

## Endpoints in Clinical Trials: Advantages and Limitations

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### Introduction

Primary endpoints in clinical trials must meet 3 criteria:

A) Clinically relevant

B) Sensitive to treatment effect

C) Measurable and interpretable. Secondary endpoints could provide a more global view of the benefit of the treatment being tested and by clarifying its risk-to-benefit ratio; may be of 2 types: A) Those

that, like primary endpoints, are clinically relevant and may be taken into consideration for drug indications; and B) “Feel-good” endpoints, which are not likely to lead to a new indication or a change in labelling but might provide reassurance about the primary endpoint along with new information about the disease. Some secondary endpoints might be exploratory analyses, although they might demonstrate biologically plausible effects, they remain hypothesis-generating and will need to be confirmed by additional studies. Table 1 and 2 shows the terms and definitions used in the outcomes of clinical trials [1-4].

Term	Definition
Biomarker (biological marker)	A characteristic that is measured and evaluated objectively as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Clinical end point	A characteristic or variable that reflects how a patient feels or functions or how long a patient survives.
Surrogate end point	A biomarker that is intended to substitute for a clinical end point, i.e., a biomarker that is expected to predict clinical benefit, harm, or lack of benefit or harm.
Intermediate end point	A characteristic that is intermediate in the causal pathway between an intervention and the clinical end point.

**Table 1:** Shows the outcomes in major clinical trials.

Endpoints	Definition	Advantages	Limitations
<b>Overall Survival (OS)</b>	Time from randomization* until death from any cause	Universally accepted measure of direct benefit Easily and precisely measured	May require a larger trial population and longer follow-up to show statistical difference between groups May be affected by crossover or subsequent therapies Includes deaths unrelated to disease
<b>Progression-Free Survival (PFS)</b>	Time from randomization* until disease progression or death	Requires small sample size and shorter follow-up time compared with OS Includes measurement of stable disease (SD)	Validation as a surrogate for survival can be difficult in some treatment settings Not precisely measured (i.e., measurement may be subject to bias)
<b>Time to Progression (TTP)</b>	Time from randomization* until objective disease progression; does not include deaths	Not affected by crossover or subsequent therapies Generally based on objective and quantitative assessment	Definition may vary among trials Requires frequent radiologic or other assessments Requires balanced timing of assessment among treatment arms
<b>Time to Treatment Failure (TTF)</b>	Time from randomization* until objective disease progression; does not include deaths.	Useful in settings in which toxicity is potentially as serious as disease progression (e.g., allogeneic stem cell transplant)	Does not adequately distinguish efficacy from other variables, such as toxicity
<b>Time to Next Treatment (TTNT)</b>	Time from end of primary treatment to institution of next therapy	For incurable diseases, may provide an endpoint meaningful to patients	Not commonly used as a primary endpoint Subject to variability in practice patterns
<b>Event-Free Survival (EFS)</b>	Time from randomization* to disease progression, death, or discontinuation of treatment for any reason (e.g. toxicity, patient preference, or initiation, of a new treatment without documented progression)	Similar to PFS; may be useful in evaluation of highly toxic therapies	Initiation of next therapy is subjective. Generally not encouraged by regulatory agencies because it combines efficacy, toxicity, and patient withdrawal
<b>Time to Next Treatment (TTNT)</b>	Time from end of primary treatment to institution of next therapy	For incurable diseases, may provide an endpoint meaningful to patients	Not commonly used as a primary endpoint Subject to variability in practice patterns

<b>Overall response rate (ORR)</b>	Proportion of patients with reduction in disease burden of a predefined amount	Can be assessed in single-arm trials Requires a smaller population and can be assessed earlier compared with survival trials	Not a comprehensive measure of drug activity
<b>Duration of Response (DoR)</b>	Time from documentation of disease response to disease progression	Effect is attributable directly to the drug, not the natural history of the disease	
<b>(Quality Of Life - QOL) Symptoms Reported by Patients</b>	Outcome self-reported by patients using wellness scales, presence of adverse effects and toxicity therapeutic	Patient perspective of direct clinical benefit.	Reporting sometimes incomplete Small symptoms and signs of difficult to assess Few validated instruments Sometimes patients do not report accurately the effects adverse
<b>Toxicity</b>	Rate of adverse effects	Definition of the benefit/risk balance of therapy	Sometimes patients do not report accurately the effects adverse
<b>Other Common Endpoints</b>	<b>Response rate (RR)</b> Response rate measures disease size, usually using a scan or X-ray.	<b>Complete response (CR)</b> Disappearance of all clinical evidence of disease.	<b>Partial response (PR)</b> At least 30% reduction in size of all measureable
	<b>Stable disease (SD) or No change (NC)</b> Between a 30% reduction or <25% increase in the size of all detectable disease	<b>Progressive disease (PD)</b> Patients or proportion of patients with a $\geq 25\%$ increase in size of disease since previous measurement	Objective response rate (ORR) Percentage of patients whose disease decreased (Partial response – PR) and/or disappears (Complete response – CR) after treatment.
	<b>Disease control rate (DCR) or clinical benefit rate (CBR)</b> Percentage of patients whose disease shrinks or remains stable over a certain time period. DCR is the sum of the complete, partial and stable disease rates.	<b>Duration of response (DR)</b> Time from confirmation of a partial response (PR), complete response (CR) or stable disease (SD), until the disease has been shown to progress following treatment (progressive disease or PD).	<b>Performance status (PS)</b> Measure of how well a patient with a disease diagnosis can perform ordinary tasks in daily life before, during or after treatment. Specific numeric PS scales indicate levels of disability due to disease, and/or severity of symptoms. Two main scales are.

**Table 2:** Outcomes in major clinical trials. \*Not all trials are randomized. In nonrandomized trials, time from study enrolment is commonly used.

## References

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