Randomized clinical trials are typically thought of as the gold standard for assessing intervention efficacy. Even in analyzing results of perfectly planned trials, intercurrent events may motivate the use of targets other than the population average treatment effect, which may require complex estimation procedures and additional modeling assumptions. Considering the design of future clinical trials, limited data may be available about expected outcomes under treatments of interest in desired target populations. This talk will feature two works in progress, the first of which aims to estimate the effect of an experimental HIV vaccine in a clinical trial in which subjects were unblinded during follow up. The primary analysis revealed elevated risk of HIV infection in participants randomized to active vaccine, leading to questions regarding how the act of unblinding may have impacted participants’ sexual behavior. Utilizing the counterfactual framework, we will define and estimate standardized direct effects to account for the potential impact of unblinding in HIV infection. The second project considers the design of a future pragmatic trial of two therapies for treatment of psoriatic arthritis using data from a treat-to-target/strategy trial that examined the two therapies of interest as part of a suite of therapies given in sequence or combination according to patient progression. Results to date as well as strategies for designing clinical trials based on observational data will be discussed.