Effectiveness of Disease-Modifying Antirheumatic Drugs (DMARDs) in Reducing Sickness Presenteeism Outcomes Among Persons Living With Rheumatoid Arthritis: A Systematic Review

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Abstract

This systematic review examines the impact of disease-modifying anti-rheumatic drugs, or DMARDs, on sickness presenteeism among working age persons diagnosed with rheumatoid arthritis (one percent of the adult population). Sickness presenteeism, being at work but not fully productive due to illness, is a recognized source of paid work loss that is now being extended to aspects of life that impact workplace productivity; namely, home, family, and social and leisure activities. The advent of biologic DMARDs (bDMARDs) radically changed the prognosis from living with symptoms of pain and fatigue to reduced symptom severity and even to disease remission. Using systematic review methods, 15 articles were identified and reviewed. Work outcomes derived from experimental research designs indicated that bDMARDs reduced presenteeism to a level that was statistically and/or clinically significant. The included studies illustrate that bDMARDS can control symptoms, induce remission, decrease presenteeism, and increase work productivity. All studies reported improved presenteeism outcomes for paid work, with fewer studies reporting improved presenteeism for the interdependent spheres of household and family/social/recreation type of work. Taken together, the bDMARDs can restore quality of life and change life expectations for patients/employees, employers, and physicians.

Keywords: sickness presenteeism, disease modifying antirheumatic drugs (DMARDs), rheumatoid arthritis, systematic review, work productivity

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Dedication

This Signature Project is dedicated to my mother, Marjorie (Campbell) Moase. Her support of education was constant being one of her core beliefs.

Marjorie Moase always encouraged her children to obtain an education believing that education was good for everyone as they pursued their life roles. She saw education as an investment in society that helped to build a better world. She encouraged each of her children to obtain the education that she dearly wanted and never attained. This generous attitude made her commitment to education all the more precious.

My mother would have been thrilled to attend a UPEI graduation. Unfortunately, death intervened on October 22, 2014, just two months before her 90th birthday.

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List of Symbols

>	is greater than
<	is less than
≥	is equal to or more than
≤	is equal to or less than
%	percent
$	dollars
€	euros
£	pounds
#	count or identification number

List of Abbreviations

ABA	Abatacept (Orencia)
ACR	American College of Rheumatology
ADA	Adalimumab (Humira)
AIM	Abatacept in Inadequate responders to Methotrexate
Anti-TNF	Anti-Tumour Necrosis Factor
APaQ	Activity Participation Questionnaire
bDMARD	Biologic or biological disease-modifying antirheumatic drug
CanAct	Canadian Adalimumab Clinical Trial
CERTAIN	CERTolizumab pegol in the treatment of RA: remission INduction and maintenance in patients with LDA
COMET	Combination of Methotrexate and ETanercept
CONSORT	Consolidated Standards of Reporting Trials
CZP	Certolizumab pegol (Cimzia)
DAQ	Domestic Activity Questionnaire
DAS28	Disease Activity Score
DOI	Digital Object Identifier
DMARD	Disease-modifying antirheumatic drug
ETN	Etanercept (Enbrel)
FC	Friction Cost
HAQ	Health Assessment Questionnaire
HC	Human Capital
HLQ	Health and Labour Questionnaire
HPQ	Health Productivity Questionnaire
ID	Identifier (number or letter)
MCID	Minimum Clinically Important Difference
MTX	Methotrexate
NRAS	National Rheumatoid Arthritis Society (UK)
NSAIDS	Non-steroidal anti-inflammatory drugs
OMERACT	Outcome Measures in Rheumatology (a/k/a OM in RA Clinical Trials)
OPERA	Observation of Productivity in Employed Patients with Rheumatoid Arthritis
OS	Observational Study
PASS	Patient Acceptable Symptom State
PICO	Participants, Intervention, Comparison, Outcomes
PQ	Patient Questionnaire
PREMIER	Patients Receiving Methotrexate and Infliximab for the Treatment of Early Rheumatoid Arthritis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRIZE	Productivity and Remission in a Randomized Controlled Trial of ETN
PROs	Patient Reported Outcomes
RA	Rheumatoid arthritis
RAPID	Rheumatoid Arthritis Prevention of Structural Damage (RCT)
RCT	Randomized Controlled Trial
SDAI	Simplified Disease Activity Index

SP	Sickness Presenteeism
TNF	Tumour Necrosis Factor
VAS	Visual Analogue (Analog) Scale (Score)
VBBA	de vragenlijst beleving en beoordeling van de arbeid *(Dutch). The English equivalent is QEEW (Questionnaire Experience and Evaluation of Work) or Dutch Questionnaire on the Experience and Assessment of Work (1994).*
VOLP	Valuation of Lost Productivity (Long Version & Short Version)
WAI	Work Ability Index
WIS-RA	Work Instability Scale- Rheumatoid Arthritis
WLQ25	Work Limitations Questionnaire (long form with 25 items)
WPAI-RA	Work Productivity and Activity Impairment – Rheumatoid Arthritis (Specific)
WPS-RA	Work Productivity Survey – Rheumatoid Arthritis (Specific)

CHAPTER 1: INTRODUCTION

Persons living with a disease, such as rheumatoid arthritis, often experience the lesser known sickness presenteeism (at work with reduced work productivity due to illness) and the better known sickness absenteeism (not at work and with no productivity due to illness). Presentees and absentees may feel enticed to stay at work or return to work by financial income, social belonging, role functioning, meaning in life, and health benefits derived from work (Beaton, 2015). As stated, numerous factors influence their decision to be a presentee or an absentee.

Using figures approved by Arthritis Research Canada (JointWorks, 2017), one percent (0.7%) or one of every 136 Canadian workers lives with rheumatoid arthritis. This rate is predicted to increase to one in 68 (1.4%) by 2020. If undertreated or untreated, up to 50% of employees living with the disease are work-disabled within 10 years of onset. Among persons in the United Kingdom (UK) living with the disease, 45% were not working and 28.4% ceased to work within one year of diagnosis, with the mean time between diagnosis and leaving work being 5.4 years (NRAS, 2007). Usually diagnosed at 40-60 years of age, about 80% of affected persons are expected to have added work challenges due to co-morbidities, such as cardiovascular disease, lung disease, osteoporosis, cancer, and depression (NRAS, 2012).

Chief financial officers and benefits managers highlight the costs of employee health care and / or employee sickness absenteeism. Meanwhile, sickness presenteeism, a larger workplace expense and a larger management opportunity, goes largely unmentioned (Health Enhancement Research Organization, 2011). Sickness presenteeism is invisible, complex to measure, and easily dismissed as a cost of doing business (Goetzel et al., 2004; Quazi, 2013; Sogaard, Sorensen, Linde, & Hedtland, 2010).

Recent economic downturns have prompted some managers to view presenteeism as a source of competitive advantage (Johansen, 2012). The rationale is that human capital has surpassed physical and natural resources as a means of wealth creation (Chrysler-Fox & Roodt, 2014). However, no gold standard exists to measure sickness presenteeism. The Institute of Health and Productivity Management agrees that the lack of standardized presenteeism metric is a significant gap (with an opportunity cost). Workplace Wellness Alliance (2013) reported that among companies studied, 24% collected absenteeism metrics, but only 16% collected presenteeism metrics. The vision is that sickness presenteeism and sickness absenteeism can be managed as complements to enhance work productivity within an organizational strategy that uses workplace health for competitive advantage.

