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ANALYSIS

Deficiencies in proposed new EU regulation of clinical trials

The EU Clinical Trials Directive has been heavily criticised for being bureaucratic, confusing, and leading to a decline in the number of trials conducted in Europe. Although new proposals for regulation are much better, **Peter Gøtzsche** argues improvements are still needed for patient safety, rational use of drugs, and research planning

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The new European Union Regulation on Clinical Trials applies to all drug trials in the EU.[1] Due to be finalised early in 2013, it will replace the much criticised Clinical Trials Directive. It aims to simplify the process for application and approval of trials and make it more uniform throughout the EU. It also includes a lighter regime for low risk trials—for example, those using licensed medicines. It contains much good sense, but there are still deficiencies in providing access to information and protection to patients. Ahead of a major discussion of the proposed regulation in the European parliament, I outline ways in which the regulation could be strengthened further.

Public access to information

Applications to conduct clinical drug trials will be submitted through a single EU portal, from where the relevant national authorities will access and process the applications. All the application information, and subsequently results and data, will be publicly accessible unless confidentiality is justified to protect personal data or commercially confidential information.

This should not be a problem. Under the current proposal the EU database will contain no personal data on trial participants, and the European ombudsman has declared that there is no commercially confidential information in trial protocols or clinical study reports.[2] Furthermore, the interests of public health and the citizens' right to know should override any invocation of commercial confidentiality. Patients volunteer for research to benefit society and future patients, not to benefit a particular drug company.

Summary results must be reported to the EU database within one year of the end of the trial, but it is possible to postpone this for substantiated "scientific reasons." I believe that there should be no exceptions. A trial may be legitimately extended if there are fewer events than expected, but the results should be available when the target has been met, even if follow-up is planned after this. To ensure that this requirement is met, we need a public audit process at the EU portal, with scheduled dates for results and publication of the dates of actual posting. There should be sanctions for violations, such as a large fine for every day the one year limit is exceeded and a temporary prohibition from doing further trials.[3] Similar legislation in the United States suffers from poor enforcement, and only a fifth of trials report summary results within one year.[4]

Currently the regulation requires submission of only a summary of the results, but summaries are often biased.[5-7] We need a full clinical study report with detailed analyses in accordance with the protocol and the raw anonymised individual patient data in statistical data sheets, with statistical codes, so that other researchers can analyse the data, just as the European Medicines Agency intends to require and make publicly available.[8]

The regulation states that the protocol should include a description of the publication policy. Trial protocols often say that the data belong to the industry sponsor or that the sponsor has the right to decide whether the results will be published.[9] The regulation should therefore mention that trial data belong to society and that such clauses will lead to applications being rejected, as will any other constraints on access to the documents and data.

Trial protocol

As well as requiring a copy of the trial protocol, the regulation should require that the protocol is written in an easily accessible format, such as a searchable pdf, rather than as scanned images. It should also contain copies of the case report forms because the collected data can be influenced by how questions are framed. Furthermore, the protocol needs to contain the full statistical analysis plan. In industry trials the statistical analysis plan is often not finalised until the trial has run for quite some time, and even after the results have been seen.[9-11] An infamous example is GlaxoSmithKline study 329 of paroxetine in children, which found that the drug had no effect on depression and caused children to become suicidal. When published, however,

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the statistical analysis had been changed to such a degree that the drug seemed beneficial. [12 13]

The regulation requires that the trial protocol is based on summaries of all available information and evidence that supports the rationale for the trial, and that trial data submitted in the application dossier need to be based on trials that have been registered before their start in a public register.

These proposals need considerable modifications. Many old, unregistered trials are highly relevant for evaluating the scientific and ethical justifications of new trials. Furthermore, summaries of previous trials are not sufficient, as what superficially looks like "conflicting" results may not be conflicting at all. The rationale for a new trial must be based on a rigorous recent systematic review of all similar previous trials, including those of similar drugs, and with meta-analysis if possible. If this is not done, many unethical trials will be approved, as the type of drug might already have been shown—or could have been shown—to be either life saving or harmful.

Exclusion of older people from a trial has to be justified under the regulation, but this could go further. Industry trials routinely exclude patients above 65 years,[14] even though they are more vulnerable to harms and are more likely to receive several drugs. Trial populations should have to be similar to the populations that will be expected to use the drug.

Drug information

The regulation should require sponsors to submit certificates of analysis of both active drugs and placebos together with visual records (films or pictures) of them. Drugs and placebos often differ in texture, colour, and thickness, even though the trials are called double blind.[15] In a study of oseltamivir, for example, the cap of the placebo capsule was a different colour from that of the active drug.[16] Lack of effective blinding can be important when the outcomes are highly subjective, such as the duration of an influenza episode.

The regulation requires sponsors to supply the investigators with an "investigator's brochure." This is superfluous for drugs already on the market, and the trial protocol should describe fully what the investigators need to know so brochures are relevant only for some industry trials.

Informed consent

Importantly, the regulation requires the submission of all information that will be given to trial participants as well as the form for written informed consent. It should also require the consent form to state that all results and anonymised trial data will be made publicly available within a year after the end of the trial at the EU portal and that, if a national or local committee finds out that an approved trial is unethical, the EU portal will be notified so that the trial can be stopped in all countries.

In 2009 Pfizer started a large trial comparing celecoxib with other non-steroidal, anti-inflammatory drugs and told participants that evidence on the effects of celecoxib on heart disease and strokes was inconclusive.[17] However, the package insert had mentioned since 2005 that celecoxib increases the risk of cardiovascular events, and a 2006 meta-analysis conducted by independent researchers using data from the US Food and Drug Administration had shown that celecoxib doubles the risk of heart attacks compared with placebo.[18] The participant information was therefore misleading, and the trial was unethical.

