Is symptom duration before DMARD therapy a determinant of direct and indirect costs in DMARD-naïve RA patients?

Sahbudin, Ilfita; Singh, Ruchir; Trickey, Jen; Baranskaya, Aliaksandra; Tracy, Alexander; Raza, Karim; Filer, Andrew; Jowett, Sue; Boonen, Annelies

DOI:
10.1093/rap/rkad040

Is symptom duration before DMARD therapy a determinant of direct and indirect costs in DMARD-naïve RA patients? A systematic review

*Ilfita Sahbudin[1,2], *Ruchir Singh[1,2,5], Jeanette Trickey[1,2], Aliaksandra Baranskaya[1,2] Alexander Tracy[1,2], Karim Raza[1,2,5], Andrew Filer[1,2], Sue Jowett[3], Annelies Boonen[4,6]

1. Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.
2. NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK.
3. Health Economics Unit, Institute for Applied Health Research, University of Birmingham, Birmingham, UK
4. Division of Rheumatology, Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands
5. Department of Rheumatology, Sandwell and West Birmingham NHS Trust, Birmingham, UK
6. Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands

*IS and RS contributed equally to the study.

Corresponding author:

Dr Ilfita Sahbudin, Rheumatology Research Group, Institute Inflammation and Ageing, University of Birmingham, Birmingham, B15 2WB, UK. Email: i.sahbudin@bham.ac.uk.

Orcid ID: 0000-0003-0702-4403

Abstract

Objective. Early treatment of rheumatoid arthritis (RA) improves clinical outcomes; however, the impact on health economic outcomes is unclear. This review sought to investigate the relationship between symptom/disease duration and resource utilisation/costs and the responsiveness of costs following RA diagnosis.

Methods. A systematic search was performed on Pubmed, EMBASE, CINAHL and Medline. Studies were eligible if patients were DMARD-naïve and fulfilled 1987 American College of Rheumatology (ACR) or 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) RA classification criteria. Studies had to report symptom/disease duration and resource utilisation or direct/indirect costs as health economic outcomes. The relationships between symptom/disease duration and costs were explored.

Results. 357 records were identified in systematic search; nine were eligible for analysis. Mean/median of symptom/disease duration in studies ranged between 25 days to 6 years. Annual direct costs of RA following diagnosis showed a U-shaped distribution in two studies. Longer symptom duration before starting DMARD (>180 days) was associated with lower health care utilisation in the first year of RA diagnosis in one study. Annual direct and indirect costs six months before RA diagnosis were higher in patients with shorter symptom duration (<6 months) in one study. Given the clinical and methodological heterogeneities, association between symptom/disease duration and costs following diagnosis was not computed.

Conclusion. The association between symptom/disease duration at the time of DMARD initiation and resource utilisation/cost in patients with RA remains unclear. Health economic modelling with clearly defined symptom duration, resource utilisation and long-term productivity is vital to address this evidence gap.

Keywords: Rheumatoid arthritis, early diagnosis, direct/indirect costs, health economic outcomes

Key messages

- Association between symptom/disease duration before DMARD initiation and health economic outcomes in RA is unclear.
- Clinical and methodological heterogeneities impede direct comparison of health economic outcomes across RA studies.
- Longitudinal studies with defined symptom duration and long-term RA-associated costs will address this research question.

Lay summary

What does this mean for patients?

We studied to what extent the cost of healthcare varies depending on how quickly patients with RA receive treatment following diagnosis. This is important to allow long-term financial planning within the healthcare service. This is a systematic review study, which means we collect information from published papers that meet a set of criteria, to see if there is a clear pattern emerging across multiple papers. In this study, we selected papers that included patients with a diagnosis of RA with no previous treatment for their RA. We then studied whether there is any clear link between the delay in starting treatment for RA and costs of treating RA. In two selected studies, the costs of RA treatment (e.g. medication costs, consultation costs) showed a U-shaped distribution; that means costs were high in the initial years after starting treatment, then dropped before subsequently rising again. It was not possible to assess further whether there is a clear link between the delay in starting treatment for RA and costs of treating RA, as each study used different criteria to assess treatment delay and costs of treatment. Therefore, this study highlights there is a need for further economic modelling studies in RA.

INTRODUCTION

The impact of early treatment on clinical outcomes in rheumatoid arthritis (RA) is well-reported (1). However, the impact of early treatment on health economic outcomes is less clear. Patients with RA treated with intensive DMARD were more likely to stay in the workforce long-term (2, 3). This may result in long term overall lower indirect costs (i.e. lower loss of productivity). However, diagnostic decisions are vulnerable to false-positive and false-negative results. The consequence of over-diagnosis and over-treatment may lead to overall higher direct costs (i.e. higher medical costs) in the longer run, which may offset the cost savings made from improved productivity. Therefore, long-term economic diagnostic and treatment decision models are required to inform the optimal threshold for diagnostic/treatment decisions from an economic perspective. This will facilitate the estimation of long term RA-related costs.

Therefore, as a first step, the relationship between symptom/diagnosis duration at the time of DMARD initiation and subsequent resource utilisation/costs needs to be identified. We sought to investigate this through a systematic review of cost-of-illness and cost-effectiveness studies of DMARD-naïve RA patients.

METHODS

Full methods section is detailed in Supplementary Data S1, available at *Rheumatology Advances in Practice* online.

Protocol and Registration

Protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO 2017 CRD42017077593); https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017077593.

Study identification/Search Strategy

PubMed, EMBASE, CINAHL and Medline electronic databases were searched up to 25th January 2023. All systematic searches were conducted using the same search terms and strategy (Supplementary Data S2, available at *Rheumatology Advances in Practice* online). Additional records were identified through independent manual database

searching, external sources and reference scanning of relevant retrieved full-text articles. Study selection, data extraction and quality assessment were done independently by two authors (IS, RS); discrepancies were resolved by consensus or through a third reviewer (ABo). Table 1 shows the PICOT framework.

Study selection

Study inclusion criteria were: i)aged ≥18 years fulfilling 1987 American College of Rheumatology (ACR) or 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) RA classification criteria, ii) DMARD-naïve, iii)symptom/disease duration reported, iv)cross-sectional and longitudinal study, and v)health economic outcomes reported as costs or resource utilisation. Studies excluded were (i) studies of non-RA inflammatory arthritides; (ii) conference abstracts, systematic reviews or review articles

Data extraction

These data were extracted; (1)Study characteristics; (2)Potential determinants of RA costs; (3)Sources of (i) resource utilisation and (ii) costs; and (4)Health economic outcomes.

Quality assessment

The Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist (4) and a modified checklist by Drummond and Jefferson (5) were used for quality assessment.

Data synthesis and statistical analysis

A meta-analysis/regression on association between disease/symptom duration and costs could not be performed due to number of studies and methodological heterogeneity, especially in reporting of health economic outcomes. Cost data per patient per year for the reported duration in studies were recorded and summarised in a unifying currency of US Dollars 2021 after adjusting for Purchasing Power Parity (PPP) and Consumer Price Index (CPI) 2021 (6, 7).

Results

Nine articles were included in this systematic review. The Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) flow chart shows the literature search results (Figure 1).

Table 2 summarises study characteristics, cost categories and annual costs in international USD 2021. Six papers were cost-of-illness (8-13) and remaining were cost-utility studies (14-16). Four studies were within observational studies (8, 11, 13, 16), and five within RCTs (9, 10, 12, 14, 15).

Socio-demographic and clinical characteristics of patients are summarised in Supplementary Table S1. Cost categories, source of cost reference and results in local currency are summarised in Supplementary Table S2, both available at *Rheumatology Advances in Practice* online.

Symptom, disease or diagnosis duration variable reported at baseline varied. Two studies reported symptom duration (8, 14), six studies reported disease duration (9-13, 16) and one reported diagnosis duration (15). Only one study clearly defined symptom duration; 'first onset of joint swelling' (11). Remaining studies did not state the definitions of symptom, disease or diagnosis duration (8-15).

Resource utilisation and cost data across studies were heterogeneous (Table 1). Three studies reported costs (i.e. monetary value) but not resource utilisation (13, 15, 16). One study reported resource utilisation without monetary values (8). Three studies reported resource utilisation and costs (10, 12, 14). Two studies reported costs data as loss of productivity costs (9, 11).

Direct medical costs were reported in six studies (two observational studies(13, 16) and four clinical trials (10, 12, 14, 15). Two studies reported direct non-medical costs (10, 12). Healthcare utilisation with no monetary value was reported in one study (8).