Work losses due to rheumatoid arthritis (RA), which is a chronic progressive disease characterized by inflammation in the joints, painful deformities, and immobility in the fingers, wrists, feet, and ankles (if left untreated), can impact patients, families, society-at-large, employers, health providers, insurance companies, pharmaceutical companies, national economies, and more (Lacaille, 2009). Omission of sickness presenteeism (and multipliers) from calculations of productivity loss may underestimate losses by a factor of almost two (Sogaard et al., 2010). Presenteeism and absenteeism, each a form of absence from work activity, can cause a substantial loss in workplace productivity. A recent UK cross-country study reported that RA absenteeism ranged from 2.7 to 82 days a year, while presenteeism ranged from 4.5 hours less work a week or 27 days less work per year expressed on a per person basis (Goetzel et al., 2004; Stewart, Ricci, Chee, & Morganstein, 2003). A 2007 UK survey on work and rheumatoid arthritis reported that an employee with rheumatoid arthritis has an average of 40 days sick leave per year, exceeding the 6.5 day average reported for other persons (National Audit Office, 2009).

Since the 1990s, disease-modifying antirheumatic drugs (DMARDs) have altered work outcomes for rheumatoid arthritis patients. It is expected that younger persons who receive state-of-the-art rheumatology care will have an extended work life (Allaire, Alheresh, & Keysor, 2013). To gain insight into the future of sickness presenteeism and work productivity, I conducted a systematic review of biologic DMARDs (bDMARDs). Systematic reviews that summarize what is known and not known about a specific question are a cornerstone of evidence-based management (Briner, Denyer, & Rousseau, 2009).

This signature project is organized as follows: Chapter 1 outlines the purpose and contextual information to understand the significance of presenteeism in working age adults living with rheumatoid arthritis and prescribed bDMARDs. Chapter 2 presents relevant background information; the objective is to cover the topics required to understand aspects of work productivity central to the systematic review. Chapter 3 describes the methods used to conduct this systematic review, including selection of studies, analysis framework, data extraction, and data analysis. Chapter 4 summarizes the key findings for each step in the systematic review process, with a focus on presenteeism and related concepts relevant to work outcome measurement. Finally, Chapter 5 outlines the main conclusions regarding presenteeism and work productivity outcomes and their measurement. Limitations and future directions are noted. Collectively, the five chapters answer the question: *"In persons living with rheumatoid arthritis, can sickness presenteeism be reduced more by drug interventions using experimental disease-modifying antirheumatic drugs (bDMARDS) than by comparator drug interventions?"*

CHAPTER 2: BACKGROUND INFORMATION

This section introduces the key topics involved in this systematic review, that is, sickness presenteeism (including the measurement of presenteeism), rheumatoid arthritis, and disease-modifying antirheumatic drugs.

Sickness Presenteeism

Sickness presenteeism is the practice of going to a job unwell, or attending work while ill, and being unable to perform at capacity (Cooper, 2011). Since the 1990s, organizational psychologists and economists have sought to measure the level of productivity loss, an indirect cost that is not usually measured, accounted for, or managed, according to management experts (Hemp, 2004). The organizational role of sickness presenteeism is gaining prominence as a source of competitive advantage. Illness costs negatively impact organizational performance, making sickness presenteeism an important priority in organizations where human resources can be a source of competitive advantage (Garrow, 2016). Given the state of knowledge on presenteeism, a common management response is to create a culture of health in the workplace until knowledge evolves to the point that research can inform the measurement and management of sickness presenteeism.

Sickness presenteeism is not a lack of motivation, worker laziness, or professional deviance (Hemp, 2004; La Gosselin & Lauzier, 2011). Instead, the productivity losses attributed to sickness presenteeism are due to the health issues affecting workers, whether non-specific symptoms such as pain, fatigue, and anxiety, or specific acute or chronic phases of disease conditions such as depression, diabetes, heart disease, cancer, respiratory, arthritis, insomnia, or other conditions listed in the International Classification of Diseases (WHO, 1993). In essence, the employee qualifies to be an absentee, but is a presentee (La Gosselin & Lauzier, 2011) for organizational and/or personal reasons (Garrow, 2016).

Some experts broaden presenteeism beyond sickness to a generic term that includes anything that reduces work productivity. These employees are present but non-productive due to smoke breaks, web surfing, personal phone calls, e-mails, chatting, extended breaks, shopping, wandering, and so forth. Disengaged, underperforming employees fit the broad definition (Ashby & Mahdon, 2010). Among employees, it is estimated that 35% are fully functioning, 41% are sickness presentees, and 24% are job dissatisfied and stressed or chronically unhealthy (Cooper, 2011). However, such expanded definitions have not gained wide acceptance (Lowe, 2010).

Sickness presenteeism is subject to societal trends. Behavioural addiction has been recognized by the universally recognized DSM-V (American Psychiatric Association, 2013). Already, treatment is provided for internet addiction, video gambling, job-related embezzlement, and other behavioural addictions that occur in the workplace. The DSM-VI is expected to add these new behavioural addictions that are possible sources of sickness presenteeism in the workplace.

Relationship between presenteeism and absenteeism. Absenteeism and presenteeism (and disability, according to some sources) are two components of the broader concept of work productivity (Escorpizo et al., 2007). Absenteeism and presenteeism form a continuum where workers fluctuate back and forth across time. For example, workers may return to work before they are completely healed, thereby exhibiting a level of presenteeism that varies with the level of recovery. Employees that frequently exhibit presenteeism are at greater risk of absenteeism. In a sense, absenteeism and presenteeism are both types of absence (Arnold, 2015).

Some sources suggest that presenteeism can vary inversely with absenteeism, where one type of absence decreases as the other type of absence increases (Anis et al., 2009). A common example is an economic downturn that may increase presenteeism and decrease absenteeism because employees are substituting presenteeism for absenteeism to protect job security (Gosselin, Lemyre, & Corneil,

2013). Empirical research suggests that substitutive effects, complementary effects, or no change may occur as a result of an increase in one or the other (Arnold, 2015). In short, the relationship between presenteeism and absenteeism may vary depending on context.

Recent thinking suggests that presenteeism and absenteeism should each be subdivided into positive and negative types (Garrow, 2016). Putting pressure on genuinely sick employees requiring rest is an example of negative presenteeism. Conversely, providing support to enable an employee to work when they want to work despite unwellness is positive presenteeism.

Taking a day off because the employee has not used up sick days is negative absenteeism. On the other hand, taking a day off to avoid spreading a contagious disease is positive absence. Presentees and absentees may be the same people – people with poor health who weigh the factors relevant to them and decide to be a presentee or an absentee. Taken together, it is apparent that the relationship between presenteeism and absenteeism is yet to be clearly defined (Bierla, Huver, & Richard, 2013; Garrow, 2016).

