of the 'atypical antipsychotic' drugs, and imipramine, the first of the tricyclic class of antidepressants. Both of these drugs spawned many look-alikes. But since these early breakthroughs, no radical improvements in therapy have emerged. For example, there is still no drug for the core symptoms of autism or for the particular cognitive deficits in schizophrenia that prevent most sufferers from holding down a job.

When Novartis closed down its conventional drug-discovery programme in Basel, Switzerland, last year (see *Nature* **480,** 161–162; 2011), it was already planning to reopen with an entirely new approach at its global drug-discovery headquarters, the Novartis Institutes for BioMedical Research (NIBR) in Cambridge, Massachusetts. In its sights are neurodevelopmental diseases such as autism, schizophrenia and bipolar disorder, as well as neurodegenerative diseases such as Parkinson's and Alzheimer's disease.

Most current psychiatric drugs are based on the modulation of neurotransmitters, but the company's plan is instead to focus on connections between neurons, with the aim of addressing the precise neural circuitry that goes wrong in psychiatric disease, says Mark Fishman, the president of the NIBR. Genetics and environment both strongly influence how disease-causing circuits establish themselves.

Increasingly powerful genetic studies have begun to identify genes that might cause or contribute to the disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium *Nature Genet.* **45,** 984–994; 2013), and scientists can now efficiently model many of these defects in animals. With optogenetics — a technique introduced in 2005 that uses genetics in concert with light to activate or inhibit particular neurons — they can identify in living animals the neuronal circuits that the genes affect, and thus which genes could be targeted for therapy. In addition, stem-cell technologies now allow scientists to turn skin or hair-follicle cells from individual patients back into pluripotent stem cells, differentiate them into neurons and then study the connections that the neurons make with one another. Such induced pluripotent stem cells might one day aid the personalization of therapies to individual patients.

"We'll begin to see a lot of clinical trials within a decade or so."

All of these technologies are young. Novartis is planning to collaborate closely with academic institutions to generate more genetic clues, build disease models and deepen the understanding of neural circuits in health and disease. The science will be published, says Dolmetsch, but Novartis will have first access to mutations and circuitry that are found to be linked to a disorder, for use in the company's drug-development programme. Novartis will also have the freedom to develop drugs around any target that emerges from genetic screens that it co-sponsors. "If academic groups feel they should patent targets, and if we contributed to the screen that revealed them, then we want the option to license those patents," says Dolmetsch.

Finding good targets, and moving from a target to a safe and effective drug, will not happen overnight, Dolmetsch stresses. "Everyone realizes that this is going to take a long time to bear fruit," he says. Steve Hyman, director of the Stanley Center for Psychiatric Research in Cambridge, Massachusetts, guesses that in five years — "if we all work hard enough" — it will be clear whether or not the new approaches are likely to be useful.

Hyman, who is an adviser to Novartis and a former director of the US National Institute of Mental Health, predicts that for diseases caused by a single gene, such as some rare but devastating forms of autism or intellectual disabilities, "we'll begin to see a lot of clinical trials within a decade or so".

The vastness of the task is keeping most big drug companies out of the game, although Roche, based in Basel, is committed to a similar approach, says the company's spokesman Stepan Kracala.

The European Commission is also trying to foster a collaborative approach through its Innovative Medicines Initiative. Two of its multimillion-euro programmes — EU-AIMS (European Autism Interventions — a Multicentre Study for Developing New Medications) and NEWMEDS (Novel Methods leading to New Medications in Depression and Schizophrenia) — combine different pharmaceutical companies and academic groups in projects that probe genetic and neural circuitry in autism, schizophrenia and depression.

Dolmetsch doesn't feel that his move to Novartis has distanced him from the intellectual centre of things. "The science at the NIBR is arguably better and certainly more rigorous than in most of academia," he says. ■ SEE EDITORIAL P.141

MEDICAL RESEARCH

Secrets of trial data revealed

Records of side effects seen in clinical tests are missing from publicly available documents.

BY DANIEL CRESSEY

Drug companies, regulatory bodies and research groups are in a deadlock over plans to throw open the vaults of sensitive data gleaned from clinical trials. But just as the battle seems to be coming to a head, a study (B. Wieseler *et al. PLoS Medicine* **10,** e1001526; 2013) has revealed exactly why the restricted information could be so valuable to researchers.

According to the analysis, crucial trial information, such as mortality rates and serious side effects, is missing from much published data. But it can frequently be found in standard non-public documents prepared by industry, known as clinical study reports (CSRs). Missing information uncovered by the study includes details of depression symptoms in trials for antidepressant drugs, and details of heart attacks and strokes in diabetes-drug trials. "These are very, very important variables and outcomes," says the study's lead author, Beate Wieseler, head of the drug-assessment department at the Institute for Quality and Efficiency in Health Care in Cologne, Germany.