Loss of productivity (indirect cost) was recorded in four studies (9, 11, 14, 15). Two studies calculated productivity loss using the human capital and friction cost approach (9, 15). One study used only the human capital approach (11), and one study used only the friction cost approach (14).

Study perspective refers to the point of view adopted in the economic evaluations (17) i.e. 'who pays for the cost?'. Common study perspectives are the patient, healthcare system or society. Three studies reported societal perspectives (i.e. healthcare and productivity loss costs) (13-15). Two studies reported a partial societal perspective (productivity loss costs) (9, 11) and two studies reported costs from healthcare perspective (8, 16). In addition, two studies reported both healthcare (direct medical costs) and patient perspectives (10, 12).

Quality assessment has been included in Supplementary Data S3 and Table S3, available at *Rheumatology Advances in Practice* online.

Narrative synthesis

Luurssen-Masurel et al. (14) performed a cost-utility study in seronegative RA patients in the Rotterdam Early Arthritis Cohort (tREACH) trial. Median symptom duration was 134 days (IQR 95-205 days); follow-up duration was one year. Initial treatment strategies were methotrexate (iMTX) 25mg once weekly, hydroxychloroquine (iHCQ) 400mg daily or a tapering course of oral glucocorticoids (iGC). There was no significant difference in the mean cumulative healthcare costs over one year for treatment with iMTX, iHCQ and iGCs (Table 2). The difference in productivity costs over one year between the three groups was mainly attributed to different levels of presenteeism (Table 1). After adjusting for PPP and CPI 2021, mean total costs (healthcare and productivity costs) by treatment strategy groups in USD 2021 were $14,485, $14,988 and $14,044 for the iMTX; iHCQ, and iGC groups, respectively. The association between symptom duration and healthcare/productivity costs in the overall cohort or by treatment groups was not assessed.

Verhoeven et al. (15) reported a 5-year cost-utility analysis of an RCT comparing tocilizumab (TCZ) plus methotrexate (MTX) or TCZ monotherapy to MTX monotherapy in DMARD-naïve early RA patients. Median (IQR) symptom duration by treatment groups was 25 (16-42) days, 26 (18-45) days and 27 (15-46) days for the TCZ plus MTX, TCZ and MTX groups, respectively. Cumulative 5-year productivity cost loss (by HCA) was highest in the TCZ plus MTX group (€51,700; n=106) compared to the TCZ

monotherapy and MTX monotherapy [€39,900; n=103 and €46,500, n=108 respectively]. Cumulative 5-year productivity cost loss (HCA) was highest in the TCZ plus MTX group (€51,700) compared to the TCZ monotherapy and MTX monotherapy (€39,900 and €46,500, respectively). After adjusting for PPP and CPI 2021, total direct healthcare-related costs (mean) in USD 2021 at end of year one were $15,546, $8,350 and $17,840 per patient for the TCZ plus MTX, TCZ and MTX groups, respectively. The association between symptom duration and healthcare or productivity costs in the overall cohort or by treatment groups was not assessed.

Syngle (16) et al. reported RA-related healthcare costs in a single centre prospective observational study of three months in India. The study assessed the cost-effectiveness of synthetic DMARDs in DMARD-naive RA patients (16). Mean disease duration was 5.78 years (SD 4.84). Costs reported were average total direct medical cost per prescription per month over the three-month study period. This figure equates to 997.05 Indian Rupees per patient. After adjusting for PPP and CPI 2021, the average (extrapolated) annual direct medical costs at the end of year 1 in USD 2021 was $1008 per patient. The association between disease duration and direct medical costs was not assessed.

Kuijper (8) et al. compared health care utilisation between arthralgia and DMARD-naive early RA patients at baseline , six and 12 months in a Dutch inception observational cohort study (8). Median symptom duration for RA patients was 103 days (range 7-373). Use of DMARDs was not reported. Longer (>180 days) versus short symptom duration (90-180 days) at baseline was associated with lower levels of healthcare utilisation over 12 months [IRR of 0.65 (CI 95% 0.50-0.85, p=0.002)]. Mean number of visits to medical specialists peaked at six months in the RA group (Table 2). However, a decrease in overall healthcare visits (i.e. GP, medical specialist, physiotherapist and alternative health practitioners visits) was observed following diagnosis (Table 2). No monetary value was reported in this study. In summary, longer symptom duration (>180 days) was associated with lower health care utilisation over the first year of diagnosis.

Puolakka (9) et al. assessed impact of Stanford Health Questionnaire (HAQ) index on loss of productivity in early DMARD-naïve RA patients in the Finnish RA Combination Therapy (FIN-RACo) open-label extension clinical trial in Finland. Patients were randomised to either i)a combination of three DMARDs (sulfasalazine, methotrexate and hydroxychloroquine) and prednisolone, or ii)a single DMARD with or without prednisolone (9) for two years and were followed up for five years. Mean disease duration across the four HAQ groups was between 8 and11 months In the overall cohort and over five years, annual mean loss of productivity per patient was €8344 (95% CI 6516 - 10480) by the HCA and €1928 (95% CI 1567–2298) by the FCA. Functional capacity was assessed by HAQ at baseline and six months. HAQ score after six months of treatment, but not the level of HAQ at baseline, predicted productivity costs in the overall cohort. Over five years, the top HAQ quartile had the highest work disability days per year [mean 273; (CI 194-328)], compared to the lowest HAQ quartile [mean 34 (5-145)]. After adjusting for PPP and CPI 2021, annual mean loss of productivity in USD 2021 in the top quartile group was $40,116 by the HCA method and $6125 by the FCA method. No analysis was performed to assess the impact of disease duration on costs in the overall cohort or by HAQ groups.

Verstappen et al. (10) assessed the total annual direct costs by different follow-up periods after first DMARD in Dutch patients with RA and identified socio-demographic, clinical and psychological predictors of high costs in two RCTsPatients in the first RCT were randomised into one of four treatment arms [pyramid (non-steroidal anti-inflammatory followed by a DMARD for treatment failure), IM gold, methotrexate or hydroxychloroquine]. Patients from the second RCT were randomised into intensive vs conventional methotrexate regimes.

In this study, costs data were classified into three groups with increasing follow-up duration after diagnosis (0 to ≤2 years, 2 to ≤6 years, 6 to ≤10 years). In addition, RA patients with disease duration ≥10 years from Utrecht RA Cohort study group were included to capture costs data for patients with longstanding RA. There was a significant difference in annual direct costs between the four groups. Median annual direct costs per patient showed a U-shaped distribution, i.e. costs were high for patients with follow-up duration 0 to ≤2 years (€2923) and reduced after 2 to 6 years (€1967), but

increased again in the ≥10 years follow-up duration (€3778). Data from the shortest follow-up duration group were extracted for table 1. Functional disability (HAQ) was the most important variable associated with high costs after adjusting for sociodemographic, clinical and psychological variables. After adjusting for PPP and CPI 2021, the annual mean (median) of total direct costs per patient in USD 2021 was $14,613 ($8159). The annual direct costs of early RA follow a U-shaped distribution over ten years following the start of DMARDs. No analysis was performed to assess the impact of disease duration at baseline on costs in the overall cohort.

Merkesdal (11) et al. reported magnitude of indirect costs, changes within cost components and correlation between changes in cost and social, clinical and occupational variables within first three years of DMARD-naïve RA patients in a multi-centre observational study in Germany. Average indirect cost in early RA at 24-month follow-up was high; $11,750 per person-year (US dollar for the period 1994-1996), which related to 126 days of loss of productivity. Loss of productivity due to sick leave accounted for 84% of overall loss of productivity (sick leave, work disability and other work loss) between the onset of disease and the end of the first year after study enrolment, compared with only 25% at the end of the second year of the study enrolment (11). After adjusting for PPP and CPI 2021, mean costs associated with total sick leave, work disability and other work losses in USD 2021 were $20,180 after 12-months follow-up and $18,848 per person per year at 24-month follow-up. The relationship between disease duration and loss of productivity was not reported.