Macro and micro role of presenteeism. Seminal research on sickness presenteeism remains widely cited. Presentees may be more than 30% less productive when unwell compared to when they are well (Hemp, 2004). Sainsbury Center for Mental Health (2007) compared presenteeism and absenteeism costs and reported that presenteeism was 1.8 times more costly than absenteeism, based on the one-year cost per average employee (£605 vs. £335) and based on total cost to UK employers (£15.1 billion vs. £8.4 billion), using conservative figures. Presenteeism is more costly than absenteeism because it is more common among higher paid than lower paid staff (Sainsbury Center for Mental Health, 2007). Additionally, presenteeism losses are largely driven by poor mental health. Productivity losses involving mental illness are more likely to be expressed as presenteeism than absenteeism, as workers suffering from mental health issues often decide to be present rather than

absent when ill to avoid stigma/discrimination (Sainsbury Center for Mental Health, 2007).

An international review of broad-based health conditions also reported that presenteeism figures consistently exceed absenteeism figures. Compared to the factor of two (2) derived by the Sainsbury Center for Mental Health (2007), other sources reported productivity losses to be anywhere between 1.9 and 6.8 times those of absenteeism (Collins et al, 2005; Ozminowski, Goetzel, Chang, & Long, 2004; Stewart, Matousek, & Verdon, 2003; Tilse & Sanderson, 2005).

Countries such as the UK, Australia, member states of the European Union, and Singapore regard presenteeism as an untapped source of work productivity and therefore national competitive advantage. The UK regularly measures presenteeism among adult age workers using new survey methods (CIPD, 2016). In 2016, three in 10 employers reported presenteeism among their employees, while absence days per employee per year decreased from 7.4 in 2010 to 6.3 in 2016 (CIPD, 2016).[1] Reviews of Britain's working age population, *Black Report* (2008) and *Boorman Report* (2009),[2] led the biggest employer in Europe to recognize the magnitude of presenteeism and move policy from a 'sick note' (cannot) to a 'fit note' (can) to improve work productivity on a national scale (National Health Services, 2012).

In Australia, an Econotech Pty. Ltd. (2007) and a KPMG/Econotech (2011) study of 12 common medical conditions estimated presenteeism to cost nearly four times more than absenteeism. In the most recent study, presenteeism represented a cost of $34.1 billion nationally in 2009/2010,

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[1] These absenteeism figures do not account for leavism (or leaveism), the practice of taking allocated time off such as annual leave or banked flextime to catch up on work (Hesketh, Cooper, & Ivy, 2014; Lewis, 2016).

[2] The Black Report (2008) and Boorman Report (2009) led UK policymakers to introduce the 'fit note' whereby a physician assesses a person absent from work for seven days or more as 'not fit for work' or 'may be fit for work' and offers options for a return to work including workplace accommodations (NHS Choices, 2012). The 2010 fit note replaces the 1922 sick note where the employer expected an employee to do a specific job rather than contribute within today's more flexible workplace (NHS Choices, 2012). The fit note acknowledges that people can work alongside health issues, and that work can play an important role in recovery from illness while also reducing sickness absence (Cooper & Dewe, 2008). The fit note is intended to help workers get back to work as soon as possible while also promoting national productivity.

a 2.7% decrease in GDP in 2010, and an average of 6.5 days of work productivity lost per employee annually. The cost of presenteesim is predicted to be $35.8 billion by 2050 (with a decrease of 2.8% in GDP). As a result, policymakers in Australia have suggested that health requires the same attention as education if Australian work productivity is to compete internationally (Kyaw-Myint, Smith, Beales, Job, & Straker, 2015).

In Singapore, a survey conducted between 2008 and 2011 reported presenteeism among 27% of management and 46% of non-management employees (Quazi, 2013). The cost of presenteeism is similar for management and non-management when balanced out by pay level and type of disease. Productive time lost by management exceeded non-management (0.68% versus 0.55%) because management felt compelled to work longer hours to fulfill job demands and maintain role status (Quazi, 2013).

Finally, in Europe, data from seven European countries (OECD, 2012) indicated that the incidence of sickness presenteeism averaged 35%, and the incidence of sickness absence averaged 21%. Expressed as days per year, European workers accumulated an average number of 2.4 days for sickness presenteeism and 5.3 days for sickness absence. In this survey, presenteeism rates were less than half those of absenteeism, yet presenteeism still represented a substantial productivity loss (Arnold, 2013).

Economic evaluation of sickness presenteeism. A recent systematic review stated that presenteeism is rarely included in economic studies despite its significant cost (Kigozi, Jowett, Lewis, Barton, & Coast, 2017). Moreover, when included in analyses, presenteeism is more likely to be included in cost-of-illness analyses than cost-effectiveness or cost-utility analyses. Whether estimates should be based on the more practical friction cost approach (which considers only productivity loss in the friction period before a replacement worker is found, plus replacement costs) or the less practical human capital approach (which considers humans to be assets and

measures productivity loss as income losses due to morbidity and mortality) remains to be seen (Pauly, Nicholson, Polsky, Berger, & Sharda, 2008; Zhang & Anis, 2011; Zhang & Anis, 2014).

Jones, Payne, Gannon, and Verstappen (2016) identified the need for increased use of economic theory when developing instruments to measure presenteeism. Among more than 20 instruments that measure presenteeism, productivity theory had not been incorporated into instrument design. Only one instrument, the Valuation of Lost Productivity or VOLP, integrates productivity theory in economic terms (Zhang, Bansback, Kopec, & Anis, 2011). Ironically, the main justification for measuring presenteeism (economic) is also the main deterrent (lack of economic theory).

At least three frameworks can guide the measurement of presenteeism: Presenteeism-Absenteeism Transitioning; International Classification of Functioning, Disability, and Health Model; and Person-Environment Fit Model (Tang et al., 2011). Each model emphasizes aspects of worker productivity that must be measured to understand presenteeism, and can be applied to rheumatoid arthritis. However, none of the models are economic. Based on the literature reviewed, the appetite for an economic measure is greater than the appetite for knowledge of hours, days, or percentage rates of presenteeism. While there is a general consensus that presenteeism should be measured, there is a lack of standardized measurement methods (Kamal et al., 2017; Mattke et al., 2007; Tang et al., 2014).

Work outcomes are extremely important to workers and employers. OMERACT 1 (Outcome Measures in Rheumatology) in 1992 prioritized the need to ratify a core outcome set of indictors for rheumatoid arthritis trials (Tugwell et al., 2007). OMERACT 7 (2004) and OMERACT 8 (2006) confirmed work outcomes as a priority. OMERACT 11 focused on presenteeism, "an area with diverse conceptualization and instrumentation approaches" (Tang et al., 2014, p. 165). As stated, work outcomes have not yet been added to the core set of outcomes for rheumatoid arthritis

due to the lack of standard measurement. Establishment of an Outcome Measures Library (OML) by the European League Against Rheumatism (EULAR), which has a focus on tools and their psychometrics, is a support for the advancement of tools that measure presenteeism (Castrejon, Gossec, & Carmona, 2014).

