Analysis of FDA warning letters reveals patient safety concerns

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**Analysis of warning letters sent by the Food and Drug Administration over the past 7 years finds that patient safety violations and poor record keeping are common clinical trial concerns.**

In the US, research involving human participants is governed by federal regulations enforced by the Food and Drug Administration (FDA). The FDA's Bioresearch Monitoring Program was set up to protect the rights, welfare and safety of human subjects and safeguard the integrity of data relating to trials featuring human participants.

The FDA have the authority to access, copy and verify any documents created by the clinical investigator. Also, the FDA conduct site visits to clinical investigators, sponsors, monitors, contract research organizations, animal laboratories and bioequivalence analytical laboratories.

Typically, this happens:

* If there is a grievance about the conduct of a study
* In reply to sponsor concerns
* On termination of the clinical site
* To provide real-time evaluation of the conduct of the trial and the safety of the subjects
* On request by the FDA review division
* In connection with investigational products "of extraordinary importance."

When the FDA find that violations of significant regulations have occurred, they issue warning letters to encourage voluntary compliance and corrective action before any enforcement is initiated.

According to the FDA, a warning letter is "an informal advisory to a ﬁrm communicating the Agency's position on a matter but does not commit the FDA to taking enforcement action."

Analysis reviews 84 first warning letters issued during the period 2005-2012

To examine the extent of the violations being picked up and communicated to clinical investigators, the authors of the new study reviewed the content of 84 first warning letters sent by the FDA to 46 trial sponsors, 20 lead researchers and 18 institutional review boards during 2005-2012.


*The most common warnings for institutional boards related to failures to follow standard operating procedures and inadequate record keeping.*

The analysis shows that the most commonly raised concern from clinical trial sponsors is a failure to monitor progress according to the state schedule, followed by a failure to obtain the agreement of the principal investigator. Of these warnings, 3 out of 4 related to new devices, with a quarter relating to new drug studies.

**Of concerns raised by the FDA to lead researchers, 95% concerned failure to adhere to the stated plan for the investigation, while 55% related to failure to report side effects and protect the safety of trial participants. About 40% of these warnings concerned poor record keeping. Overall, 80% of these warnings related to drug trials.**

The most common warnings for institutional boards, meanwhile, related to failures to follow standard operating procedures and inadequate record keeping.

Comparing their results - which are published in the *Journal of Medical Ethics* - with a previous analysis from 1997, the researchers found that while regulatory compliance has improved, supervision has gotten worse.

**Also, the researchers found that two new serious violations have become a concern since the 1997 analysis. These are failing to get investigations green-lit by an institutional board before commencing the research, and submitting false data to the FDA and/or sponsors.**

"Fair and appropriate procedures for handling violations during clinical trials need to be developed and implemented globally in order to protect human rights, well-being and safety, and to raise awareness of ethical behavior," say the authors.

They also recommend that every regulatory agency that oversees clinical trials should conduct inspections of participating centers and regularly publish their findings. The authors believe these tactics may boost compliance with good practice.