Newhall-Perry et al. assessed direct and indirect costs of seropositive RA patients six months before diagnosis in a longitudinal observational study at rheumatology centres in western US and Mexico (13). All patients were DMARD-naïve, had clinically active disease with at least nine tender and six swollen joints and a positive RF. Patients were classified as disease duration of <6 months (n=87) and ≥6 months (n= 63). At baseline, mean total direct cost and indirect costs of RA six months before diagnosis were $200 per month and $281 per month in 1994 USD, respectively. Total direct cost of RA (mean ± SD) six months before diagnosis in patients with disease duration <6 months compared to ≥6 months were $240/month ± $285 and $144/month ± $149, p<0.001, respectively. Likewise, indirect costs were higher in patients with disease duration <6

months opposed to ≥6 months ($348/month ± $567 vs $188/month ± $506; p <0.005) at baseline. After adjusting for PPP and CPI 2021, annual mean total direct and indirect costs six months before diagnosis per person in USD 2021 were $12,663 for <6 months and $7174 for ≥6 months groups. Overall, annual direct and indirect costs six months prior to RA diagnosis were higher in patients with shorter symptom duration (<6 months).

Van Jaarsveld (12) et al. assessed annual direct cost related to RA during the first six years and identified socioeconomic and clinical determinants of these costs in an RCT conducted in the Netherlands. Patients were recruited between 1990 and 1996, and cost questionnaires were sent to those not lost to follow-up in April 1996. Mean annual direct costs by follow-up duration (year 1-6) followed a U-shaped distribution; (i) Dutch Florin (Dfl.) 14,455/patient in year 1; (ii) Dfl.13,800/patient in year 2; (iii) Dfl. 9,457/patient in year 3; (iv) Dfl. 6,233/patient in year 4; (v) Dfl. 13,005/patient in year 5 and (vi) Dfl. 11,158/patient in year 6. After adjusting for PPP and CPI 2021, total direct costs per patient (mean) in USD 2021 was $24,094 after one-year follow-up duration. The annual direct costs of early RA showed a U-shaped distribution over six years following start of DMARDS. No analysis was performed to assess the impact of disease duration at baseline on costs in the overall cohort.

A number of studies were excluded as study participants can receive at least one DMARD before study enrolment ((18-21)). Tables 3 and 4 summarise the direct and indirect costs in USD 2021, respectively, and outcomes by increasing symptom or disease duration.

DISCUSSION

This study highlighted several interesting findings. Firstly, two studies reported U-shaped distribution of costs over disease duration following an RA diagnosis. Total costs were high during initial years, slightly lower thereafter, then high again for disease duration of ≥5 years (12) and disease duration of >10 years (10). This indicates that costs are not a linear function of disease duration.

Secondly, functional disability was a predictor of productivity costs in three studies (9, 10, 12). In one study, patients from the highest HAQ group had the highest work disability days/year; therefore the highest loss of productivity costs (9). This finding is highly relevant. It supports the hypothesis that aggressive early treatment can reduce costs in the longer term, as those treated earlier are less likely to have higher level of disability, which then translates to lower loss of productivity costs in the long term.

One study reported the annual direct and indirect costs six months before diagnosis were higher in those with symptom duration of <6 months before start of DMARD compared to those with symptom duration ≥6 months (13). In contrast, another study reported that longer symptom duration before diagnosis (>180 days) was associated with lower health care utilisation over the first year of diagnosis (8). The contrasting trend between the two studies can be explained by the difference in the timing of when the health economic outcomes were recorded. Health care utilisation over the first year following RA diagnosis was recorded in the latter study; however, costs before RA diagnosis was recorded in the first study.

In this review, we could not delineate the aggregated level data related to the relationship between symptom/disease/ diagnosis duration and cost categories due to the heterogeneity of 1)timing and duration of data collection regarding resources and costs, 2)type of resources/cost-categories reported, and 3)inconsistency in reported disease, symptom or diagnosis duration (Figure 2). Moreover, duration of cost data recorded (i.e. six months vs six years) also differed across studies (Figure 2).

Before the era of early treatment, RA costs were related to established disease. Patients had more frequent hospitalisation (22), joint replacement than the general population (23) and a majority were unable to work. The early introduction of biological and targeted synthetic DMARD therapy has resulted in high medications costs (23). However, high drug cost can potentially be offset in the long-term, at least partly, by reducing disease-related costs (e.g. loss of productivity due to work disability, hospitalisation and joint surgery). In addition, patients treated early were more likely to achieve DMARD-free remission (1). Therefore, this would reduce the proportion of patients on long-term DMARDs (24).

Clear definitions of RA 'onset' and 'duration' have been proposed (25) as reporting in clinical studies is currently heterogeneous (25). RA duration may be timed from: i)onset of RA symptoms, ii)onset of joint swelling, iii)when RA classification criteria were first fulfilled, or iv)time of RA diagnosis. Using a clearly defined 'onset' will allow meaningful comparison of clinical outcomes and health economic outcomes between early RA studies.

A strength of this review is the broad range of health economic outcomes and type of health economic studies that were included. Both direct and indirect costs, and cost-of-illness and cost-utility studies were within the scope of this review. Observational and clinical trials were also included.

However, only a small number of studies fulfilled our strict inclusion criteria. In addition, studies which enrolled patients who have recently been treated with DMARDs prior to study recruitment were not included in this review. Secondly, meta-analyses/regression were not possible due to different types of health economic outcomes reported.

This review is the first to highlight a vital evidence gap in early arthritis; what is the financial consequence of diagnosing and treating patients with RA during the early disease phase? Health economic modelling with carefully defined symptom duration, resource utilisation, treatment and long-term productivity costs is vital to address this important question.

Acknowledgment

We wish to thank Stephen Yates and Jennifer Manders, University Hospitals Birmingham Foundation NHS Trust, who conducted the systematic search for this review.

Funding Statement:

This work was supported by the National Institute for Health and Care Research (NIHR)/Wellcome Trust Clinical Research Facility and NIHR Birmingham Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust. This work was also supported by the Arthritis Research UK Rheumatoid Arthritis Pathogenesis Centre of Excellence (Arthritis Research UK grant number 20298), the European Community's Collaborative project FP7-HEALTH-F2-2012-305549 'Euro-TEAM' and Versus Arthritis Research into Inflammatory Arthritis Centre (Versus Arthritis UK grant number 22072). The views expressed are those of the author(s) and not necessarily those of the MRC or Arthritis Research UK. IS is supported by the University of Birmingham via a clinical lectureship. KR and AF are supported by the NIHR Birmingham Biomedical Research Centre.

Disclosure statement:

Karim Raza: Personal fees from Abbvie, Sanofi. Grant/research support from Bristol Myers Squibb. Andrew Filer: Personal fees from Abbvie, Roche, Janssen. Grant/research support from Roche, UCB, Mestag, GSK, Janssen. The remaining authors have declared no conflicts of interest.

Data availability statement:

The data underlying this article will be shared on reasonable request to the corresponding author.

References:

1. van der Linden MP, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TW, et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum. 2010;62(12):3537-46.
2. Wolfe F, Hawley DJ. The longterm outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients. J Rheumatol. 1998;25(11):2108-17.
3. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum. 2005;52(1):36-41.
4. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
5. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.
6. Purchasing power parities (PPP) (indicator) OECD (2021). doi: 10.1787/1290ee5a-en. Accessed on 25 March 2022 [
7. Inflation (CPI) (indicator) OECD (2021) doi: 10.1787/eee82e6e-en. Accessed on 25 March 2022 [
8. Kuijper TM, Luime JJ, Alves C, Barendregt PJ, van Zeben J, Bindels PJ, et al. Quality of life and health care use in patients with arthralgias without synovitis compared with patients diagnosed with early rheumatoid arthritis: data from an early arthritis cohort. Arthritis Care Res (Hoboken). 2014;66(3):379-86.
9. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al. Use of the Stanford Health Assessment Questionnaire in estimation of long-term productivity costs in patients with recent-onset rheumatoid arthritis. Scand J Rheumatol. 2009;38(2):96-103.
10. Verstappen SM, Verkleij H, Bijlsma JW, Buskens E, Kruize AA, Heurkens AH, et al. Determinants of direct costs in Dutch rheumatoid arthritis patients. Ann Rheum Dis. 2004;63(7):817-24.
11. Merkesdal S, Ruof J, Schoffski O, Bernitt K, Zeidler H, Mau W. Indirect medical costs in early rheumatoid arthritis: composition of and changes in indirect costs within the first three years of disease. Arthritis Rheum. 2001;44(3):528-34.
12. van Jaarsveld CH, Jacobs JW, Schrijvers AJ, Heurkens AH, Haanen HC, Bijlsma JW. Direct cost of rheumatoid arthritis during the first six years: a cost-of-illness study. Br J Rheumatol. 1998;37(8):837-47.
13. Newhall-Perry K, Law NJ, Ramos B, Sterz M, Wong WK, Bulpitt KJ, et al. Direct and indirect costs associated with the onset of seropositive rheumatoid arthritis. Western Consortium of Practicing Rheumatologists. J Rheumatol. 2000;27(5):1156-63.
14. Nathalie LM, Mulligen VE, Maria W, Wilhelmina HJM, Pieter JPH. Comparing cost-utility of DMARDs in autoantibody-negative rheumatoid arthritis patients. Rheumatology (Oxford). 2021;60(12):5765-74.
15. Verhoeven MMA, Tekstra J, van Laar JM, Pethö-Schramm A, Borm MEA, Bijlsma JWJ, et al. Effect on Costs and Quality-adjusted Life-years of Treat-to-target Treatment Strategies Initiating Methotrexate, or Tocilizumab, or Their Combination in Early Rheumatoid Arthritis. J Rheumatol. 2021;48(4):495-503.
16. Syngle A, Kaur S, Verma I, Syngle T, Syngle V. Cost-effective analysis of disease-modifying anti-rheumatic drugs in rheumatoid arthritis. Clin Rheumatol. 2017;36(8):1715-20.
17. Perspective York York Health Economic Consortium; 2016 [Available from: https://yhec.co.uk/glossary/perspective/.

18. Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S. Cost-effectiveness and cost-utility of combination therapy in early rheumatoid arthritis: randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone. COBRA Trial Group. Combinatietherapie Bij Reumatoide Artritis. Br J Rheumatol. 1998;37(10):1102-9.
19. Ter Wee MM, Coupe VM, den Uyl D, Blomjous BS, Kooijmans E, Kerstens PJ, et al. Cost-utility of COBRA-light versus COBRA therapy in patients with early rheumatoid arthritis: the COBRA-light trial. RMD Open. 2017;3(2):e000502.
20. Korthals-de Bos I, Van Tulder M, Boers M, Verhoeven AC, Ader HJ, Bibo J, et al. Indirect and total costs of early rheumatoid arthritis: a randomized comparison of combined step-down prednisolone, methotrexate, and sulfasalazine with sulfasalazine alone. J Rheumatol. 2004;31(9):1709-16.
21. Pazmino S, Boonen A, Stouten V, De Cock D, Joly J, Van der Elst K, et al. Two-year cost-effectiveness of different COBRA-like intensive remission induction schemes in early rheumatoid arthritis: a piggyback study on the pragmatic randomised controlled CareRA trial. Ann Rheum Dis. 2020;79(5):556-65.
22. Hsieh P-H, Wu O, Geue C, McIntosh E, McInnes IB, Siebert S. Economic burden of rheumatoid arthritis: a systematic review of literature in biologic era. Annals of the Rheumatic Diseases. 2020;79(6):771-7.
23. Kalkan A, Hallert E, Bernfort L, Husberg M, Carlsson P. Costs of rheumatoid arthritis during the period 1990-2010: a register-based cost-of-illness study in Sweden. Rheumatology (Oxford). 2014;53(1):153-60.
24. van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis. 2014;73(5):861-70.
25. Raza K, Saber TP, Kvien TK, Tak PP, Gerlag DM. Timing the therapeutic window of opportunity in early rheumatoid arthritis: proposal for definitions of disease duration in clinical trials. Annals of the Rheumatic Diseases. 2012;71(12):1921-3.

Figure 1. PRISMA flow chart of the four searches conducted.

EMBASE: Excerpta Medica Database; MEDLINE: Medical Literature Analysis and Retrieval System Online; CINAHL: The Cumulative Index to Nursing and Allied Health; DMARD: disease-modifying anti-rheumatic drugs; RA: rheumatoid arthritis

Figure 2. Timing and duration of which the respective health economic outcomes reported and the symptom duration pre-DMARD initiation.

The blue arrows indicate the symptom/disease duration reported in each study. The green arrows indicate the timing and duration of health economic outcomes reported in each study. Puolakka et al. reported six groups of patients stratified by HAQ groups. *Verstappen at al. reported four groups of patients based in disease duration (defined as time elapsed from study recruitment). Van Jaarsveld et al. reported six groups of patients based on disease duration (defined as time elapse from study recruitment). **Kuijper et al and Newhall-Perry et al reported disease duration at the time of study enrolment.

HCA; Human capital approach. FCA; Friction cost approach.

Table 1. PICOT framework to capture studies cost or resource utilisation as an outcome by symptom or disease duration in patients with DMARD-naive rheumatoid arthritis

Population	DMARD-naïve rheumatoid arthritis
Intervention	Any DMARDs
Comparator	Any other DMARDs treatment
Outcome	Direct costs Medication costs Indirect costs Productivity costs Resource use
Time	Duration immediately preceding study inclusion or DMARDs start or the period following it
Context	Disease or symptom duration in relation to the costs/resources

PICOT: patient, intervention, comparison, outcome and time; DMARDs: disease-modifying anti-rheumatic drugs.

Table 2. Study characteristics, health economic outcomes and annual costs in US Dollars 2021

Author Country , Year	Objective Study design Study setting	Patient characteristics Symptom duration	Outcome Study perspective	Results as resources or costs by category (e.g. days hospitalised) or type (total healthcare; productivity)	Results as total resources or cost in local currency at time of the study	Cost per person per year in USD 2021 after adjusting for purchasing power parity and consumer price index 2021 (OECD, 2021)(1, 2)
Luurssen-Masurel et al. Netherlands , 2021	**Objective:** To assess cost-effectiveness of three different initial treatments in seronegative DMARD-naïve RA patients* *Patients from the tREACH trial with intermediate probability of developing persistent arthritis who fulfilled RA 2010 criteria, and were RF and ACPA negative at baseline. **Study design:** Cost-utility study in the context of clinical trial of one-year duration. **Study setting:** Patients recruited from eight rheumatology centres	**N**: 116 **F:** 69.8% **Age (average):** 54.8 **Symptom duration, days, (median, IQR):** 134 (95-205)	**Outcomes:** 1. Incremental cost-effectiveness ratio (ICER) ratio between two of the three initial treatment strategies. 2. Loss of productivity per year by: friction cost approach (including productivity loss due to presenteeism) valued at age- and sex-dependent standard costs per hour. **Study perspective:** 1. Partial societal 2. Healthcare	**Currency:** Euros 2019 **Total healthcare costs by treatment strategy group per patient during 1 year of follow-up** **mean (SD)** **iMTX:** 2584 (2196) **iHCQ:** 2123 (2172) **iGC:** 3050 (3461) **Total productivity costs by treatment strategies group** **mean (SD)** **iMTX:** 8249 (14,171) **iHCQ:** 9085 (11,571) **iGC:** 7453 (10,446)	**Total costs (healthcare and productivity costs) by treatment strategies group per patient per year** **Mean** **iMTX:** 10,832 **iHCQ:** 11,208 **iGC:** 10,502	**Total healthcare costs by treatment strategy group, per patient in USD2021 , mean** **iMTX** 3456 **iHCQ** 2839 **iGC** 4079 **Total productivity costs by treatment strategies group in USD 2021** **iMTX** 11031 **iHCQ** 12149 **iGC** 9967 **Total costs (healthcare and productivity costs) by treatment strategy groups in USD 2021:** **Mean** iMTX 14,485 iHCQ 14,988 iGC 14,044