Quantifying presenteeism. The elements of health-related productivity measurement fall into three categories; namely, presenteeism, absenteeism, and employee turnover and replacement costs (American College of Occupational and Environmental Medicine, 2003). Presenteeism includes 1) time not on task, 2) quality of work (including incidence and magnitude of mistakes, capacity for peak performance, injury rates, and caregiver costs), 3) quantity of work (work capacity or output), and 4) personal factors (social, mental, physical, emotional, and functional status). Absenteeism includes workers' compensation, short-term disability, long-term disability, sick leave, family medical leave, personal time off, and unpaid leave. Worker productivity usually includes absenteeism (work time missed due to health reasons) and presenteeism (impaired work performance due to health reasons) (Escorpizo et al., 2007). A Canadian study reported that more employees than employers (53% vs. 32%) saw presenteeism as a serious issue in their workplaces. In contrast, more employers than employees (52% vs. 43%) saw absenteeism as a serious issue in their workplaces (Allen & Bourgeois, 2015). Stress, a form of sickness presenteeism, was regarded as a source of both presenteeism and absenteeism.

A compilation of presenteeism outcomes identified 13 outcomes, namely: 1) degree or percentage of impairment, 2) proportion or percentage of time, 3) frequency of impaired work, 4) overall work performance, 5) own versus others' performance, 6) quality/quantity of performance, 7) efficiency or percentage being effective, 8) effect on well-being, 9) degree of agreement on work limitations, 10) amount/level/degree of difficulty with work, 11) number of difficulties, 12) time missed due to delays in starting work, and 13) number of hours of reduced productivity (Escorpizo

et al., 2007). VOLP, a newer presenteeism tool, adds economic indicators to the list (e.g., monetary value of productivity loss due to presenteeism and absenteeism) (Zhang et al., 2015).

Experts advise paying attention to modern medical treatments and work accommodations for rheumatoid arthritis which may impact the amount of presenteeism and absenteeism experienced by employees in the workplace. Health-economic appraisal of biologics and their impact on presenteeism is of high priority for at least four reasons: 1) the lengthy or indefinite treatment period, 2) the relatively large patient population, 3) the initiation of the disease in middle age or work years, and 4) the much higher cost of biologic agents compared to conventional therapies (van Vollenhoven, Cifaldi, Ray, Chen, & Weisman, 2010). Currently, health-economic assessments report the cost per quality-adjusted life year to be well in the accepted range. The cost of biologics is in the catastrophic drug range, but the cost of *not* adequately treating rheumatoid arthritis is enormous. Descriptive information indicates that biologics can improve work outcomes, including presenteeism (Kavanaugh et al., 2009; van Vollenhoven et al., 2010). The higher cost of biologics may be offset by the value of greater participation in the workplace, home, and other societal contexts, the level of personal income due to longer duration of work participation, the decrease in cost of orthopedic surgery for severe rheumatoid arthritis, and related cost factors.

Quantification of presenteeism in cases where rheumatoid arthritis is affecting on-the-job productivity suffers from a lack of standardization of measurement and monetization (Burton et al., 2006). Established questionnaires use self-reported productivity loss to measure presenteeism. Only two articles summarized definitions of presenteeism (Beaton et al., 2009; Escorpizo et al., 2007) and only 11 tools have received any level of endorsement by an authoritative source (Beaton et al., 2009; Gignac, 2014; Ospina, Dennett, Waye, Jacobs, & Thompson, 2015; Tang et al., 2014), with none of these tools being an economic tool like VOLP.

Rheumatoid Arthritis

Traditionally considered a debilitating disease, rheumatoid arthritis usually starts in the prime of adult work life. In Canada, approximately one in 100 persons develop rheumatoid arthritis, which is in the range of 0.5% to 1.0% of adults cited for developed countries (Scott et al., 2010). The risk of rheumatoid arthritis is increased with one or more of the following characteristics: female sex (two to three times the male rate), age 40 to 60 years, smokers, overweight or obese, family history of rheumatoid arthritis, and certain environmental exposures (Mayo Clinic, 2017; Wasserman, 2011).

Disease process. Rheumatoid arthritis is an autoimmune disease wherein the body attacks itself. The immune system starts attacking healthy synovium membrane that surrounds a joint and contains synovial fluid. The abnormal immune reaction causes inflammation of the synovium which destroys collagen, narrows the joint space, and damages the bone. Progressive rheumatoid arthritis destroys cartilage causing fluid and immune cells to accumulate in the synovium, and form a pannus or growth of thickened synovial tissue. Gradually, the inflammation destroys the cartilage and bone in the joint and the tendons and ligaments holding the joint together become weak and stretched. As a result, the joint loses shape and alignment. In early rheumatoid arthritis, the smaller joints are affected (joints that attach fingers to hands and toes to feet). As the disease progresses, larger joints are affected (joints in wrists, knees, ankles, elbows, hips, and shoulders). Prolonged inflammation leads to persistent pain, loss of body function, disability, and diminished quality of life. The body can suffer stiffness, tenderness, swelling, restricted motion, fatigue, malaise, and flares that interfere with work (A.D.A.M., n.d.; Klareskog, Catrina, & Paget, 2009; Mayo Clinic, 2017).

The disease course for rheumatoid arthritis is neither obvious nor predictable. If remission occurs spontaneously or in response to treatment, it can extend work productivity. Untreated

rheumatoid arthritis causes joint weakness, stiffness, and deformity, with 20% to 30% of affected persons becoming permanently work-disabled within three years of diagnosis (Rindfleisch & Muller, 2005). Drug treatment halts the disease in most cases (Scott et al., 2010). This disease is an associated cause of cardiovascular disease and premature mortality (Deloitte Access Economics, 2013).

Using clinical tests to support diagnosis and remission. Rheumatoid arthritis can be difficult to diagnose or can be easily diagnosed, depending on the stage of disease and the rate of progression when seeking diagnosis. Clinician opinion is essential, "since even the best criteria will have false positives and false negatives" (van Vollenhoven, 2016, p. 5). When making a diagnosis, clinicians consider blood tests (rheumatoid factor, erythrocyte sedimentation rate, C- reactive protein, anti-CCP antibody), biomarkers (joint destruction), and imaging (x-ray, ultrasound, magnetic resonance imaging). A physical assessment is essential to add general health, functional disability, pain, fatigue, morning stiffness, and swollen/tender joint information (A.D.A.M., n.d.).

The clinical data collected are interpreted using the classification criteria of national professional rheumatology organizations (e.g., American College of Rheumatology, Canadian Rheumatology Association, and European League Against Rheumatism), consensus statements, latest medical updates, and clinician opinion. Knowing the importance of early drug intervention, the recent revisions of rheumatoid arthritis classification criteria are aimed at early diagnosis and early treatment in pursuit of remission (Combe et al., 2016; van Vollenhoven, 2016).

Once a person has developed rheumatoid arthritis, the disease may alternate between flares (active joint inflammation) and remissions (inactive disease). About one-third of cases are mild (few flares) and two-thirds are more severe. The worst cases have a continuously active disease that progressively worsens over time, causing deformities (as the inflammation process damages joint structures and disrupts joint functions). Besides joint pain, stiffness, and swelling, some persons report difficulty sleeping, extreme tiredness, and feeling like they have a bad flu (Scott et al., 2010).

