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Press Release

Investigation casts doubt over trial used to support top-selling anti-clotting drug

- Pivotal drug trial under scrutiny over defective device
- New flaws in device regulation system exposed
- Calls for independent investigation and release of trial data to clarify drug's benefits

An investigation published by **The BMJ today** raises new concerns about the top-selling anti-clotting drug, rivaroxaban (Xarelto).

It questions the validity of a pivotal trial - known as the ROCKET-AF trial - that was used to gain approval for rivaroxaban from the US and European regulators.

The trial, published in the New England Journal of Medicine (NEJM) in 2011, compared rivaroxaban with the older anti-clotting drug warfarin for preventing strokes in patients with irregular heartbeat (atrial fibrillation).

But there are now concerns about the trial results after The BMJ discovered that the blood clotting test device used during the trial had been recalled in December 2014 after giving falsely low test results.

In a special report, The BMJ's Associate Editor, Dr Deborah Cohen, says: "In terms of the trial results, it could make rivaroxaban seem safer than it was with respect to the risk of bleeding and throws doubt onto outcomesused to support the use of the world's best selling new oral anticoagulant."

Doctors and scientists are now calling for an independent investigation and access to the original trial data to clarify the drug's benefits and harms.

Rivaroxaban, manufactured by Bayer and marketed in the US by Johnson and Johnson, belongs to a class of medicines known as the 'direct oral anticoagulants' (DOACs).

It works by preventing blood from clotting and is marketed as a better alternative to warfarin because patients don't need regular tests to check if they have the right amount of drug in their bloodstream. A patient's blood must be "thin" enough to protect against stroke, but not so "thin" that it risks major bleeding.

In November 2015, the European Medicines Agency (EMA) told The BMJ they were investigating, while US Food and Drug Administration (FDA) said they were "aware of concerns regarding the INRatio device and its use in the ROCKET-AF trial and is reviewing relevant data."

The makers of the INRatio device confirmed to The BMJ that the fault dates back to 2002. However, neither they nor the FDA responded to questions about why nothing had been done about the problem earlier.

In the meantime, Harlan Krumholz, Professor of Medicine at Yale University said the NEJM should place an "immediate Expression of Concern" on the paper to notify the medical community, and that there should be "an investigation by an independent group of experts to quickly determine if there are grounds for retraction."

In December, Duke University's Clinical Research Institute, who carried out the trial on behalf of the manufacturer, said further analyses "are consistent with the results from the original trial and do not alter the conclusions of ROCKET-AF."

But former FDA reviewer, Dr Thomas Marciniak, told The BMJ that he would not rely on any re-analyses done by Duke, Johnson and Johnson or the FDA. He added that the data need to be released as "the only solution that would lead to unbiased analyses."

But previous attempts to do this have been thwarted by Bayer who told The BMJ that they have only signed up to sharing information on "study reports for new medicines approved in the US and the EU after January 1, 2014."

According to former FDA clinical pharmacologist, Bob Powell, once a drug is on the market, the regulators lack a mandate to act without a safety signal.

"It is this lack of safety signal that appears to be hindering the FDA in their desire to pursue tailored dosing for DOACs. If it turns out that the issue with the INRatio device changes the safety profile of rivaroxaban, this very well may constitute the safety signal necessary for the FDA to act in this regard," he said.

Today's investigation also exposes flaws in the US device regulation system that allows manufacturers only to show that their devices are "substantially equivalent," or similar, to one already on the market.

The system has been criticized by the Institute of Medicine for not providing enough evidence that a device is safe and effective. Johnson and Johnson, however, has lobbied against tightening up this aspect of device regulation and the need to provide more evidence.

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Note to Editors
Feature: Rivaroxaban: can we trust the evidence?
http://www.bmj.com/cgi/doi/10.1136/bmj.i575

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