Verhoeven et al. Netherlands, 2021 (15) (3)	**Objective:** To assess cost-effectiveness of initiating tocilizumab (TCZ) ± methotrexate (MTX) versus initiating MTX as treat-to-target treatment strategies over 5 years in early DMARD-naïve RA. **Study design:** Cost-utility study in the context of a clinical trial (2 years) and post-clinical trial follow-up (3 years). **Study setting:** 21 rheumatology outpatients clinic in the Netherlands	**N:** 317 **F: n (%)** **TCZ+MTX:** 65 (61) **TCZ:** 78 (76) **MTX**: 69 (64) **Age, years, median (IQR)** **TCZ+MTX:** 53.0 (46.0 – 60.0) **TCZ:** 55.0 (47.0-63.0) **MTX:** 53.0 (44.5 – 62.0) **Symptom duration, days, median (IQR)** **TCZ+MTX:** 24.5 (16.0-41.5) **TCZ:** 25.5 (18.0-45.0) **MTX:** 27.0 (15.0-46.0)	**Outcomes:** 1. Incremental cost-effectiveness ratios (ICER), between two treatment strategies. 2. Productivity loss costs by human capital approach and friction cost approach. **Study perspective:** 1. healthcare 2. partial societal	**Currency:** Euros 2017 **Costs** (€, rounded to the nearest hundreds) by treatment strategies group, means **Medication costs** **TCZ + MTX:** 17,900 **TCZ:** 18,400 **MTX:** 4,400 **Direct healthcare costs (excluding medication costs)** **TCZ+MTX:** 6,100 **TCZ:** 7,200 **MTX:** 7,000 **Indirect non-healthcare related costs** **TCZ+MTX:** 1,100 **TCZ:** 1,600 **MTX:** 1,500 **Productivity costs loss using human capital approach** **TCZ+MTX:** 6,700 **TCZ:** 5,600 **MTX**: 6,500 **Productivity loss costs using friction cost approach** **TCZ+MTX:** 2,500 **TCZ:** 2,300 **MTX:** 2,500	**Total costs (healthcare and productivity costs) by treatment strategies group in euros 2017) Mean per patient per year, at end of year 1** **Direct healthcare-related costs** **TCZ+MTX:** 6,100 **TCZ:** 7,200 **MTX:** 7,000 **Total medication costs** **TCZ + MTX:** 17,900 **TCZ:** 18,400 **MTX:** 4,400 **Total productivity costs loss using human capital approach** **TCZ+MTX**: 6,700 **TCZ:** 5,600 **MTX:** 6,500 **Total productivity loss costs using friction cost approach** **TCZ+MTX:** 2,500 **TCZ:** 2,300 **MTX:** 2,500 **Indirect non-healthcare related costs** **TCZ+MTX:** 1,100 **TCZ:** 1,600 **MTX:** 1,500	**Total costs (healthcare and productivity costs) by treatment strategies group in USD 2021: Mean per year, at end of year 1** **Direct healthcare costs (excluding medication costs)** **TCZ + MTX:** 15,546 **TCZ:** 18,350 **MTX:** 17,840 **Total medication costs** **TCZ + MTX:** 45,620 **TCZ:** 46,894 **MTX**: 11,214 **Total productivity costs loss using human capital approach** **TCZ + MTX:** 17,076 **TCZ:** 14,272 **MTX:** 16566 **Total productivity loss costs using friction cost approach** **TCZ + MTX:** 6371 **TCZ:** 5862 **MTX:** 6371 **Indirect non-healthcare related costs** **TCZ + MTX:** 2803 **TCZ:** 4078 **MTX:** 3823

Syngle et al. India , 2017 (4)	**Objective:** To assess the cost and effects of synthetic DMARDs in treatment-naïve RA patients. **Study design:** Cost-utility study in the context of longitudinal observational study **Study setting:** One rheumatology outpatient clinic	**N:** 98 **F:** 86% **Age:** 47.8 (SD 12.3) **Disease duration at inclusion:** 5.8 (SD 5.0 years)	**Outcome:** 1.Average cost-effectiveness ratio (ACER). Cost is measured in monetary value and the effectiveness of treatment measured as change in HAQ-DI. **Study perspective:** Healthcare	**Currency:** Indian Rupees 2017 **Direct medical costs** 1. Medication costs (average/month) i. DMARDs = 398 ii. Steroids = 136.3 iii. NSAIDs = 16.66 iv. Medicines to prevent Adverse drug reaction = 48.8 2. Monitoring Costs (average/month) i. Lab Costs = 354 ii. Radiology = 24.3 iii. Ophthalmology = 5.97 3. Doctor consultation charges (average/month) = 10	**Average direct medical costs per RA prescription per month in Indian Rupees 2017:** 997 **Average direct medical cost per patient per year in Indian Rupees (2017):** 11,965	**Total healthcare (drugs and monitoring) cost per patient per year adjusted in USD 2021:** 1008

Kuijper et al. Netherlands, 2014 (8)	**Objective**: Comparison of disease burden between RA patients and arthralgia in an early arthritis cohort. **Study design:** Inception cohort study. **Study setting:** Patients recruited at first consultation with general practitioners or Rheumatology outpatient of five hospitals.	**N:** 244[§§] **F:** 68% **Age**: 54 (SD 13.7) **Symptom duration at study inclusion*:** 103 (7-373) days	**Outcome:** Health care utilisation (number of visits) i. GP ii. Specialist iii. Physiotherapist iv. Alternative **Study perspective**: Healthcare	**Healthcare utilisation (HCU)** **At baseline** (number of visits) i. GP 2.8 visits ii. Specialist visits 1.4 iii. Physiotherapist visits/5 = 0.5 iv. Alternative visits = 0.1 All visits: 4.7 visits **At 6-month time-point** i. GP 0.5 visits ii. Specialist visits 2.6 iii. Physiotherapist visits/5 = 0.6 iv. Alternative visits = 0.1 All visits= 3.9 visits **1. At 12-month time-point** i. GP 0.4 visits ii. Specialist visits 1.6 iii. *Physiotherapist visits/5 = 0.5 iv. Alternative visits = 0.1 All visits= 2.6 visits	**total Healthcare Utilisation (HCU) units for the first 12 months post DMARD initiation:** 6.5 visits per patient per year	Monetary value not reported

Puolakka et al. Finland, 2009 §§§ (9)	**Objective:** To assess the impact of HAQ on productivity loss in early RA patients. **Study design:** Data collection at 5-year follow-up in an extension of a randomised controlled trial. **Study setting:** 18 recruitment centres for FIN-RACo Trial.	**HAQ GROUP 1** **N:** 13 (F: 31%) **Age:** 45 (SD 9) **Disease duration at inclusion:** 11(9) months	**Outcome:** 1. Work disability days 2. Indirect costs; Loss of productivity per year by: i. Human capital approach ii. Friction cost approach **Study perspective:** Partial societal	**Values given as mean per patient per year (95% CI)** **HAQ GROUP 1:** Work disability (days per year): 34 (5-145) Loss of productivity per year (HCA),euros: 440 (137-896) Loss of productivity per year (FCA), euros: 353 (118-712)	**Loss of productivity costs per patient per year in USD 2021, mean** HCA: 736 FCA: 590
		HAQ GROUP 2 **N:** 65(F: 62%) **Age:** 45 (SD 9) **Disease duration at inclusion:** 8 (5) months		**HAQ GROUP 2:** Work disability (days per year): 33 (19-57) Loss of productivity per year (HCA) euros: 2704 (1457-4606) Loss of productivity per year (FCA), euros: 1360 (963-1870)	**Loss of productivity costs per patient per year in USD 2021, mean** HCA: 4523 FCA: 2275
		HAQ GROUP 3 **N:** 65 (F: 68%) **Age:** 47 (SD 4) **Disease duration at inclusion:** 8 (5) months		**HAQ GROUP 3:** Work disability (days per year): 146 (112-185) Loss of productivity per year (HCA), euros: 12072 (8788-15758) Loss of productivity per year (FCA), euros: 2452 (1902-3153)	**Loss of productivity costs per year in USD 2021, mean** HCA: 20191 FCA: 4101
		HAQ GROUP 4 **N:** 16 (F: 69%) **Age:** 50 (SD 9) **Disease duration at inclusion:** 10 (7) months		**HAQ GROUP 4:** Work disability (days per year): 272 (194-328) Loss of productivity per year (HCA), euros: 23985 (16448-33141) Loss of productivity per year (FCA), euros: 3662 (2518-5237)	**Loss of productivity costs per year in USD 2021, mean** HCA: 40116 FCA: 6125

Verstappen et al. Netherlands, 2004 (10)	**Objective:** To estimate annual direct costs and their predictors in patients with four disease duration groups. **Study design:** Cost-of-illness study within open-label extension of two randomised clinical trials. Patients in RCT 1 were randomly assigned to 1 of 4 treatment regimes[§]. Patients in RCT 2 were allocated to either intensive or conservative methotrexate treatment. [Questionnaires were sent out in Oct 1999 and April 2000.] **Study setting:** Seven rheumatology OPA clinic in the Utrecht region[ψ]	**N: 509** **N:** 96 from group with disease duration follow-up: 0 to ≤2 years **F:** 73% **Age:** 54 (SD15) **Disease duration at inclusion** : 0.9 (0.6) year	**Outcome:** Direct medical costs i. Consultations with health care workers ii. Admissions to health care facilities (hospital including surgical procedures, rehab centre, nursing home) iii. Medication iv. Laboratory tests v. Devices to perform daily activities and adaptations at home. vi. Alternative medicine vii. Other costs **Study perspective**: Healthcare and patient	**Currency:** Euros; publication year 2004. **Unit:** Mean (median) (range) 1. Consultation with healthcare workers: 1448 (1433) (0-8090) 2. Admission to care facilities: 1391 (7283)(0-57930) 3. RA related medication 478 (406)(0-2895) 4. Devices and adaptations 963 (2247)(0-15571) 5. Laboratory tests 296 (131)(75-975) 6. Alternative therapies 103 (338)(0-6080) 7. Total extra costs 554 (1094) (0-6080)	**Direct costs per patient per year** **Unit:** Mean (median) (range) 5235 (2923) (570-74080)	**Mean of total direct costs per patient per year in USD 2021:** 14,613 **Median of total direct costs per patient per year in USD 2021:** 8159

