therapy exists, and where the efficacy and safety of the established therapy is reasonably predictable or uniform, an active control might be the preferred clinical trial design. Consider the hypothetical where a new drug is compared with a placebo. Assume the new drug works better than the placebo. However, even if the new drug works better than the placebo, the results do not provide any direct information on whether the drug works better than the established therapy. This comparison can only be established in a clinical trial where one arm contains the study drug, and where a control arm contains an active control that is an established therapy.

Examples of an active control are disclosed in the schema appearing above, that is, in the clinical trials of Perez et al. (91) (Fig. 2.5), Untch et al. (92) (Fig. 2.7), Puhalla et al. (93) (Fig. 2.8), and Sekine et al. (94) (Fig. 2.9). The FDA has specifically warned investigators that when choosing a drug for the active control to avoid using an active drug that is outmoded or that has been replaced by another drug (95).

Sobrero and Guglielmi (96) noted the phenomenon where, over the course of decades, clinical trials in oncology using an active control design have produced diminishing returns. In other words, with the passing of decades, it is easy to discover new anti-cancer drugs, but it becomes progressively more difficult to find a new anti-cancer drug that works significantly better than other recently available drugs.

Where a new drug is devised, but where it is not certain if a significant difference will be found between the new drug and an active control, the trial design may shift its perspective. The shifted perspective takes the form of a non-inferiority trial. The main goal of a non-inferiority trial is to show that the study drug is not less effective than the active control.

A clinical trial on a study drug that shows non-inferiority to the active control can provide marketing advantages to the study drug, for the following reasons. As summarized by Lesaffre (97) these advantages include:

- While the efficacy of the study drug may be merely non-inferior to the active control drug, the study drug may have a far better safety profile

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[92] Untch M, Möbus V, Kuhn W, et al. Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. *J Clin Oncol*. 2009;27:2938–2945.

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[96] Sobrero A, Guglielmi A. Current controversies in the adjuvant therapy of colon cancer. *Ann Oncol*. 2004;15(Suppl 4): iv, 39–41.

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