Translated from *Rev Prescrire* January 2008; **28** (291): 69-70

Evaluation of treatment benefits: clinical endpoints relevant to patients

● **Evaluation of treatment benefits needs to focus on the health outcomes of greatest importance to patients. Endpoints for evaluating treatment efficacy should be based on clinical outcomes.**

● **"Surrogate" endpoints do not directly affect patients' health but can be useful in some clinical situations. The adverse effects of treatment must also be assessed.**

Will this treatment help relieve my suffering? Will it cure the disease? Will it substantially reduce my risk of illness?

These are some of the explicit and implicit questions patients ask healthcare professionals.

Their answers should be based on the available clinical evidence. And when choosing efficacy endpoints for curative or preventive drug and non-drug treatments, the first step is to take into account the health effects most important to patients (1).

Clinical outcomes relevant to patients. Death, pain, disability, effects on activities of daily living and quality of life are all endpoints that are important to patients (1). Most relevant endpoints are clinical outcomes that patients can perceive (**a**).

When choosing an endpoint with which to assess the effectiveness of an intervention, it is first necessary to understand the natural course of the disease in question.

For example, the risk of death, or the mortality rate, is clearly a relevant outcome for patients treated for myocardial infarction. After coronary stenting, a more relevant outcome for patients is the risk of myocardial infarction or death rather than the incidence of new stenoses detected by angiography.

In contrast, mortality is not the most relevant treatment outcome for patients with osteoarthritis. The effects on pain, joint mobility and quality of life are clearly more important to patients.

Surrogate endpoints: use with caution. Surrogate endpoints are often used in clinical trials because it is easier and faster to show, for example, that a drug reduces blood pressure or cholesterol levels than to wait for a possible reduction in the incidence of cardiovascular events.

The use of surrogate endpoints is likely to give drug companies a faster return on investment. It is also easier and faster for caregivers to measure the effect of treatment on a surrogate endpoint.

But treatments that are effective on a surrogate endpoint may be ineffective, or even harmful, when assessed on the basis of their impact on outcomes that are meaningful to patients (2,3).

The prevention of complications such as stroke and myocardial infarction is the most relevant health outcome for hypertensive patients. Simply measuring changes in blood pressure in a clinical trial cannot show whether there will be concrete cardiovascular benefits for patients. Doxazosin, an alpha blocker, lowers blood pressure, as does hydrochlorothiazide, a thiazide diuretic. But hydrochlorothiazide is far more effective than doxazosin in preventing cardiovascular complications in hypertensive patients (4,5).

Similarly, teriparatide, a human parathyroid hormone derivative, and alendronic acid, a bisphosphonate, both increase mineral bone density in postmenopausal women with osteoporosis. But only alendronic acid has been shown to prevent new non-vertebral fractures (6).

Surrogate endpoints. In some circumstances, however, the only option is to use surrogate endpoints to evaluate treatment outcomes. But there must be solid evidence demonstrating a good correlation between changes in the surrogate endpoint and clinical outcome (2,3,7).

For example, given the severity of AIDS if left untreated, a placebo-controlled trial in which mortality is the primary endpoint would clearly be unacceptable for AIDS patients. Viral load and the CD4 lymphocyte count were found to be satisfactory surrogate endpoints for antiretroviral efficacy, as there is a good correlation with the risk of opportunistic diseases and death (8,9).

Some surrogate endpoints are relevant, albeit indirectly, to patients, particularly when the disease progresses slowly or carries a risk of death or disability.

Risk-benefit balances. However, even when a surrogate endpoint is correlated with the clinical outcome of a specific disease, it may not reflect treatment effects in other areas.

Thus, clofibrate, a fibrate, was approved on the basis of its beneficial impact on blood cholesterol levels. It was only after it had been on the market for some time that it was shown to increase mortality, owing to an increase in cancer (10,11).

Similarly, torcetrapib not only increased HDL cholesterol levels but also the mortality rate in a clinical trial; its development was therefore abandoned (12).

Surrogate endpoints alone, such as blood pressure, cholesterol levels, bone density and the number of ventricular extrasystoles on the ECG, cannot prove that a specific treatment will offer patients concrete benefits.

In summary. In order to evaluate the benefits of a preventive or curative intervention, the choice of endpoints should ideally reflect the health outcomes of greatest importance to patients. However, therapeutic decisions also have to take into account the risk of adverse effects and other therapeutic options, based on comparison of the risk-benefit balances.

a- There are some special cases where an endpoint is useful even though it does not directly concern the patients receiving treatment. For example, the mortality rate among the elderly in nursing homes is a useful outcome measure for evaluating the benefits of influenza vaccination among staff working in these institutions (ref 13).

Selected references from Prescrire's literature search.

1- Prescrire Rédaction "Critères cliniques" *Rev Prescrire* 1989; **9** (84): 150.

2- Prescrire Rédaction ""Critères intermédiaires", "critères de substitution". À ne pas confondre avec "critères cliniques"" *Rev Prescrire* 1989; **9** (85): 200.

3- Greenhalgh T "Papers that report drug trials". In: Greenhalgh T "How to read a paper" *BMJ* Publishing Group.

4- Prescrire Rédaction "Hypertension artérielle: diurétique en première ligne. Confirmation par un grand essai" *Rev Prescrire* 2003; **23** (238): 299-301.

5- Prescrire Editorial Staff "Results of ASCOT-BPLA trial" *Prescrire Int* 2006; **15** (83): 112.

6- Prescrire Editorial Staff "Osteodensitometry in healthy postmenopausal women" *Prescrire Int* 2008; **17** (94): 68-72.

7- Kassaï B et al. "Critères intermédiaires et critères de substitution" *Médecine thérapeutique* 2006; **12** (2): 96-103.

8- Prescrire Rédaction "Les lymphocytes T CD4+ dans l'infection HIV" *Rev Prescrire* 1993; **13** (132): 467-469.

9- Prescrire Rédaction "Antirétroviraux: de nouveaux critères européens d'AMM" *Rev Prescrire* 1998; **18** (181): 117.

10- Prescrire Editorial Staff "Cholesterol-lowering drugs" *Prescrire Int* 1999; **8** (42): 116-120.

11- Prescrire Rédaction "Hyperlipidémies. Quelle place pour les fibrates en prévention cardiovasculaire?" *Rev Prescrire* 2001; **21** (219): 555-556.

12- Prescrire Editorial Staff "Torcetrapib: development abandoned" *Prescrire Int* 2007; **16** (89): 114.

13- Prescrire Rédaction "Soignants: se faire vacciner contre la grippe. Un service rendu aux patients à risque" *Rev Prescrire* 2000; **20** (209): 603-604.