Merkesdal et al., Germany 2001(5) (11)	**Objective:** To assess 1) the extent of indirect costs, 2) changes in cost components, and 3) correlations between changes in cost and social, clinical, and occupational variables within the first 3 years of RA. **Study design:** Longitudinal prospective observational study. **Study setting:** Four rheumatology centres	**N:** 133 **F:** 63 **Age, mean (SEM):** 47 (0.8) **Disease duration at inclusion, mean (SEM):** 7 months (0.3).	**Outcome:** 1. Indirect costs Loss of productivity due to i. sick leave ii. work disability iii. other work loss **Study perspective**: Partial societal	**Currency:** US dollars for the period 1994-1996. Unit : Mean (SEM) **Sick leave** Time 0 – time 2: 10530 (990). Time 2 – time 3: 2520 (580). Time 0 – time 3: 7640 (740). **Work disability** Time 0 – time 2: 1210 (360). Time 2 – time 3: 4570 (960). Time 0 – time 3: 2520 (550). **Other work loss** Time 0 – time 2: 840 (370). Time 2 – time 3: 2800 (780). Time 0 – time 3: 1590 (480). **Definition of time-point:** Time 0 = Joint swelling onset. Time 2 = 12 months from study enrolment. Time 3 = 24 months from study enrolment.	**Currency:** US dollars for the period 1994-1996. **Total productivity costs (sick leave, work disability & other work loss)** **Unit:** Mean (SEM) Time 0 – time 2: 12,580 (1030). Time 2 – time 3: 9890 (1210). Time 0 – time 3: 11,750 (1120).	**Cost per person per year in USD 2021 after adjusting for purchasing power parity and Consumer Price Index 2021** **Total productivity costs (sick leave, work disability & other work loss)** **Unit**: Mean Time 0–time 2: 20,180 Time 2–time 3: 15, 865 Time 0–time 3: 18, 848

Newhall-Perry et al. USA , 2000 (6) (13)	**Objective:** To examine direct and indirect costs of RA during the first year of disease. **Study design:** Longitudinal observational study. **Study setting:** Patient recruited at 26 Rheumatology centres in western US and Mexico. (3 practices are University medical centres, 23 community practices.	**N:** 150 **F:** 80% **Age:** 51 (SD 13) **Disease duration at inclusion:** 5.9 months (SD 2.9 months)	**Outcome:** 1. Direct costs 2. Indirect costs **Study perspective:** 1. Healthcare (direct costs) 2. Partial societal (indirect costs)	**Currency:** US dollars 1994 **Disease duration <6 months** (n=87) **Unit:** Mean (SD) **Direct costs per month** 240 (285) 1. Medication costs: 62 (101) 2. Healthcare visits: 65 (69) 3. Radiographs 65 (196) 4. Laboratory tests: 27 (26) 5. Hospitalisations: 0(0) 6. Assistive devices: 3(6) 7. Non-traditional treatments 1(3) 8. In-home assistance 9 (47) 9. Outpatient procedures 8(49) **Indirect cost per month** 348 (567) **Disease duration ≥6 months** **Unit:** Mean (SD) **Direct costs/month** 144 (149) 1. Medications costs: 43(36) 2. Healthcare visits 37 (28) 3. Radiographs 26 (30) 4. Laboratory tests 13 (12) 5. Hospitalisations 6. 16 (97) 7. Assistive devices 3 (11). 8. Non-traditional treatments 2 (9) 9. In-home assistance 3 (16) 10. Outpatient procedures 1 (5) **Indirect cost per** month 188 (506)	**Results in local currency and year of assessment** **Unit:** Mean (SD) **Total RA costs (direct & indirect cost/month)) in patients with disease duration < 6 months:** 586 (686) **Total RA costs (direct & indirect cost/month) in patients with disease duration ≥ 6 months:** 332 (585)	**Cost per person per year in USD 2021 after adjusting for purchasing power parity and Consumer Price Index 2021** **Total costs (direct and indirect costs) of RA per year per patient for overall cohort, mean:** 10,372 Direct costs per year per patient for overall cohort, mean: 4,322 Indirect costs of per year per patient for overall cohort, mean: 6,072 *Cost by disease duration groups:* Indirect costs < 6 months, mean: 7,520 Indirect costs ≥ 6 months, mean: 4,063 Direct costs < 6 months, mean: 5,186 Direct costs ≥ 6 months, mean: 3,112 **Total RA costs (Direct and indirect)** < 6 months, mean: 12,663 **Total RA costs (Direct and indirect)** ≥ 6 months, mean: 7174

Van Jaarsveld et al. Netherlands, 1998 (7) (12)	**Objective:** Estimation of: 1. Annual direct RA related costs in the first 6 years. 2. Socio-demographic and clinical predictors of these costs. **Study design:** Cross-sectional data collection of direct costs for all patients recruited in randomised clinical trial. [First patient in trial was enrolled 1990. Results represented as the total group independent of the treatment arm. Study questionnaire sent in April 1996] **Study setting:** Six rheumatology centres in Utrecht region.	**N:** 363 **N**: 63 from patient with symptom duration at 1 year follow-up. **F:** 64% **Age, median (range):** 57 (19-84) **Disease duration at inclusion:** 0-1 year	**Outcome:** 1. **Direct medical cost:** i. Healthcare workers cost ii. Days in care facilities iii. Medication iv. Medication side effects monitoring v. Alternative medicine 2. **Direct non-medical costs** i. Devices and adaptations at home ii. Other costs: travel expenses, medication not provided by national health service, additional costs of energy, telephone and clothing, payments to friends for care, payment for help around the house, and other costs specified by the patients. **Study perspective:** Healthcare and patient	**Currency:** Dutch Florins; Sept 1997. **Direct medical costs for disease duration 0-1year** Mean (SD) Median per patient per year Total direct cost 14455 (20411) 7370 Subtotal direct medical cost† 9882 (1898) 4444 1. Consultations with Health care worker 3355 (3112) 2340 2. Days in care facilities 4620 (15521) 0 3. Medication 1340 (682) 1170 4. Monitoring for side-effects 484 (311) 416 5. Alternative medicine 83 (299) 0 Subtotal direct non-medical cost 4573 (8934) 2268 1. Adaptations and devices 2814 (6797) 150 2. Other costs 1759 (3101) 600	**Direct medical cost for disease duration 0-1year** **Mean (SD) Median** per patient per year in Dutch florins (Dfl) **Total direct costs** 14455 (20411) 7370 **Subtotal direct medical cost†** 9882 (1898) 4444 **Subtotal direct non-medical cost** 4573 (8934) 2268	**Cost per person per year in USD 2021 after adjusting for purchasing power parity and Consumer Price Index 2021** **Mean (Median)** per patient per year in USD 2021 (for at the end of year 1 of follow-up. **Total direct costs** 24,094 (12285) **Subtotal direct medical cost†** 16472 (7407) **Subtotal direct non-medical cost** 7623 (3780)

ΨCollaborating in the Utrecht RA cohort study group; §Pyramid, IM gold, methotrexate or hydroxychloroquine; §§ n = 330 arthralgia patients recruited; *median (range); §§§Outcome data were split into four groups based on HAQ: Group 1 (HAQ 0 at baseline and 6 m), Group 2 (HAQ>0 at baseline, 0 at 6m), Group 3 (HAQ≥0 at baseline, >0 but <1.0 at 6m), Group 4 (HAQ≥0 at baseline, ≥1.0 at 6m); †Subtotal of medical cost includes costs due to contacts with health care workers, days spent in care facilities, medication, monitoring for side effects and alternative medicine. Subtotal of non-medical direct cost includes costs of adaptations in the home, devices and other costs. ΨΨ HCA= Mean productivity per day over a five-year follow-up was calculated for each patient and multiplied by the cumulative number of their days off work to yield the patients' loss of productivity by the HCA. FCA= estimation of loss of productivity with the assumption that someone replaces the disabled worker after the friction period, and the initial production level is restored, that production losses are confined to the friction period**.** RA-related work disability days were obtained from the official register, divided by the duration (in years) of follow-up during which the patient had not retired due to other diseases or because of age. All final cost column states the cost per person per year in USD 2021 after adjusting for purchasing power parity and Consumer Price Index 2021.

