Researchers question design of fatal French clinical trial

UK's Royal Statistical Society among those demanding more information after the release of trial's protocol.

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Scientists are voicing concerns over the design of a French drug trial that left one participant dead and several others with severe health problems — and they are calling for more information to be released.

The researchers, including those in the UK's Royal Statistical Society (RSS), have examined a document that describes how the trial was conducted, and say that major pieces of information are still missing.

Scientists in the dark after French clinical trial proves fatal

In particular, the researchers note a lack of information about whether the design included adequate time intervals between the individuals given the multiple-dose regimen of the drug that caused the problems. Such intervals allow investigators to watch for possible side effects in one volunteer before they expose subsequent volunteers to the drug. The incorporation of such delays was identified as important both by an RSS working group and the European Medicines Agency, after a clinical trial went disastrously wrong in the United Kingdom in 2006.

"A key aspect is a proper interval of time between dosing of successive volunteers," says biostatistician Sheila Bird of the Medical Research Council Biostatistics Unit at the University of Cambridge, UK, who is a member of the RSS working group, which focuses on 'first-in-human' clinical trials.

The RSS is now calling on the Portuguese company Bial, which sponsored the trial (conducted by French contract-research oranization Biotrial in Rennes), to release further information about its design and the tests that preceded it.

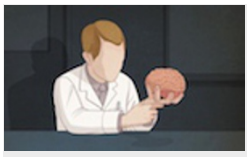
Time for one-person trials

Bial spokesperson Susana Vasconcelos told *Nature* that the company denounces the release of the protocol, as well as "discussion on this subject without knowing the results of the current investigations and all clinical data regarding the volunteers of the clinical trial".

Protocol released

In the days after the trial went wrong — the first public acknowledgement of the incidents came on 15 January — little information was available, frustrating those who wanted to understand what had happened. Then, on 22 January, France's National Agency for Medicines and Health Products Safety (ANSM) released the protocol of the drug trial, after the newspaper *Le Figaro* published a version of the same document.

The document identifies, for the first time, the chemical makeup of the drug — which was aimed at treating anxiety and motor disorders associated with Parkinson's disease, and chronic pain in people with cancer and other conditions — and the regimen that the study volunteers followed. But it still leaves many questions unanswered.



Neuroscience: My life with Parkinson's

Such phase I trials are conducted in healthy volunteers to determine the safety and dosing of a drug, before moving on to studies that test the effectiveness of drugs in people with a particular condition.

In the study, the first volunteers received either just a single dose of the oral drug, which is known as BIA 10-2474, or a placebo. After this, different volunteers were given a single administration of increasingly higher doses of the drug. The six volunteers who were hospitalised — some with severe symptoms such as bleeding or dying tissue in the brain — were the first to receive multiple doses of the drug, administered on successive days. (The first patient to fall ill died on 17 January; one other has recovered sufficiently to be discharged from hospital, and the health of the remaining patients has improved.)

Basic facts about the trial

- The trial recruited 128 healthy volunteers aged 18–55, who were paid €1,900 (US$2,060) each.

- Ninety people received different doses of the drug, and the remainder a placebo.
- The trial had tested escalating single doses of the drug without observing any serious adverse side effects.
- The six participants who fell ill were the first to receive repeat higher doses over the course of several days.
- The first participant to fall ill experienced adverse symptoms on 10 January and died on 17 January.
- Biotrial halted the trial on 11 January; the other five affected people were hospitalized in the days that followed.
- At least one of these patients has since been discharged, and the health of the remaining patients has improved.
- Of the 84 other subjects who received lower doses of the drug, 28 have been given neurological check-ups since the accident, and none has shown any of the symptoms seen in those hospitalized.
- Biotrial filed an application for the trial to the French National Agency for Medicines and Health Products Safety (ANSM) on 30 April last year and the agency authorized it on 26 June, with the final sign off given by the French equivalent of a local institutional review board (Comité de Protection des Personnes) in Brest on 3 July.
- The trial began on 9 July in Biotrial's clinical facilities in Rennes.

According to the newly released protocol, the participants in this part of the trial were to receive one dose of the drug each day for ten consecutive days. But Bird says that the protocol does not state whether there was any interval between the individuals who were beginning this regimen, or the dosage that these participants received.

Intervals recommended

After the 2006 UK trial of the antibody treatment TGN1412, which led to the hospitalization of six volunteers, Bird's working group recommended that such intervals be included in the design of phase I trials. Guidelines drafted by the EMA after that disaster also underscores the importance of these intervals and says that their length should be justified by previous data collected in humans and animals.

Overhaul complete for EU clinical trials

According to the timeline detailed by France's health minister, Marisol Touraine, those who fell ill had begun to take the experimental treatment on the same day, 7 January, and adverse symptoms appeared in the first subject — who was hospitalized with brain death — on 10 January. The trial was halted on 11 January, and the five others were hospitalized in the days that followed.

Catherine Hill, a biostatistician who previously served on the ANSM's scientific advisory board, says that it was "a big mistake" to begin giving the six volunteers the drug on the same day. She says that the trial should have incorporated a delay between volunteers as they started the multiple-dose regimen. "You have to do things reasonably, and I think it's an unreasonable protocol," she says.

Bial's Vasconcelos says: "We reiterate that the development of this molecule has been conducted since the beginning in accordance with all the good international practices, with the completion of tests and preclinical trials, particularly in the area of toxicology. The results obtained in accordance with international guidelines have permitted the start of the clinical trials in humans."

Brazilian courts tussle over unproven cancer treatment

In a statement on 22 January, the RSS called for the publication of the 'investigator brochure', which details the preclinical studies that led up to the trial. According to the ANSM, Bial declined to publish the brochure and another document, citing French laws that protect the release of trade secrets.

Bird says that the release of such information is important to ensure the safety of participants in other clinical studies. "There are other studies going on around the world right now, and we want to know what the design problems were."

On the same day, the British Pharmacological Society published a statement calling for improved early access to data from catastrophic clinical trials, following the recent disaster in France.

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Updates & Corrections

Updated: The story has been updated to include mention of the statement from the British Pharmacological Society.

Corrected: The story has been updated to include the latest information on the health of the clinical trial participants.