fears about a possible bird flu pandemic, governments around the world began stockpiling Tamiflu. In 2009, fears about a possible swine flu pandemic drove the stockpiling of Tamiflu to new heights. In the US, 65 million treatments of Tamiflu were amassed at a cost of $1.3 billion and in the UK, the government spent over half a billion dollars on Tamiflu. In 2009, 0.5% of Britain's entire National Health Service budget was spent on the drug. The stockpiling of Tamiflu was so extensive that 96 counties accumulated enough Tamiflu to treat 350 million people. In the 15 years between 1999 and 2014, over $18 billion was spent on the drug worldwide.

Up until 2009, all results published in the academic literature suggested that Tamiflu was a safe and effective treatment for influenza which reduced flu-like symptoms and prevented secondary complications such as pneumonia. In 2009 the Cochrane Collaboration reviewed the efficacy of Tamiflu. The researchers conducted searches of the Cochrane central register of controlled trials, which contains the Acute Respiratory Infections Group's specialised register, Embase, and post-marketing pharmacovigilance data and comparative safety cohorts. In total, 20 clinical trials on Tamiflu were included in the review. Analysis of these trials found some evidence that Tamiflu does indeed reduce symptoms of influenza and the rate of complications such as pneumonia. However, one of the academic papers included in the review was based on unpublished and inaccessible data.

It was not until a Japanese paediatrician, Keiji Hayashi, left a comment posted informally underneath the Tamiflu review that the reliability of the data was questioned. Hayashi pointed out that the positive conclusion of the Cochrane review was based on the results of one paper, an industry-funded meta-analysis of 10 previous trials. However, only 2 of these 10 trials had ever been published in the academic literature, so the results of the meta-analysis were based on inaccessible data from 8 trials. The lead author of the Cochrane review, Dr Tom Jefferson, admitted that he had made a mistake and sought out the Clinical Study Reports for the unpublished trials to complete the review, sparking off a remarkable quest for hidden data.

At first, manufacturer Roche agreed to hand over the full Clinical Study Reports, but only under the condition that the Cochrane reviewers sign a confidentiality agreement that would prevent them

from publicising the methods or results of the unpublished trials. Roche also demanded the Cochrane researchers never discuss the terms of the agreement, or even acknowledge it existed.

After some to and fro, Roche sent seven documents to the Cochrane researchers, comprising excerpts of company documentation on each of the 8 unpublished clinical trials. The documents were not comprehensive enough to allow the Cochrane team to verify the claims made in the meta-analysis they had reviewed; in order to fully analyse the efficacy of Tamiflu, the researchers needed access to the Clinical Study Reports of each trial.

Thus, the Cochrane researchers published an updated review that excluded those 8 trails, which still remained unpublished. The updated Cochrane review found that Tamiflu did not reduce the number of hospitalisations and found that, on average, it only cut flu-like symptoms from seven days to 6.3 days. The reviewers noted that none of the clinical trials had been conducted independently of the drug's manufacturer, and that all were conducted by pitting Tamiflu against a placebo, rather than against standard drugs for relieving flu symptoms, such as paracetamol. The Cochrane team concluded that

> *"Because of the moderate effectiveness of neuraminidase inhibitors, we believe they should not be used in routine control of seasonal influenza."*

The Cochrane review also indicated that the negative side effects of Tamiflu outweighed its benefits. Documented side effects of Tamiflu included nausea, vomiting, diarrhoea and headache, and in some cases even severe psychiatric episodes.

Dr Carl Henegen, professor of evidence-based medicine at Oxford University, commented that

> *"This drug was given to 1,000 people a week over a phone line, but it was no better for symptom relief than over-the-counter medication – and you're talking about potentially serious complications. I wouldn't prescribe it to my patients."*

Roche contested the findings of the review, charging that "[t]he [Cochrane] report's methodology is often unclear and inappropriate," and insisting that Tamiflu is a safe and effective treatment for influenza.

A later attempt by Cochrane to yet again analyse all available data on Tamiflu also ran into problems. A recent discussion of lessons learnt from the Tamiflu saga noted that:

> *"Cochrane collaboration decided to undertake a complete analysis of the clinical trial data set. However, they had difficulties in accessing the data, and it was not before protracted efforts lasting from 2009 to 2013 that they could gain access to all the materials. They needed full data set to formulate exhaustive and scientifically robust evidence. Cochrane had correspondence with WHO, US FDA, CDC, EMA, and European center for disease prevention and control. And it came as another surprise as none of them possessed full data…*
> *There had been no mention of adverse effects associated with the use of this drug in the published trials. Post-marketing surveillance had uncovered adverse effects like raised liver enzymes, hepatitis, neuropsychiatric events, cardiac arrhythmia… benefits had been overplayed, and harms had been underplayed in the reporting of the trials.*
> *Stockpiling by the countries was based on assumptions and not hard data… Access to full methods and results was not available to regulatory authority."*

A blog by Peter Doshi, Kenneth Mandl, and Florence Bourgeois published in March 2016 revealed that even within the United States, different federal agencies have come to different conclusions about Tamiflu because they had been looking at different sets of evidence:

> *"[T]he CDC's [Center for Disease Control's] official recommendations for influenza antivirals—a lengthy document last updated in 2011—claims statistically significant reductions in pneumonia and hospitalizations among adults treated with oseltamivir [Tamiflu], citing a manufacturer authored pooled analysis of 10 randomized trials. The Food and Drug Administration (FDA) however—which had complete access to all trial data comprising the research program for oseltamivir—formally instructed [manufacturer] Roche to cease from making a claim about reducing influenza complications in promotional materials."*

In 2010, the shelf life of Tamiflu was extended from five to seven years, so stocks bought in 2009 are considered stable until 2016. However, in 2013, the UK government destroyed Tamiflu stockpiles valued at £74 million. The patents for Tamiflu expire in 2016 and 2017, meaning that in future, the drug can be made by a generic manufacturer for a fraction of its previous price. It is therefore unlikely that that such large sums of money will be spent on stockpiling Tamiflu again.

A financial analyst in London was cited by the BMJ as saying that:

> *"Tamiflu was a nice little earner. It reflected opportunistic action by a multinational corporation, which was able to be a little bit sharper in its marketing practices than you could now, given the debates over the disclosure of clinical data and how effective the drug was."*

So how high are the human and financial costs of hidden clinical trials? In the case of Tamiflu, in Britain alone, 240,000 people were given the drug. Globally, more than $18 billion were spent on Tamiflu. But Tamiflu is just one drug among thousands on the pharmaceutical market – and it is certainly not the only one whose "benefits had been overplayed, and harms had been underplayed."

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