Table 3. Direct costs in USD 2021, symptom duration and outcomes according to increasing symptom or disease duration.

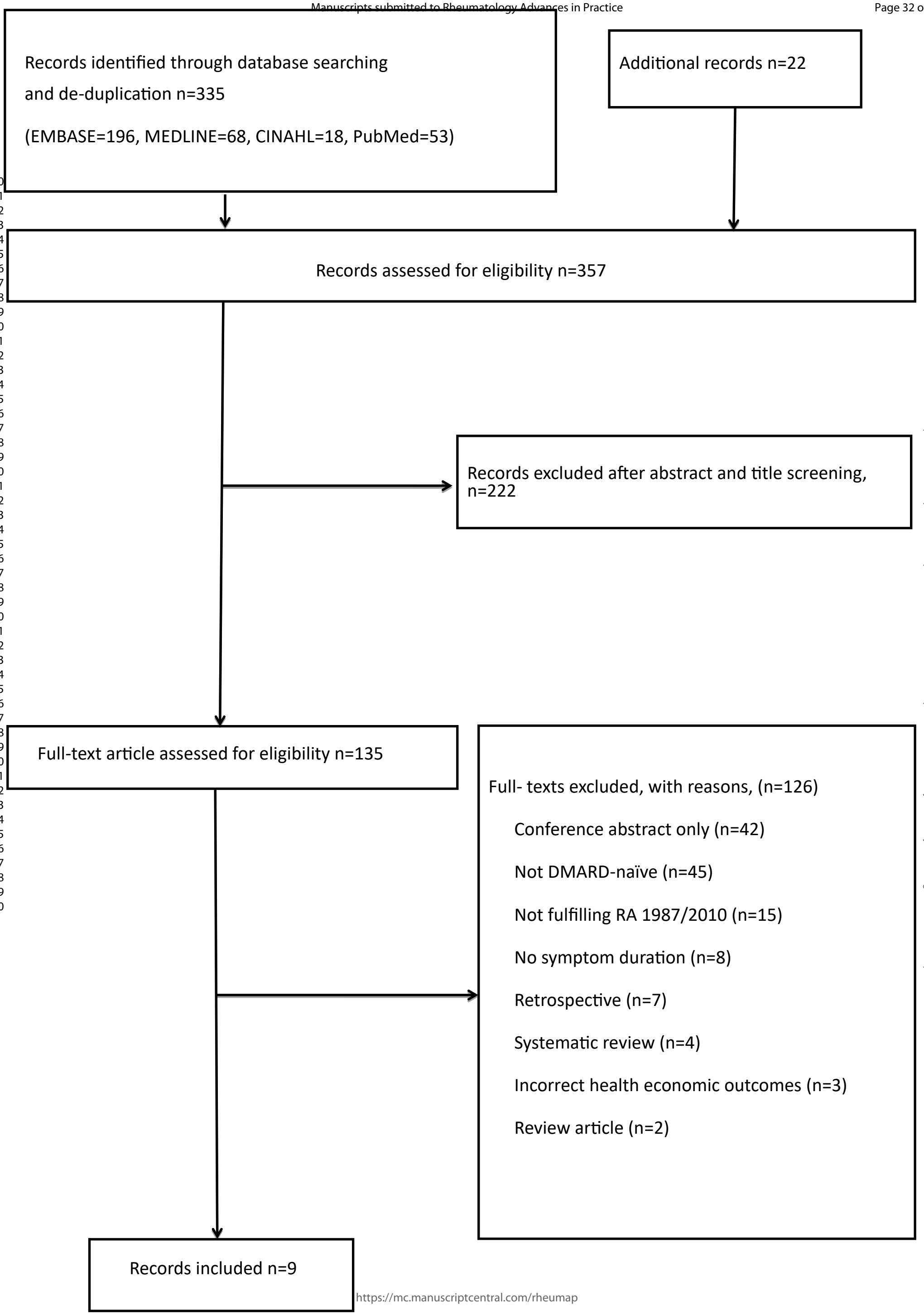
Author, Country, Year	Symptom or Disease Duration	Symptom or disease duration (Days)	Currency in USD 2021	Outcome
Verhoeven et al. Netherlands, 2021 (15)	Symptom duration	Median, TCZ+MTX: 24.5 TCZ: 25.5 MTX: 27.0	Mean, TCZ + MTX: 15,546 TCZ: 18,350 MTX: 17,840	Direct healthcare-related costs by treatment strategy group, per patient per year
Luurssen-Masurel et al. Netherlands , 2021 (14)	Symptom duration	Median: 134	Mean iMTX 3,456 iHCQ 2,839 iGC 4,079	Healthcare costs by treatment strategy group, per patient per year
Verstappen et al. Netherlands, 2004 (10)	Disease duration	Mean: 329	Mean: 14,613 Median: 8,159	Total direct costs per patient per year
Van Jaarsveld et al. Netherlands, 1998 (12)	Disease duration	Inclusion criteria 0 - 365	Mean: 16,472	Direct medical cost per person per year, per patient
Syngle et al. India , 2017 (16)	Disease duration	Mean: 2117	Average: 1,008	Direct medical cost per patient per year

TCZ: tocilizumab; MTX: methotrexate; iMTX: initial treatment strategy with methotrexate; iHCQ: initial treatment strategy with hydroxychloroquine; iGC: initial treatment strategy with glucocorticoids.

Table 4. Indirect costs in USD 2021, symptom duration and outcomes according to increasing symptom or disease duration.

Author, Country, Year	Symptom or disease duration	Symptom or disease duration (days)	Currency in USD 2021	Outcome
Merkesdal et al., Germany 2001, 11	Disease duration	Mean: 213	Mean: Time 0–time 2: 20,180 Time 2–time 3: 15, 865 Time 0–time 3: 18, 848	Loss of productivity costs: Total sick leave, work disability & other work loss
Luurssen-Masurel et al. Netherlands , 2021 (14)	Symptom duration	Median: 134	Mean: iMTX 11,031 iHCQ 12,149 iGC 9,967	Total productivity costs by treatment strategy group
Verhoeven et al. Netherlands, 2021 (15)	Symptom duration	Median: TCZ+MTX: 24.5 TCZ: 25.5 MTX: 27.0	Human capital approach TCZ + MTX 17,076 TCZ 14,272 MTX 16,566 Friction cost approach TCZ + MTX 6,371 TCZ: 5,862 MTX 6,371	Loss of productivity costs loss using human capital approach and friction cost approach by treatment strategy group
Puolakka et al. Finland, 2009 (9)	Disease duration HAQ Group 1	Mean 335	Mean HCA: 736 FCA: 590	Loss of productivity cost by human capital approach and friction cost approach by HAQ group
	HAQ Group 2	243	HCA: 4,523 FCA: 2,275	
	HAQ Group 3	243	HCA: 20,191 FCA: 4,101	
	HAQ Group 4	304	HCA: 40,116 FCA: 6,125	

TCZ: tocilizumab; MTX: methotrexate; iMTX: initial treatment strategy with methotrexate; iHCQ: initial treatment strategy with hydroxychloroquine; iGC: initial treatment strategy with glucocorticoids; HAQ; Health Assessment Questionnaire; time 0: onset of disease; time 2: reassessment at 12 months following baseline assessment; time 3: reassessment at 24 months following baseline assessment.



