In a clinical trial on nonsmall-cell lung cancer, Rosell et al. (122), used an add-on design. The new drug was an antibody (cetuximab). The established therapy was the combination of two small molecules, namely, cisplatin and vinorelbine. In the words of the investigators, "[t]he main purpose of this study was to assess the add-on activity of cetuximab."

Add-on design clinical trials were also used to gain FDA approval of anakinra and abatacept. Unfortunately, as observed by Ottolenghi et al. (123), the report from the add-on design study did not provide a list of adverse events that were unambiguously caused by the study drug alone, but only provided adverse events that are caused by the combination of the study drug and the previously approved drug.

c. Three-Arm Study—Clinical Trial With Two Different Active Control Arms

Clinical trials can include more than one control arm. In addition to an arm that receives study drug, the trial design can also include two active control arms, each receiving a different active control. In a clinical trial for *Staphylococcus aureus* infections, Stryjewkski et al. (124), included a study drug arm (telavancin), plus a first active control arm (vancomycin) and a second active control arm (penicillin), as summarized below:

- Study drug arm (telavancin)
- First active control arm (vancomycin)
- Second active control arm (penicillin).

Two active control arms were used for the following reasons. First, vancomycin and penicillin are both standards of care, that is, they are both suitable for use as an active control. Secondly, the infecting agent, *S. aureus*, is heterogeneous. This heterogeneity took the following form. *Staphylococcus aureus*, occurs in methicillin-resistant (MRSA) and methicillin-susceptible (MSSA) forms. Vancomycin is effective against MRSA, but may not be effective against MSSA (125). Conversely, penicillin is effective against MSSA, but not MRSA. If only one active control had been used, the results of this clinical study could have led investigators to overstate the efficacy of the study drug, relative to the efficacy of the standard of care.

Clinical study design using two different active controls can be used in studies of infections, as well as for clinical studies in oncology, immune disorders, metabolic diseases, and neurological disorders.

d. Dose Modification and Dose Discontinuation

Dose modification is a component clinical trial design that encompasses dose reductions, dose increases, and interruptions or delays in dosing. Dose discontinuation refers to permanent cessation of dosing to a particular study subject.

Although a dose modification and discontinuation can be indicated in the study schema diagram, they are more often indicated only in the text of the Clinical Study Protocol. Dose

[122]Rosell R, Robinet G, Szczesna A, et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. Ann. Oncol. 2008;19:362–9.

[123]Ottolenghi L, et al. Limits of add-on trials: antirheumatic drugs. Eur. J. Clin. Pharmacol. 2009;65:33–41.

[124]Stryjewski ME, Chu VH, O'Riordan WD, et al. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. Antimicrob. Agents Chemother. 2006;50:862–7.

[125]Stryjewski ME. E-mail of October 10, 2010.