Hemophilia is a congenital bleeding disorder characterized by an excessive tendency to bleed, which, if untreated, can lead to crippling arthropathy. Hemophilia can be effectively treated with factor replacement, which in turn can be complicated by development of inhibitory alloantibodies. Generating good clinical evidence on efficacy and safety of available treatments for a congenital chronic disorder like hemophilia is a challenging task for researchers and clinicians. Using as examples current and past hemophilia trials and addressing answered and unanswered clinical questions relevant to the management of hemophilia, we will discuss how the theory of clinical epidemiology and the practice management of hemophilia have enriched each other.