7.4.5 Primary Endpoints

Traditional primary endpoints for pivotal efficacy trials may or may not be used in the confirmatory biosimilar efficacy trial. Since the goal of the biosimilar trial is to confirm "sameness" or similarity to the reference product, and clinical testing is far less sensitive in discovering differences than analytical methods, the primary endpoint of the clinical trial has to focus on the biological effect of the molecule where there is greater sensitivity to pick up a difference.

7.4.5.1 Case Study

As mentioned above and outlined in Figure 7.2, ACR 20 in the evaluation of anti-TNF biologics is not sufficiently sensitive. Regulatory authorities' views on this topic have evolved, and they have now accepted the use of endpoints that can be evaluated sequentially and are not dichotomous. The routine biosimilar trials in rheumatoid arthritis often used ACR 20 as a primary endpoint measured after 6 months of treatment. As the regulatory mindset has evolved over time, it is acceptable now to use DAS28 (disease activity score in 28 joints) for the assessment of efficacy in rheumatoid arthritis patients (Hoffmann-La Roche, 2010; NRAS, 2016). Importantly, DAS28 can be measured repetitively and earlier on in the clinical trial, and some regulators understand that differences between biologics could be better documented on the upswing of drug exposure to these biologics which happens earlier in the clinical trial.

Transitioning to oncology studies, primary endpoints in trials for regulatory approval are overwhelmingly focused on the overall survival of patients after treatment with a new agent. This is appropriate as one wants to understand whether the new treatment actually has an impact on the survival of patients. Measuring other parameters such as size of the tumor after treatment or overall response could reveal a difference in tumor mass that does not benefit the patient's survival. Since trials looking at overall survival may take substantial time, some regulatory authorities, such as the FDA, came up with approaches for accelerated approval using progression free survival (PFS). Drugs approved using a primary endpoint of progression free survival are usually required to ultimately demonstrate a positive impact on overall survival.

However, for confirming "sameness" for a biosimilar after all of the analytics have demonstrated similarity of the molecules, conducting an oncology study using a primary endpoint of overall survival is not appropriate. Such an approach does not provide sensitivity to pick up differences between the molecules due to many confounding factors and would require huge and unfeasible studies. Biosimilar confirmatory clinical trials often focus on an aspect related to the biology of the biosimilar that is more sensitive to pick up differences between the molecules.

7.4.5.2 Case Study

For the biosimilar confirmatory clinical trial for trastuzumab, which is an anti-HER2 mAb, authorities and sponsors initially proposed clinical trials in metastatic breast cancer patients using a primary endpoint of PFS. As the understanding of biosimilar clinical trial design matured, most sponsors then focused on early breast cancer specifically using neoadjuvant treatment. In such patients, it is possible to