General introduction
Rheumatoid arthritis
In the Netherlands, approximately 1% of the population suffers from the chronic disease rheumatoid arthritis (RA). The impact of this disease influences many aspects of patients’ life, such as performing daily activities. To categorize all these aspects, the World Health Organization developed a framework to assess the impact of a disease: the International Classification of Functioning, Disability and Health (the WHO ICF) framework (2001). In this framework the impact of a disease can be assessed through five components: ‘body functions and structures’, ‘activities’, ‘participation’, ‘environmental factors’ and ‘personal factors’, as shown in Figure 1.[1] All these components influence each other.

Most articles published on RA use a disease perspective, only reporting on body functions and structures and activity measured as functional ability. The WHO ICF framework also incorporates a functioning perspective in which the influence of personal and environmental factors on performing activities, participation and body functions and structures is measured.[3]

![WHO ICF framework](image)

*Figure 1: WHO ICF framework [1]*
**The disease perspective**

RA is an autoimmune disease characterized by synovial inflammation of joints. In a later stadium the cartilage and bone of affected joints are damaged, which is mostly irreversible. Patients suffer from pain, the most fundamental symptom of RA, swollen joints, morning stiffness, fatigue, and negative emotions, all part of the component ‘body functions’. Physical health and joint damage are usually measured by the components of the WHO-ILAR core set,[4] including indices such as the disease activity score (DAS), and the Sharp van der Heijde Score (SHS) for joint damage. The true impact of the disease on performance of activities is challenging for several reasons. These include variability of pain and associated avoidance, as well as coping behaviour. In the field of rheumatology, performing daily activities is often measured by generic health status measures such as the Health Assessment Questionnaire (HAQ), that only assesses the possibility to perform a certain activity.[3] Medical treatment of the disease aims at improving the above mentioned aspects. Suboptimal treatment of RA leads to deformations and functional limitations, but also to comorbidities such as elevated risk on cardiovascular diseases and osteoporotic fractures.

The treatment of RA patients has altered throughout the years. Earlier, the pyramid model was used as drugs became available: starting with non-steroidal anti-inflammatory drugs (NSAIDs); when not efficient enough, monotherapy with a disease modifying anti rheumatic drug (DMARD), such as sulfasalazine (SSZ), methotrexate (MTX) or hydroxychloroquine (HCQ) was added, and so on.[5-7] What we learned from these trials was that DMARDs need approximately three to six months to start exerting their effect, and that damage of joints already occurred during this period. Eventually the reverse pyramid model became more and more accepted, in which aggressive treatment was started, and medication was only tapered on clinical improvement. The hypothesis was that initial aggressive treatment would have a positive effect on long-term outcome, the so-called “window of opportunity”. Ultimately, this would result in less disability. The original COBRA (COMbinatietherapie Bij Reumatoïde Artritis) study,[8] later on the Behandel STRategieën trial (BeSt),[9] the Finnish Rheumatoid Arthritis Combination therapy trial (FIN-RACo)[10], as well as the PROMPT study [11] are examples of combination strategies applying the reverse pyramid model.

The original COBRA study showed that patients treated with either sulfasalazine (monotherapy) or a combination of SSZ, MTX and initially high
dose prednisolone (60mg/day) tapered to 7.5 mg/day in seven weeks, was effective in suppressing disease activity, increasing functional ability, and preventing short and long-term radiological joint progression.[8, 12] Later on, the BeSt trial was performed in which the COBRA strategy was compared to monotherapy with DMARDs, step-up therapy, and a biological (infliximab, a TNFα-blocking agent plus MTX). Biological treatments were discovered in the past two decades and were developed through biotechnology. These drugs target several cytokines: not only tumour necrosis factor (TNFα), but also IL-6, B-cells and T-cells. They proved to be very effective in the treatment of RA, alone or in combination with DMARDs.[13] The BeSt trial showed that COBRA strategy was superior to sulfasalazine monotherapy, step-up therapy and as effective as infliximab treatment plus MTX, as can been seen in Figure 2.[9]