Rheumatoid arthritis and work life. For persons afflicted by this disease, fatigue, pain, physical limitations, and time off sick are among the major barriers to remaining in employment. Less frequently cited barriers include problems with colleagues, work adaptations, lack of support by employer and/or family, and lack of transport (National Rheumatoid Arthritis Society in Scotland, 2010). Rheumatoid arthritis can lead to a significant reduction in work years, with work loss starting in the 40s or 50s, or even earlier. Workers lose current and retirement income, while employers lose skilled workers. Among employed patients, hidden costs include reduced earning potential due to changing occupations to accommodate the disease, limitations on career progression, and reductions in work time (National Rheumatoid Arthritis Society, 2010).

Within a year of developing rheumatoid arthritis, approximately 15% of employees experience some degree of work disability, although this figure is expected to decrease with the availability of new treatment options. In Scotland, an in-depth national survey of patients diagnosed with rheumatoid arthritis, attending 117 different hospitals, indicated that approximately 60% were employed (29.3% full time, 21.7% part time, 5.6% self-employed, and 2.5% long term sick leave) and 40% were not employed with pay (National Rheumatoid Arthritis Society, 2010). However, a paradigm shift in disease management ("go low, go slow" step-down approach to control symptoms vs. "go strong, go fast" step-up approach to seek remission) is gradually rendering published studies out-of-date and thus less informative and less relevant (Schipper & van Riel, 2011).

Disease-Modifying Antirheumatic Drugs

Starting in the 1990s, rheumatoid arthritis strategy has undergone a paradigm shift, with the goal of treatment moving from symptomatic relief to low disease activity or remission (van Vollenhoven, 2016). Biologics, or biologic response modifiers, are new drugs that can target individual molecules and take effect sooner than conventional disease-modifying antirheumatic drugs (DMARDs). Biologics are genetically-engineered proteins designed to inhibit specific

immune factors that fuel inflammation (i.e., suppress the immune system where the fundamental abnormality occurs in rheumatoid arthritis). Biologics are usually administered to persons who do not respond to or do not tolerate conventional DMARDs. Further, these drugs may induce remission of rheumatoid arthritis, thereby preserving joint function and work ability. The first five drugs (listed below) show improvement on the same day or the day after (rather than in two to three months as with conventional DMARDs). Radiographics, tolerance, and drug safety are comparable or better than with previous drugs (van Vollenhoven, 2016). Advances in treatment of early rheumatoid arthritis have altered the rate of disease progression when measured by radiographic changes. Baseline scores were similar in pre-1990 and post-1990 cohorts (2.10% vs. 2.20%), and progression rates were halved after 1990 (0.68% vs. 1.50%). The reduction was attributed to new biologics, the treat-to-target treatment approach, and intensive use of the cDMARD methotrexate (Carpenter at el., 2016).

The new biologics or biologic disease-modifying antirheumatic drugs (bDMARDs) are known by the generic names (brand names) of etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab (Cimzia), golimumab (Simponi), anakinra (Kineret), rituximab (MabThera or Rituxan), abatacept (Orencia), and tocilizumab (Actemra or Roactemra). These biologics have replaced older synthetic disease-modifying antirheumatic drugs (sDMARDs), also known as conventional disease-modifying antirheumatic drugs (cDMARDs). Only one drug from the older synthetic group, methrotrexate, remains in wide use (vanVollenhoven, 2016).

The value and effectiveness of biologics. Much evidence exists to support the value of biologics. First, disease remission is now a realistic goal. Second, the new biologics are considered "extremely effective" in reducing disease, destruction of joints, and adverse events. Third, costs are in the present time and potential savings are in the future. Fourth, early use of biologics has focused on persons in greatest need, with cost-effectiveness being a consideration in some drug access

programs. Fifth, accumulated clinical and economic data support the use of biologics (Kobelt & Kasteng, 2009). Biologics can deliver reduced disability, increased work participation, and favourable employment status when balanced against risk of toxicity and high costs (Tanzi, 2012; ter Wee, 2012).

A Canadian study of 1,777 patients (12 years disease duration) who received a new biologic reported that, after the first year of biologics, 31.3% met remission criteria, 22.1% met minimal disease activity criteria, and the remaining 46.6% met moderate or high disease activity criteria (Barnabe et al., 2012). In another study of recent onset cases, 11% of the patients experienced sustained remission after five years, while twice as many, almost 25%, experienced point remission at three, four, and five years (Jayakumar et al., 2012). More recently, the Canadian Early Arthritis Cohort (N=1,840) reported that remission was attained by 34%, clinical practice remission by 41%, and Simplified Disease Activity Index (SDAI) remission by 39%, where 55% to 60% of these persons achieved sustained remission by the same three criteria. Early remission increased the likelihood of sustained remission (Kuriya et al., 2014). About 30% to 40% of rheumatoid arthritis patients do not experience low disease activity or remission with biologics (Jacobs, 2012).

It is generally agreed that the biologics have been introduced into routine clinical practice. This paradigm change has dramatically changed rheumatoid arthritis care and benefited patients. However, the biologic revolution, like many revolutions, may have overestimated the benefits, both clinical and economic, at the outset. Clinical experience and research are gradually tempering the initial enthusiasm for biologics and driving a new level of change that rationalizes costs and benefits, thereby discovering the true value of biologics (Scott et al., 2014). Wailoo, Hernandez, Scott, Ibrahim, and Scott (2014) reported that triple therapy (two DMARDs and short-term glucocorticoids) is both clinically effective and cost-effective, thereby providing support for three combination trials (TICORA, COBRA, and BeST). More recently, a concise review of

non-biological and biologic DMARDs traced the revolution in rheumatoid arthritis drug therapy and concluded that "combination therapy with conventional DMARDS is not inferior to biologics in the management of RA and is a feasible cost-effective option," that is, triple therapy can be of similar efficacy as anti-TNF agents and metrotrexate (Parida, Misra, Wakhla, & Agarwal, 2015, p. 278). Unfortunately, inadequate adherence to anti-TNF drug regimens by 27% of patients one or more times within six months is associated with poorer patient outcomes (Bluett et al., 2014). Country level results are inconclusive regarding the use of biologics among early rheumatoid arthritis patients (six months or less) who were DMARD naive (CADTH, 2013).

Importance of early intervention. Regardless of drug regimen, early diagnosis and early intervention are paramount if the disease process is to be halted and functional capacity maintained to protect work life. "If you wait six months and you have active rheumatoid arthritis, you will have irreversible damage," stated an eminent rheumatologist, who also noted that family physician delay in recognition of symptoms and related delays in treatment or referrals remain key challenges in Canada (Barton, 2012, p. 1). The *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis* (Singh et al., 2016) provided recommendations for treating early rheumatoid arthritis (symptoms of less than six months) and established rheumatoid arthritis (symptoms of six months or more), thereby mitigating outcomes such as presenteeism and related work outcomes.