Author, year	Symptom/disease duration pre-DMARDs initiation	DMARD start	Timing and duration of health economic outcomes recorded	Type of health economic outcomes recorded
	70 // 12 11 10 9 8 7 6 5 4 3 2 1 Months before DMARDs initiation	0	1 2 3 4 5 6 7 8 9 10 Years after DMARDs initiation	
Luurssen-Masurel et al 2021				Incremental cost-effectiveness ratio (ICER) and productivity loss for one year
Verhoeven et al 2021	TCZ & MTX TCZ MTX			ICER and productivity loss during a clinical trial (2 years) & post-clinical trial follow-up (3 years)
Syngle et al 2017				Average cost-effectiveness ratio (ACER) and direct medical cost during the first 3 months of diagnosis
Kuijper et al 2014**				Health care utilisation since symptom onset
Puolakka et al 2009	HAQ group 1 HAQ group 2 HAQ group 3 HAQ group 4			Indirect medical cost (loss of productivity and work disability) for five years
Verstappen et al 2004*			0 to ≤2 years 2 to ≤6 years 6 to ≤10 years >10 years	Direct medical and non-medical costs for three months
Merkesdal et al 2001				Indirect costs for 24 months
Newhall Parry et al 2000**	Disease duration < 6 months Disease duration ≥ 6 months			Direct and indirect costs for six months
Van Jaarsveld et al 1998			0-1 year 1-2 years 2-3 years 3-4 years 4-5 years 5-6 years	Direct medical and non-medical costs for one year
	70 // 12 11 10 9 8 7 6 5 4 3 2 1 Months before DMARDs initiation	0	1 2 3 4 5 6 7 8 9 10 Years after DMARDs initiation	

The blue arrows indicate the symptom/disease duration reported in each study. The green arrows indicate the timing and duration of health economic outcomes reported in each study. Puolakka et al. reported four groups of patients stratified by HAQ groups. *Verstappen et al. reported four groups of patients based on disease duration (defined as time elapsed from study recruitment). Van Jaarsveld et al. reported six groups of patients based on the disease duration (defined as time elapse from study recruitment). **Kuijper et al. and Newhall Parry et al. reported at the time of study enrolment.
HCA; Human capital approach. FCA; Friction cost approach

Jyseleca® ▽ filgotinib

A 2nd generation, JAK1 preferential inhibitor for moderate to severe RA[1-6]

While 1st generation JAK inhibitors are relatively non-selective,[2-6] JYSELECA has over 5x greater potency for JAK1 over JAK2/3 and TYK2[1]*

Balancing sustained efficacy[7-11] with acceptable tolerability[1,12]

Indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs.[1] May be used as monotherapy or in combination with methotrexate.[1]

*From biochemical assays, the clinical relevance of which is uncertain.
JAK, Janus kinase; RA, rheumatoid arthritis; TYK, tyrosine kinase.

Learn more at strengthofbalance.co.uk

Refer to Summary of Product Characteristics (SmPC) before prescribing, and for full prescribing information.

JYSELECA® ▽ filgotinib 100 mg or 200 mg film-coated tablets. **Indication:** Jyseleca is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX). **Dosage:** Adults: 200 mg once daily. Taken orally with/without food. It is recommended that tablets are swallowed whole. Laboratory Monitoring: Refer to the SmPC for information regarding laboratory monitoring and dose initiation or interruption. Elderly: A starting dose of 100 mg once daily is recommended for patients aged 75 years and older as clinical experience is limited. Renal impairment: No dose adjustment required in patients with estimated creatinine clearance (CrCl) ≥ 60 mL/min. A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Not recommended in patients with CrCl < 15 mL/min. Hepatic impairment: Mild/moderate hepatic impairment: no dose adjustment required. Severe hepatic impairment: not recommended. Children (< 18years): Safety and efficacy not yet established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis (TB) or active serious infections. Pregnancy. **Warnings/Precautions:** See SmPC for full information. Immunosuppression: Combination use, with immunosuppressants e.g., ciclosporin, tacrolimus, biologics or other Janus kinase (JAK) inhibitors is not recommended as a risk of additive immunosuppression cannot be excluded. Infections: Infections, including serious infections such as pneumonia and opportunistic infections e.g. tuberculosis (TB), oesophageal candidiasis, and cryptococcosis have been reported. Risk benefit should be assessed prior to initiating in patients with risk factors for infections (see SmPC). Patients should be closely monitored for the development of signs and symptoms of infections during and after filgotinib treatment. Treatment should be interrupted if the patient is not responding to antimicrobial therapy, until infection is controlled. There is a higher incidence of serious infections in the elderly aged 75 years and older, caution should be used when treating this population. Tuberculosis: Patients should be screened for TB before initiating filgotinib, and filgotinib should not be administered to patients with active TB. Viral reactivation: Cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies (see SmPC). If a patient develops herpes zoster, filgotinib treatment should be temporarily interrupted until the episode resolves. Screening for viral hepatitis and monitoring for reactivation should be performed. Malignancy: Immunomodulatory medicinal products may increase the risk of malignancies. Malignancies were observed in clinical studies (see SmPC). Fertility: In animal studies, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed (see SmPC). The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown. Haematological abnormalities: Do not start therapy, or temporarily stop, if Absolute Neutrophil Count (ANC) <1 × 10^9 cells/L, ALC <0.5 × 10^9 cells/L or haemoglobin <8 g/dL. Temporarily stop therapy if these values are observed during routine patient management. Vaccinations: Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. Lipids: Treatment with filgotinib was associated with dose dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased (see SmPC). Cardiovascular risk: Rheumatoid arthritis patients have an increased risk for cardiovascular disorders. Patients should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care. Venous thromboembolism: Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib. Caution should be used in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery, and prolonged immobilisation. Lactose content: Contains lactose; patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take filgotinib. **Pregnancy/Lactation:** Filgotinib is contraindicated in pregnancy. Filgotinib should not be used during breast-feeding. Women of childbearing potential must use effective contraception during and for at least 1 week after cessation of treatment. **Driving/Using machinery:** No or negligible influence, however dizziness has been reported. **Side effects:** See SmPC for full information. Common (≥1/100 to <1/10): nausea, upper respiratory tract infection, urinary tract infection and dizziness. Uncommon (≥1/1000 to <1/100): herpes zoster, pneumonia, neutropenia, hypercholesterolaemia and blood creatine phosphokinase increase. Serious side effects: See SmPC for full information **Legal category:** POM **Pack:** 30 film-coated tablets/bottle **Price:** UK Basic NHS cost: £863.10 **Marketing authorisation number(s):** Great Britain Jyseleca 100mg film-coated tablets PLGB 42147/0001 Jyseleca 200mg film-coated tablets PLGB 42147/0002 Northern Ireland Jyseleca 100mg film-coated tablets EU/1/20/1480/001 EU/1/20/1480/002 Jyseleca 200mg film-coated tablets EU/1/20/1480/003 EU/1/20/1480/004 **Further information:** Galapagos UK, Belmont House, 148 Belmont Road, Uxbridge UB8 1QS, United Kingdom 00800 7878 1345 medicalinfo@glpg.com Jyseleca® is a trademark. **Date of Preparation:** January 2022 UK-RA-FIL-202201-00019

▽ Additional monitoring required

Adverse events should be reported.
For Great Britain and Northern Ireland, reporting forms and information can be found at yellowcard.mhra.gov.uk or via the Yellow Card app (download from the Apple App Store or Google Play Store).
Adverse events should also be reported to Galapagos via email to DrugSafety.UK.Ireland@glpg.com or 00800 7878 1345

References: 1. JYSELECA SPC. Available at: www.medicines.org.uk. Last accessed: June 2022. **2.** Angelini J, *et al.* Biomolecules 2020;10(7):E1002. **3.** Banerjee S, *et al.* Drugs 2017;77:521–546. **4.** O'Shea JJ, *et al.* Nat Rev Rheumatol 2013;9(3):173–182. **5.** Traves PG, *et al.* Ann Rheum Dis 2021;0:1–11. **6.** McInnes IB, *et al.* Arthr Res Ther 2019;21:183. **7.** Combe B, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219214. **8.** Genovese MC, *et al.* JAMA 2019;322 (4):315–325. **9.** Westhovens R, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219213. **10.** Combe B, *et al.* Arthritis Rheumatol 2021;73(suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-filgotinib-treatment-in-an-ongoing-long-term-extension-trial-of-ra-patients-with-inadequate-response-to-mtx-initially-treated-with-filgotinib-or-adalimumab-during-th/. Last accessed: June 2022. **11.** Buch MH, *et al.* Arthritis Rheumatol 2021;73 (suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-ongoing-filgotinib-ra-long-term-extension-trial-of-biologic-dmard-inadequate-responders-initially-on-filgotinib-or-placebo-in-a-phase-3-trial/. Last accessed: June 2022. **12.** Winthrop K, *et al.* Arthritis Rheumatol 2021;73(suppl 10). Available at: https://acrabstracts.org/abstract/integrated-safety-analysis-update-for-filgotinib-in-patients-with-moderately-to-severely-active-rheumatoid-arthritis-receiving-treatment-over-a-median-of-2-2-years/. Last accessed: June 2022.

Galápagos

June 2022 GB-RA-JY-202205-00033