# Clinical evaluation: too many endpoint changes during trials

● A study of several hundred randomised trials in oncology has found that a change was made to the primary endpoint in about half of the trials, in most cases with a complete lack of transparency.

Double-blind randomised clinical trials are the most robust tool for evaluating a treatment's clinical efficacy. Provided that their design and the analysis of their results are sufficiently rigorous to ensure they provide high-level evidence, particularly in relation to the primary endpoint (1).

A study conducted by researchers in the United States has analysed changes made to the primary endpoints for evaluating drug efficacy during randomised trials. These trials were identified using the US clinical trials registry ClinicalTrials.gov, from its launch in 2000 through February 2020 (2,3).

The study included 755 phase 3 oncology drug trials for which at least one primary endpoint was reported.

In about two-thirds of the trials, the protocol was not published prior to the start of the trial, which makes it impossible to tell whether the primary endpoint changed during the trial (2).

In 145 of the 282 trials for which the protocol had been published, the primary endpoint changed after the trial had started. The most common changes, each accounting for about one-third of cases, were: a primary endpoint became a secondary endpoint; a secondary endpoint became a primary endpoint; or the definition of the primary endpoint was changed. In 102 trials (about 70%), this change was not disclosed in the published article that reported the results, making it harder to detect potential bias. In about 20% of these trials, the result for the initial primary endpoint was not reported (2).

The results of trials in which a change was made to the primary endpoint were statistically more often in favour of the drug: this was the case in 89 of 145 trials with an endpoint change (61%), versus 309 of 610 trials in which no change was detected (51%) (2).

These primary endpoint changes, which are far from trivial and often made with a complete lack of transparency, show the extent to which the evaluation of many of these drugs lacks robustness, in what is considered to be a highly profitable therapeutic area for the pharmaceutical industry.

They also confirm the importance of trial registries, and of systematically consulting these databases when considering basing a treatment decision on trial results.



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**References** **1-** "Prouver l'efficacité d'un traitement. Les essais comparatifs randomisés en double aveugle, fondement d'une démarche scientifique rigoureuse" *Rev Prescrire* 2023; 43 (473): 200-204. **2-** Florez MA et al. "Incidence of primary end point changes among active cancer phase 3 randomized clinical trials" *JAMA Netw Open* 2023; 6 (5): 8 pages. **3-** "ClinicalTrials.gov Background". clinicaltrials.gov accessed 7 May 2024: 3 pages.

# European "pharmaceutical package": letter on clinical data exclusivity

In March 2024, along with over 20 European civil society groups, Prescrire signed a joint letter to members of the European Parliament responsible for handling the revision of European pharmaceutical legislation (known as the "pharmaceutical package"). This letter asked them not to extend the "data protection" period during which clinical data pertaining to originator products enjoy regulatory protection, and to put public health, healthcare users and patients before the interests of pharmaceutical companies (1).

Unfortunately, this view was not reflected in the plenary vote held in the Parliament on 10 April 2024, with members opting to practically obliterate the reduction in the duration of regulatory data protection periods that had been proposed by the European Commission, and is supported by civil society (2).



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**References** **1-** "Patients say NO to extending the duration of intellectual property protection for medicines" 5 March 2024: 2 pages. **2-** "P9_TA(2024)0221 (...) European Parliament legislative resolution of 10 April 2024 on the proposal for a regulation (...)": 160 pages.