Early intervention is impaired when initial help-seeking is delayed. As a result, clinical outcomes are suboptimized, health care costs increased, and work productivity reduced (Simons, Mallen, Kumar, Stack, & Raza, 2015). Person non-adherence, such as not taking costly medication, drug holidays (stopping drugs for a period of time), and catch-up dosing (increases to catch up on missed doses) can also compromise outcomes (Hope et al., 2016). Finally, unrestricted use of bDMARDs is unaffordable. A European study by the London School of Economics reported

country-level disparities in both clinical guidelines and access to biologics. Variation in the number of treatment rounds (none, three, six), drug intolerance (MTX 20 mg), severity of the RA (DAS≥5.1, 4.2 or 3.2), wait time for referral to a specialist (immediate, a few weeks, or longer), availability of rheumatologists (none, limited, adequate), and other factors determine whether access to biologics coincides with the window of opportunity. Access to biologics varies across countries, ranging from 5% to 30%. Focusing on direct costs of DMARDs at an individual level, rather than considering the implications at a system-wide level, means that system productivity is compromised (Hockley & Costa-Font, 2012). Only a system- wide analysis can capture the full impact of DMARDs on a health care system.

CHAPTER 3: METHODS

The PICO Analytical Framework

The PICO analytical framework for the systematic review was used to derive the research question. The elements of the PICO analytical framework are displayed in Figure 1. Participants (adults living with diagnosed rheumatoid arthritis) enrolled in Interventions (using disease-modifying antirheumatic drugs or DMARDs) that have Comparators (control, placebo, head-to-head, or other) were used to assess presenteeism and related Outcomes (in the intermediate term of three to 12 months, or a longer term of up to two years). The PICO question read: *"In persons living with rheumatoid arthritis, can sickness presenteeism be reduced more by drug interventions using biological disease-modifying antirheumatic drugs than by comparator drugs?"* This question was further divided into three questions:

1) *What DMARD drug interventions have been used to reduce sickness presenteeism in working age persons living with rheumatoid arthritis?*

2)What work productivity tools have been used to measure the impact of the DMARD drug interventions on sickness presenteeism?

3)What is the impact of the drug interventions on sickness presenteeism? Have the DMARD drug interventions reduced sickness presenteeism and/or increased work productivity?

Study selection criteria. The PICO question and analytical framework guided study selection (AHRQ, 2012; Samson & Schoelles, 2012). Primary studies were selected according to six basic eligibility criteria: 1) participants were working age adults with a diagnosis of rheumatoid arthritis based on an internationally recognized standard (Aletaha et al. 2010; Arnett et al., 1988); 2) interventions were disease modifying antirheumatic drugs administered alone or in combination for a minimum time of three months (the usual time used to decide if a drug is to be continued or switched); 3) comparators were another dosage of the same drug, the methrotrexate cornerstone drug, placebo, best available care, usual care, gold standard, head-to- head, or other comparator; 4) outcomes could be any presenteeism outcome; best practice favoured a broad assessment of outcomes that included workplace, household, personal roles, recreation, and leisure; 5) timing was open to any year, although it was indirectly restricted in time by the fact that DMARDs have been available only since the 1990s; and 6) studies were primary studies with randomized controlled study designs; observational study designs were also accepted, since observational designs are said to be complementary (Faraoni & Schaefer, 2017; Higgins & Green, 2011).

Search methods and results. The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2011) was the main reference that informed the conduct of the systematic review. Additionally, the Center for Evidence-Based Management or CEBMa (http://www.cebma.org/) was the main source of business-specific information for the systematic review. I searched for full-text sources, with no restriction on publication date, type, language, or country. The two search terms were “presenteeism” and “rheumatoid arthritis.” Search sources

included the Cochrane Library, bibliographic databases (23 relevant databases available through the UPEI Library), clinical trial registries, health technology assessments, comparative effectiveness studies, bibliographies, conference abstracts, and lead author contacts. PubMed Experts was hand-searched, ResearchGate was used to network and monitor, and AMEDEO Rheumatoid Arthritis provided weekly updates of medical studies.

As depicted in the PRISMA flow chart (Figure 2), 1,907 publications were identified in the main search. Thirty-four (1.8%) underwent detailed assessment using the eligibility criteria and a corresponding template to record the results of the detailed assessment. Seven articles met the inclusion criteria. Periodic updating of the search between 2012 and 2017 identified eight additional publications, resulting in 15 included publications. The included articles appeared in several bibliographic databases, but Google Scholar captured practically all the articles in one bibliographic database.

Data extraction, management, analysis, and reporting. Data were extracted from the selected studies and entered into a table of findings. Numerical outcomes were converted to narrative outcomes to ensure uniform interpretation. I used this information to answer the main PICO question and the three sub-questions that underlie this systematic review.

CHAPTER 4: FINDINGS

Chapter 4 summarizes the findings of the systematic review. First, the results of the bibliographic search are summarized. Second, the included articles are used to answer the three questions outlined in the previous section.

Overview of Included Studies

Baseline demographics of participants. Seven demographics (age, sex, race, education, annual family income, profession, and household occupants) were reported in the reviewed studies,

with only two demographics (age and sex) reported in all 15 papers. The mean age across all studies was 51 (range: 43.07-55.4) and samples were predominantly female (range: 53.3%-94.4% female). The majority of participants across all studies self-identified as white, Caucasian, or West European (range: 68.7%-100%); samples were clearly biased toward Caucasians. In recent years, investigators have called for ethnic representation more representative of the prevalence of rheumatoid arthritis in the population (Ovseiko et al., 2016; Runnels, Tudiver, Doull, & Boscoe, 2014). Even though the included drug trials were almost all registered, multi-center, and international, their ethnic diversity did not reflect the general population of the country of study. The Food and Drug Administration (2005) agency has provided guidance for industry with regard to the collection of race and ethnicity data. Increased care is required to report race or ethnicity and other relevant demographic factors. Such factors influence the initiation of biologics (Innala et al., 2014; Jawaheer et al., 2012; Yelin et al., 2014), highlighting the importance of representative samples.

Profile of reviewed studies. Among the 15 included publications were nine randomized controlled trials (RCT), five observational studies (OS), and one mixed study (RCT+OS), published between 2008 and 2016 (Table 1). The data reflected 16 drug trials, five DMARDs, nine published presenteeism tools, and 42 health-related baseline measures (27 health status and 15 disease state). The samples ranged in size from 59 (exploratory study) to 1,601 (Phase III study), with 7,742 subjects reported in all 15 studies (combined). Systematic reviews usually include Phase II trials (effectiveness studies with 25 to 300 subjects) and Phase III trials (safety and effectiveness studies with different populations, dosages, and drug combinations applied to samples of several hundreds to 3,000 subjects). The studies included in this systematic review contain typical sample sizes for the type of trial reported. For example, RAPID 1 and RAPID 2 were 52- and 26-week Phase III trials with 982 and 629 subjects (1,601 in total), respectively (Kavanaugh et al., 2009). Regulatory agencies and methodological experts inform the sample size.

When I summarized the data contained in the 15 articles, I observed that they describe a wide range of subject demographics, medications, indicators of health status and rheumatoid disease activity, and work outcomes. This wide range of variables highlights the need to scope data and pre-select key variables upfront, rather than use the non-standard data provided in the studies. However, with a new drug with limited study and only 15 included publications, and with the diverse presenteeism tools used in the studies, this is presently impossible.

PICO Question 1

What DMARD drug interventions have been used to reduce sickness presenteeism in working age persons living with rheumatoid arthritis?