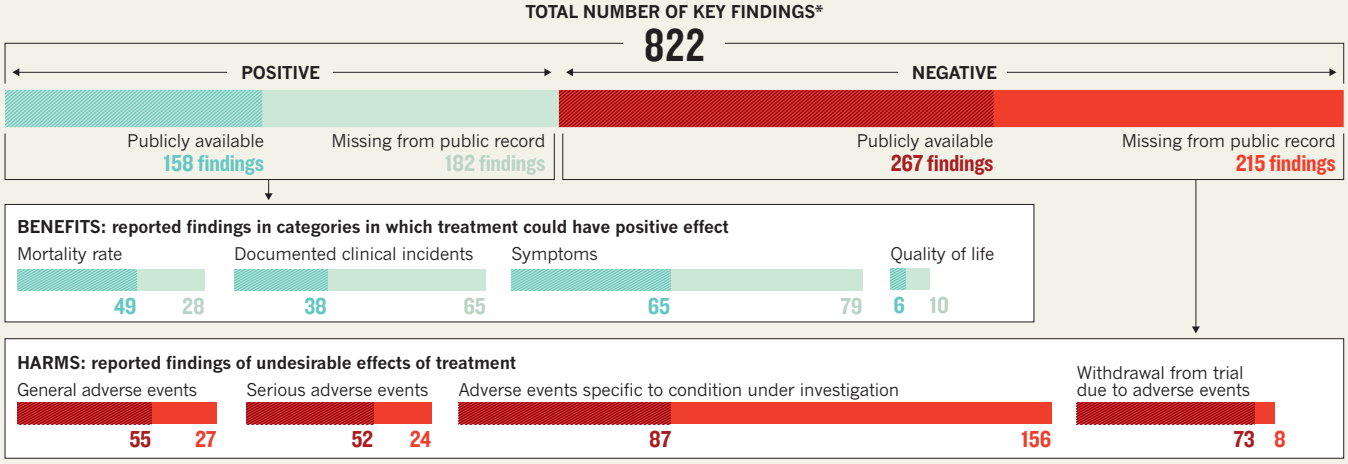
Wieseler strongly supports making all CSRs publicly available. "That is not an option, but a necessity," she says. "There should be no question that these documents be made available."

The issue of CSR access is shaping up to be a key sticking point in a major European push to make available more data from clinical trials. Drug companies send the reports to the European Union's European Medicines Agency (EMA) when they apply for licences to sell their products, and the agency has made clear that it would like to release the forms as part of a drive to increase transparency. It is currently drawing up a policy to that effect. Advocates of transparency say that such a policy will allow greater scrutiny of the benefits and harms of drugs, and will help researchers who are working on cures for diseases.

Some companies, including pharmaceuticals giants Roche, based in Basel, Switzerland, and GlaxoSmithKline in London, have already said that they will make their CSRs available to vetted researchers. But industry has pushed back against the wider moves to greater transparency.

INSIDE DRUG-COMPANY DATA VAULTS

In data from 86 clinical trials, investigators recorded 822 important findings, ranging from effect on mortality rate to fatal heart attacks. A review compared the information that was made publicly available with that available only in unpublished drug-company reports. The public information was found to omit crucial facts.



*For trials with both unpublished clinical study report (CSR) and public record; only findings with complete information shown.

SOURCE: B. WIESELER *ET AL. PLOS MEDICINE* **10**, E1001526; 2013

In an e-mail to *Nature*, Richard Bergström, the director-general of the European Federation of Pharmaceutical Industries and Associations (EFPIA), said that in their current state, CSRs are fundamentally unsuitable for publication. The EFPIA believes that the EMA's proposed mechanisms for protecting the commercially sensitive and personal details contained in many of these documents are inadequate — the mechanisms require that information be 'de-identified' and released only for bona fide research purposes. Such personal data must be properly redacted if these documents are to be made public, says Bergström.

"My members are very concerned about this," he says. "If the EMA accepts our redactions, we have no problem." If the agency disregards the EFPIA's concerns, however, Bergström warns that there may be a series of lawsuits against the EMA.

The EMA has already been taken to court by two biotechnology companies, AbbVie of North Chicago, Illinois, and InterMune of Brisbane, California, to block release of their information under existing rules, whereby any researcher can request information. The cases are ongoing and have severely restricted releases of other requested data.

But advocates of greater transparency are fighting for the EMA to release all data, which they say can easily be anonymized.

In the study, Wieseler and her team examined the information in 101 CSRs given to them by pharmaceutical companies, and compared it with the information about the same clinical trials that is available in the public domain, found in journal publications and reports in trial registries.

The unpublished sources provided considerably more information on the key findings, or outcomes, relating to the treatments being assessed, including mortality rates and adverse events. In total, the team found 1,080 outcomes relevant to patients. Complete information was available for 86% of these in the CSRs, but for only 39% in the publicly available information. When looking only at outcomes related to harm — such as adverse reactions to a drug — the researchers found that complete information was found for 87% of outcomes in the CSRs, but for only 43% in public records. In some cases, no public information was available at all for a given CSR. But when looking only at cases in which there was both a CSR and a public document, the researchers found similar proportions of missing information in the publicly available records (see 'Inside drug-company data vaults').

"What's portrayed in the journal world does not reflect the whole truth."

"Does it surprise me? No. Is this stuff really important? Yes," says Carl Heneghan, director of the Centre for Evidence-Based Medicine at the University of Oxford, UK, and co-founder of a group called AllTrials, which campaigns for more clinical-trial transparency. "It's becoming obvious that what's portrayed in the journal world does not reflect the whole truth."

In a public consultation that ended last week, the EMA's proposals attracted support from other quarters. The Medicines and Healthcare Products Regulatory Agency, the UK drug regulator, says that it welcomes the EMA's proposals, "and will work to align our position with theirs".

A joint response from UK biomedical-research funders, including the Wellcome Trust and the Medical Research Council also backs the EMA's plans. However, the group voices concerns over the sharing of data from individual patients; it says that more safeguards should be put in place to ensure that data are given only to trusted researchers who will not "wrongfully contradict" the results of trials.

The EMA hopes to have its policy in place by the start of next year. Documents without sensitive personal data will be made available for download from its website, whereas those that do contain such data will be available only after anonymization to vetted researchers. Documents with commercially confidential information will be released separately. ■

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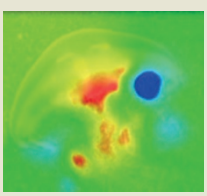

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