Accountability and archiving

The sponsor's signature will confirm that the information provided is complete. The signed statement should also make explicit that, to the sponsor's knowledge, no trials relevant for the evaluation of the application (whether conducted by the sponsor, registered, or published) have been left out. The sponsor should also confirm that all important harms of the sponsor's drug and similar drugs have been described and quantified. This is important because, on average, only one fifth of previous trials have been cited in trial reports, which make new trials look far more impressive, needed, and ethical than they really are.[19]

The regulation requires the sponsor and investigator to archive the content of the clinical trial master file for at least five years. Since the purpose of a master file is to permit evaluation of the conduct of a trial and the quality of the data, this is completely inadequate. All documents, including the original case report forms with trial data, should be archived electronically, and there should be no time limit for storage, because the data might be crucial in litigation cases or for interpreting the trials (Tom Jefferson, personal communication). Those parts of the master file that do not allow identification of individual patients should therefore be made available at the EU portal.

Approval of trials

The new regulation states that the reporting member state (the country responsible for leading the assessment of the application) will assess the expected therapeutic and public health benefits of a trial. The assessors should not have conflicts of interest; should be independent of the sponsor, the institution of the trial site, and the investigators involved; and should be free of any other undue influence. If the public is to have confidence that the assessments are impartial, the assessors should post a declaration in the EU database of their conflicts of interest, or a statement that they have none. People on the advisory committees of national drug agencies often have financial conflicts of interest in relation to drug companies,[20] although, according to laws of public administration, they should have none.

Changes to the trial protocol

The regulation states that when modifications to an approved trial have a substantial effect on the safety or rights of the participants or on the reliability and robustness of the data generated, they should be subject to an authorisation procedure similar to the initial one.

Yet it is up to the sponsor to decide whether a modification is substantial, and the sponsor has a conflict of interest. At the very least, it should be required that any protocol modifications should be dated and submitted to the portal so that they become part of the public record. Drug companies and academics often make far reaching changes to the protocol without revealing it. In a cohort of trial protocols submitted to ethics committees in Denmark, changes to primary outcomes were made by the time of publication in 63% of them,[10] and many important changes to the statistical analyses were also made.[11] This creates a risk of circular evidence, which occurs when the same data are used to raise a hypothesis and to test it. Without access to all protocol changes, it is impossible for a reader to judge whether what is reported is reliable.

Trial conduct

The regulation rightly states that blinding shall be maintained for people responsible for the conduct of the trial (such as the managers, monitors, and investigators) and those responsible for analysing the data and interpreting the results at the conclusion of the trial. Unblinded information is accessible only to those responsible for safety evaluations during the trial.

However, industry sponsors often have access to unblinded data while the trial is running. In 44 protocols of industry trials submitted to Danish ethics committees the sponsor had access to accumulating data in 16, but only one disclosed such access in the published article.[9] An additional 16 protocols noted that the sponsor had the right to stop the trial at any time, for any reason. Thus, the sponsor had potential control over a trial in progress in 32 (73%) of these studies, which creates a risk that a trial will be reported at a time that happens to favour the sponsor's product.

It is difficult to safeguard against unrecorded peeks at the accumulating data, but one possibility would be to let academic trial centres handle the data instead of a drug company or contract research organisation. Blinded data analysis could be extended to blinded manuscript writing, where the investigators approve two versions of the manuscript (one assuming A is the placebo group and the other assuming B is) before the code is broken.[21]

Reporting of serious adverse events

The regulation requires sponsors to report adverse events that affect the benefit-risk balance of the clinical trial through the EU portal only if they are unexpected. Thus if the sponsor expects a drug to cause myocardial infarction then myocardial infarction need not be reported. I would argue that all serious adverse events should be reported because they might affect the benefit-risk balance.

This requirement should also apply to serious adverse events occurring in trials outside the EU. Drug companies have sometimes failed to report serious harms with their drugs to the FDA with the excuse that they did not originate in trials conducted in the US.

The regulation states that, once the trial has ended, the investigator does not need to monitor the participants for adverse events, and that serious adverse events should be reported to the sponsor only if the investigator becomes aware of them. However, for many drugs serious harm can take some time to develop. Patients should therefore be followed up closely for some time after they come off a drug, particularly if they drop out of a trial (which may be because of an unrecognised harm). As an example, many patients on selective serotonin reuptake inhibitors develop abstinence symptoms similar to those seen with benzodiazepines when they stop taking the drug,[22] and some may even commit suicide or murder.[23]

Time for action

The drug industry is lobbying the European Commission and members of the European parliament to prevent greater transparency about their trials and public access to all results and data. The lead rapporteur, Glenis Willmott MEP, is preparing arguments for amendments to the European Commission proposal that will be discussed in February by the parliament's environment and health committee. The time to influence the final form of this new regulation is now.

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Improvements needed in EU regulation

- Citizens' right to know should override commercial confidentiality
- Results and data should be provided within one year after trial completion, with no exceptions
- Violations of the one year deadline should be punished
- A public audit process should be established
- Clinical study reports and raw data should be published on the portal, not simply summaries
- Trial data belong to society, not to the sponsor
- Trial protocols should be easily accessible and all amendments should be dated and submitted to the EU portal
- The protocol should contain the full statistical analysis plan and case report forms
- The scientific and ethical justification for a trial should be based on a systematic review of similar trials, whether registered or not
- Trial populations should be similar to the populations expected to use the drug
- Certificates of analysis of both active drugs and any placebos should be submitted together with visual records
- The consent form should state that all results and anonymised trial data will be made publicly available within a year after the end of the trial
- The clinical trial master file should be stored indefinitely, in electronic formats
- All serious adverse events should be reported without delay
- Patients should be followed up closely for some time after they come off a trial drug