Among the five drugs tested in the drug trials (Table 1) were the conventional DMARD methrotrexate (MTX) and four bDMARDS, namely, abatacept (ABA), adalimumab (ADA), certolizumab pegol (CZP), and etanercept (ETN). In these studies, MTX doubles as a background drug and a comparator drug. MTX is considered the cornerstone for the management of rheumatoid arthritis even after the introduction of the biologics within the past two decades (Coury & Weinblatt, 2010). MTX is a longstanding anchor drug, usually used as double- or triple-combination therapy, which is known to be more effective than monotherapy. Approximately one-third of the 16 approved DMARDs in the pharmaceutical armamentarium for the treatment of rheumatoid arthritis are represented in this systematic review. With the regular introduction and approval of new types of antirheumatic drugs, these drugs will look less representative of all antirheumatic drugs as time passes.

The four bDMARDs in the included studies are prescribed for individuals living with rheumatoid arthritis who have tried conventional drugs (usually several cDMARDs, including MTX), and have either not responded favourably, or have experienced side-effects from the drugs. These four bDMARDs target individual molecules and work faster than conventional DMARDs (days rather than months). Three of the four biologics are also anti-TNF drugs because they target

TNF or tumour necrosis factor (excess amounts of TNF increases inflammation if excessive amounts occur in the blood or joints, but the anti-TNF reverses this effect). As stated, all four biologics may be prescribed with MTX to increased effectiveness. Recent studies are asking whether less costly cDMARDs might be effective when used in triple therapy or with biologics (O'Dell et al., 2013), and whether principles need to be applied to achieve quality care at a lower cost (Westhovens & Annemans, 2016). Experts agree that early intervention is necessary to prevent structural damage to the body and thereby prevent dysfunction and disability (Singh et al., 2016). How to achieve this goal remains a question. With less than three decades of clinical experience to inform their use and with new types of drugs entering the market, it will be necessary to study bDMARDs in varying populations, dosages, combinations, background drugs, drug sequences, and research designs to determine DMARD potential, optimal administration, and role in drug pharmacopeias (O'Dell et al., 2013; Ruderman, Mandelin, & Perlman, 2016; Westhovens & Annemans, 2016).

Current clinical practice guidelines promote *early* diagnosis, *early* treatment, and *treat-to-target* management to achieve early results (within 8 to 12 weeks, and sometimes less) (Singh et al., 2016). Early results reduce or avert inflammation and structural damage to the joints and other parts of the body, thereby preserving body function. The improved body health minimizes work loss in the form of sickness presenteeism (and other forms such as absenteeism, disability, and sick days) (Overman et al., 2014; ter Wee, Lems, Usan, Gulpen, & Boonen, 2013).

DMARDs improve health, even inducing remission, in approximately 60%-70% of cases, yet fail to improve outcomes in approximately 30%-40% of cases (O'Dell et al., 2013). It appears that many different treatment options exist; however, their relative effectiveness will not be known until these new drugs undergo head-to-head drug trials coupled with long-term patient experience. For example, triple therapy (such as MTX and two bDMARDs) can achieve results, but it is not known

how long results can be sustained or if some other combination of cDMARDs can achieve the same results (O'Dell et al., 2013).

Did the drug interventions improve health status, thereby suggesting that work status might also be improved? As shown in Table 2, all 15 studies provided health status and disease activity information at baseline. Endpoint health status was not reported with the same rigour. At baseline, functional disability and disease activity scores were reported for all drug trials (except for studies #10 and #12). Functional disability was consistently reported using the Health Assessment Questionnaire-Disability Index (HAQ-DI). This questionnaire assesses eight categories of daily activity (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities). At baseline, 14 of the 15 trials reported HAQ-DI scores which were usually in the 1.5 to 1.7 range (minimum=0.5, maximum=1.8). With lower scores on the 0- 3 scale denoting better scores, the scores indicate that physical function was affected, but not seriously. Disease Activity Scores (28 joints) or DAS28 ranged from 1.69 to 6.6. Usually, scores were in the 4 to 6 range at baseline, where scores greater than 5.1 indicate very active disease, and scores greater than 3.2 but lower than 5.1 indicate moderate disease activity. Scores lower than or equal to 3.2 indicate inactive disease, with scores under 2.6 indicating remission. As expected, active disease was the norm at baseline.

Three symptoms of rheumatoid arthritis that greatly impact workability were widely reported in the drug trials – pain, fatigue, and joint assessments. Pain was reported by eight of the 15 studies using SF-36 BP (Short Form 36-Body Pain,) VAS Pain, or Brief Pain Inventory; scores were in the 60 to 70 range (minimum=35, maximum=70), where 0 is no pain and 100 is unimaginable pain. Pain scores thus indicated suffering. Fatigue scores were reported by seven of the 15 studies using a range of tools (FACIT, FACIT-Fatigue, Fatigue Severity Score, VAS- Fatigue, or FAS 0-10). Scores were widely dispersed, with one group in the 30 to 40 range and another group in the 60 to

70 range. Joint assessment was reported for 10 of the 15 studies. Like pain, fatigue and joint dysfunction are common complaints for rheumatoid arthritis and are drivers of presenteesim (Lenssinck et al., 2012). The SF-36 was used to report physical and mental health. Scores were in the 30 to 60 range and usually below population scores (the lower the score, the greater the disability, measured on a 0-100 scale).

Without seeing health endpoints, some observations can be made on the basis of other information provided. First, drug trials are usually registered as a quality control measure (e.g., scrutiny by peers). All but two were registered in this systematic review. All included articles describing drug trials were published in peer-review journals (with impact factors ranging from 2.2 to 12.3). Lastly, all studies were published between 2008 and 2016, a time when positive results dominate the scientific literature and negative results are less frequently published (Matosin, Frank, Engel, Lum, & Newell, 2014; O'Hara, 2011), although the situation is starting to change (Ivanov et al., 2017). Overall, however, the reviewed literature does suggest that these drugs are effective and should exert a positive impact on presenteeism (see PICO Question 3).

PICO Question 2

What work productivity tools have been used to measure the impact of the DMARD drug interventions on sickness presenteeism?

The included articles mentioned 13 published tools as measures of work productivity in the form of presenteeism (Tables 1 and 3). These include the Activity Participation Questionnaire (APaQ), Domestic Activity Questionnaire (DAQ), Health and Labour Questionnaire (HLQ-DA), Questionnaire of Experience and Evaluation of Work (QEEW in English and usually listed by Dutch abbreviation VBBA), Valuation of Lost Productivity (VOLP), Visual Analogue Scale (VAS), Work Ability Index (WAI), Work Instability Scale (WIS), Work Limitations Questionnaire (WLQ), Work Productivity and Activity Impairment (WPAI), and Work Productivity Survey (WPS). Among the 15 included papers measuring presenteeism, 13 papers

measured workplace productivity, seven papers measured household productivity, two papers measured family/social/leisure activities, and one paper measured usual activities (the usual activities that a person engages in during the day – i.e., workplace, household, family/social/leisure).

