(PRO) (28,29) the question of objectivity and subjectivity depends on the exact outcome that is being measured. The Patient-Reported Outcomes of migraine headaches (30) hot flashes (31) and tinnitus (32) are relatively objective. But the Patient-Reported Outcomes of fatigue or depression are relatively subjective.

For oncology clinical trials, various scales and questionnaires that are used include ECOG performance status, Karnofsky performance status, and health-related quality of life (HRQoL).

e. Using multiple endpoints, and choosing the endpoint on which to base conclusions

The ICH Guidelines provide a general warning, applicable to many diseases, regarding endpoint choice. According to the ICH Guidelines (33):

> *When two treatments are used for the same disease or condition, they may differentially affect various outcomes of interest in that disease, particularly if they represent different classes or modalities of treatment. Therefore, when comparing them in a clinical trial, the choice and timing of endpoints may favor one treatment or the other. For example, thrombolytics in patients with acute myocardial infarction can reduce mortality but increase hemorrhagic stroke risk. If a new, more pharmacologically active, thrombolytic were compared with an older thrombolytic, the more active treatment might look better if the endpoint were mortality, but worse if the endpoint were a composite of mortality and disabling stroke. Similarly, in comparing two analgesics in the management of dental pain, assigning a particularly heavy weight to pain at early time points would favor the drug with more rapid onset of effect, while assigning more weight to later time points would favor a drug with a longer duration of effect.*

While any given drug may have three distinct benefits, and where each benefit can be measured at three different time points, failure to be aware of these variables can result in artifactual conclusions from the clinical trial. The next few chapters detail the endpoints used in clinical trials of oncology, clinical trials in multiple sclerosis, and clinical trials on hepatitis C virus. The chapters on oncology endpoints provide guidance on deciding which endpoints to include in the clinical trial, for example objective response, progression-free survival (PFS), time to progression (TTP), disease-free survival (DFS), and overall survival. These chapters document the fact, for example, that

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