Musculoskeletal disorders are a common cause of sickness absence. Various prospective studies have identified a large array of prognostic factors for return to work (RTW), such as individual characteristics, work-related factors, experienced pain and functional limitations, and general health perceptions. Interestingly, those risk factors that play a major role in the onset of musculoskeletal disorders and subsequent sick leave are not necessarily similar to the prognostic factors for prolonged or reduced duration of sick leave. Recent systematic reviews have summarised the effects of interventions including behavioural change techniques, physical exercises, and workplace adaptations. Overall, the effects were modest with an overall reduction in days of sickness absence of 1.1 (IQR 0.3–3.2). Site of musculoskeletal pain, duration of the intervention, and type of intervention were not associated with the effect size, but there is some indication that time-intensive interventions were less effective than simple interventions. These evaluations must be interpreted with great care. The effectiveness of an intervention is not a fixed trait, but strongly influenced by the characteristics of the population and the specific delivery in that population. This is illustrated by examination of the effects of structured interventions for workers on sick leave due to low back pain on return to work (RTW). Complete RTW curves were collected from literature and mathematically fitted to a Weibull distribution. The cost-benefits of a RTW intervention were determined by the overall effect of the intervention, duration of the intervention, costs of the program, natural course of RTW in the target population, and timing of enrolment of persons into the intervention. The latter factors are seldom taken into consideration, whereas their impact may easily exceed the influence of effect size.