降圧薬臨床試験のmisconductと市販後の医師主導臨床試験のあり方

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Misconduct in investigator-initiated clinical trials on antihypertensive drugs and the future of clinical trials in Japan

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Abstract

Evidence–based medicine (EBM) has been widely accepted in Japan since the mid-1990s, and a movement has emerged to generate clinical evidence on ethnic differences in Japanese population for certain diseases. In the past 10 years, investigator-initiated clinical trials looking at the effects of antihypertensive and antihyperlidemic drugs on cardiovascular diseases have been reported. In some trials on antihypertensive drugs, misconduct was suspected and as a result, reports on two trials have been retracted.

There are two main features characterizing these investigator-initiated clinical trials. Firstly, primary endpoint is a composite endpoint, composed of various clinical endpoints including soft endpoints. Secondly, the study design adopted is PROBE (prospective, randomized, open, blinded-endpoints) design. Significant differences between groups are often observed in soft endpoints which the endpoint review committee cannot confirm.

The level of basic research in Japan is relatively high. On the other hand, clinical research has not yet fully developed and the literacy in clinical research among clinicians is still low. Under these circumstances, there are those who insist that ICH-GCP should be applied to any clinical trial. However, GCP is a regulation that is applied to registration trials which are typicaly efficacy trials usually sponsored by a pharmaceutical company, whereas the clinical trials in question now are effectiveness trials which look at drug effects in the real world setting. These clinical trials are regarded as low-risk trials, in which drugs are used according to approved indications and doses in unblinded situation. In its 2011 report, the OECD (Organisation for Economic Co-operation and Development) recommended a risk-based approach to clinical trial supervision in which the regulations are decided according to the nature, objectives and risks of clinical trials.

In the UK, many high quality investigator-initiated clinical trials had been conducted in the past. However, since the introduction of the EU Clinical Trials Directive which requires the application of ICH-GCP in any pharmaceutical clinical trial, there has been a significant decrease in the number of investigator-initiated clinical trials, while the cost and the time required from application to the conduct of such trials have significantly increased.

Therefore, in order for Japan to excel in clinical research, we should first improve clinical trial literacy of Japanese clinicians, and at the same time, be mindful that we not repeat the same mistake as the EU.

Key words
clinical trial, GCP, EU Clinical Trials Directive

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