Although proven to be very effective in the treatment of RA, ten years after the COBRA trial, the COBRA strategy was only marginally used in daily practice. In in depth focus-interviews, physicians expressed hesitation to use the strategy mainly for fear of possible side effects of GCs, while, strikingly, the patients were less worried about the side effects, because of the favourable effects on disease activity.[14-16]

During these interviews, rheumatologists were also asked what they prescribe to the patients in daily practice. All mentioned only MTX and different dosages of prednisolone, varying from low dose to higher oral dosages, and parenteral injections: this variation is clearly suboptimal. Based on that, the COBRA-light strategy was born, as a compromise between rheumatologists. This strategy comprises start with high dose MTX (25 mg/week) and 30 mg/day prednisolone, tapered to 7.5 mg/day in nine weeks. To assess if this light version was non-inferior to the original COBRA strategy, the COBRA-light trial was performed. Study questions of this trial were: 1) is COBRA-light non-inferior to COBRA strategy after 26 weeks of treatment (chapter 1.1). 2) After 52 weeks, is non-inferiority maintained; did radiological joint progression occur; what is the effect of additional etanercept (chapter 1.2). And 3) is COBRA-light therapy as cost-effective as COBRA strategy (chapter 1.3)?
The functioning perspective

To apply the whole ICF framework, the components ‘activities and participation’ and environmental and personal factors’ should also be considered. These items comprise daily activities (such as performing household, self-care), relationships with others, leisure time activities, participating at work (paid and unpaid), and social network. Unfortunately, these items are often disregarded in daily practice and research. Therefore, as an initiative of the European League Against Rheumatism (EULAR), the Rheumatoid Arthritis Impact of Disease (RAID) score was developed in 2008.[17] Aim of this initiative was to develop a score entirely based on patient-reported outcome (PRO) which could be used in clinical trials in RA. As the domains of the RAID were initially identified by ten patients, including one Dutch representative, we deemed it necessary to document content validity in Dutch patients as well as comprehensibility before implementation in The Netherlands. In chapter 2.1, we assessed if all items included in the score are an adequate reflection of the construct that the score aims to measure. This was done both by comparing the RAID score with the WHO ICF core set for RA, and by focus group interviews with patients, aimed at eliciting which domains their disease had impact on.

The components ‘Activities and participation’ and ‘Environmental factors’ also include performing paid (or unpaid) work, and all items related to performing a job. Although we are now more able to control disease activity, RA still has a major impact on work participation. Compared to the general

![Graph showing percentage of patients in remission (DAS44<1.6) over time, per group in the BeSt trial.](image-url)
population, patients with RA in the Netherlands have approximately 12-20% less paid jobs, experience 2-3 times more days of sick leave, and are about 7 times more work disabled.[18] At this moment, a so called continuum of work is being recognized (Figure 3): presenteeism (productivity loss at work) may lead to absenteeism (days on sick leave), and long absence from work may lead to work disability.[2] Therefore, benefits of therapy can emerge from preventing both work disability and loss of work productivity. This is especially pertinent in the case of biological agents, as their cost-prices are high, strongly increasing the overall health care costs of RA in recent years.[19-21] It has been proposed that early treatment with biological agents can improve work productivity, decrease sick leave and work disability, compared to standard of care. This would result in a decrease in indirect costs, compensating the high cost price of these therapies, and possibly decreasing total (societal) costs of RA. Studies of the effect of biological treatment on indirect costs are increasing, but little is known about their effects on productivity at work (presenteeism), and sick leave (absenteeism). We performed a systematic review in this topic, presented in chapter 2.2.

Only a few studies have assessed the effect of conventional DMARD treatment (such as COBRA and COBRA-light strategy) on work outcome. Therefore, we wanted to know whether intensive treatment with combination therapy (COBRA and COBRA-light) also resulted in positive work outcome in early RA patients, and if we were able to find associations between several disease, personal and work related factors at baseline, and eventually predict sick leave over a one-year period. This is described in chapter 2.3.

Figure 3: Continuum of work [2]
REFERENCE LIST