The original plan for this review was to study only paid work loss among working age adults living with rheumatoid arthritis. However, examination of the included studies indicated that it was necessary to broaden the scope. This is because, when presenteeism outcomes were reviewed, the authors usually noted the relationship between sickness presenteeism and absenteeism (Bierla et al, 2013). Both were recognized to be forms of absence from work and therefore lost work productivity. Some authors interpreted presenteeism as not only work loss but as a sign that absenteeism was about to occur. Conversely, other authors interpreted absenteeism as a sign that presenteeism was occurring in the workplace because workers may reduce the number of lost workdays by working as long as possible and returning to work as soon as possible despite illness (Arnold, 2015; Bierla et al., 2013; Cooper & Dewe, 2008).

To better understand the measures of work productivity used in the 15 included papers, the work measures were categorized into three groups – presenteeism, absenteeism, and other measures (Table 3). These categories were purposeful. Presenteeism is the subject of this systematic review. Absenteeism is a complement to presenteeism (Bierla et al., 2013), thereby providing a better picture of the total work loss attributable to rheumatoid arthritis. Lastly, the other measures included a wide variety of work-related measures, but usually describing work status, total work loss (in time and economic costs), and miscellaneous measures. All 15 articles accounted for paid or employed work outcomes, and eight studies reported other aspects of life productivity such as unpaid work, home/household, family/social/leisure, or usual activities (meaning all daily activities). As of 2017, measuring all types of daily activity or personalproductivity is the recommended approach because

of the recognition that interdependence exists between the spheres of life activity, just as is obvious in work-life balance discussions (Gignac et al., 2014). In the included papers, economic outcomes were analyzed by the human capital method (never by the friction method).

Measurement of presenteeism. When I examined presenteeism, absenteeism, and other columns in Table 3, it became obvious that much variation exists in the concepts used to assess presenteeism or reduced work productivity due to rheumatoid arthritis. Presenteeism was measured by estimation, degree to which work was reduced (on a 0-100 scale), open-ended question asking why work was reduced, statement asking respondents to compare sickness productivity to usual work output, numerical comparison of sickness productivity to lifetime best productivity, number of work difficulties encountered, type of work difficulties encountered, number of days that work productivity was reduced by 50% or more, level of interference with work (0-10 scale), and economic cost of presenteeism losses. Absenteeism was measured by amount of missed, reduced, or stopped work time, task modification, and economic cost of absenteeism.

Much less variation existed in the concepts and units used to measure absenteeism than presenteeism. The measures reported reflected the four constructs identified by Brown et al. (2014) as sources of presenteeism or impaired productivity at work; namely: 1) psychological well-being, 2) social or role functioning, 3) physical tolerance, and 4) work performance. The measures also reflect the work of Matte et al. (2007) who conceived presenteeism as being 1) perceived impairment, 2) comparative productivity, and 3) unproductive time while at work. It is worth noting that the environment was not reflected in the measures, although work productivity experts such as Noben et al. (2014) stress the importance of context in work productivity (i.e., by modifying the environment, one can increase or decrease productivity). In addition to the factors mentioned, both empirical and anecdotal evidence indicates that a wide range of other factors act and interact in impacting work performance. Even instruments used to measure presenteeism have been

empirically demonstrated to be a source of variation (HLQ, HPQ, WLQ, and WPAI). As a result, "further research on instrument design and implications for a standardized approach to estimate lost time due to presenteeism is needed" (Zhang et al., 2010, p. 1805).

While presenteeism and the related factor of absenteeism were the variables of interest in this systematic review, I also examined the "other" concepts to understand what related concepts researchers thought worthy of informing presenteeism and absenteeism. The "other" category tended to measure employment status, changes in employment status, the economic aspect of lost work productivity (which can represent presenteeism, absenteeism, or their total), and unpaid work (whether household or family/social/leisure). When compared to the previous two categories, especially the presenteeism category, these "other" measures further reinforce the overlap and inconsistency that characterizes the measurement of presenteeism.

Measurement issues. In line with the findings of this systematic review, many past publications have highlighted the measurement issues associated with presenteeism (e.g., Mattke et al., 2007; Verstappen, Fautrel, Dadoun, Symmons, & Boonen, 2012; Zhang, Gignac, Beaton, Tang, & Anis, 2010). First, the questions/items used to measure presenteeism fall into two groups because tool developers believe that presenteeism is both 1) measureable (in time, money, rate of interference, etc.), and 2) descriptive (focusing on reasons why presenteeism is occurring). Inspection of Table 3 by tool name indicates that a wide range of measures are used to describe presenteeism (with less variation in the measures for absenteeism). The tools usually collect information about the amount and the nature of presenteeism; however, some tools ask questions to understand the source of presenteeism. For example, the WLQ (long version) measures task level and job level using categories of questions (time management, physical demands, mental demands, mental interpersonal demands, and work output demands), measured on a 5-point scale. The summary score indicates the difference between employees with health- related work limitations

and those without. The WLQ is a well-established tool which does not measure time loss (in units of time) or effort loss (in percentage effectiveness), as many other tools do (Lerner et al., 2001; Tang, Beaton, Boonen, & Bombardier, 2011). Only two tools, the WAI and the APaQ, use a single question/item to measure presenteeism without inquiring about the underlying reasons (Li, Wells, Westhovens, & Tugwell, 2009; Tuomi, Ilmarinen, Jahkola, Katajarinne, & Tulkki, 1998). In short, presenteeism has a quantitative and a qualitative nature and studies almost always capture both. The conceptual issues impeding the measurement of presenteeism are hence also both quantitative and qualitative in nature.

Second, the measurement of absenteeism, the complementary measure to presenteeism, appears much more straightforward. Countries such as the Netherlands routinely use the VBBA or WAI to monitor workplace performance (European Network for Workplace Health Promotion, 2006). When management uses VBBA or WAI scores as an indication of workplace performance or work productivity, and to inform decisions on how to improve performance, they are essentially using feedback from presenteeism-type questions to help improve work productivity and thereby manage presenteeism.

Third, of note are the recent single-item tools used to encompass the notion of presenteeism under all circumstances. The APaQ question regarding presenteeism is: "*During the past 30 days, how often were you able to perform your usual activities completely, in spite of your rheumatoid arthritis*," where "usual activities" includes paid work, unpaid work, household chores, personal care, and other usual daily activities (Li et al., 2011, p. 363). The WAI question is: "*Assume that your work ability at its best has a value of 10 points. How many points would you give your current work ability"* (Tuomi et al., 1998, p. 35). In short, single-item tools measure the amount of presenteeism without explaining the reason(s) for the amount (as occurs in the other, longer tools).

Fourth, the concepts in the questions identified in this systematic review match the list of concepts developed by Escorpizo et al. in 2007 (p. 1374). There are also other, newer measures in this review that reflect new tools developed since 2007. The continued search, since 1992, for an adequate tool to measure presenteeism, including the economic impact of presenteeism, suggests that existing measures may not be capturing presenteeism in a way that is relevant for researchers, clinicians, economists, and/or managers. Meanwhile, each new tool usually increases the level of non-standardization in the data, making it more difficult to complete systematic reviews which require standardized measures for cross-study comparisons. The tools measuring presenteeism require further conceptualization, definition, and standardization, in order to be comparable across studies and therefore useful to researchers and managers. This observation is well-established in the literature (e.g., Beaton et al., 2009; Braakman-Jansen, Taal, Kuper, & van de Laar, 2012; & Noben et al., 2014). Recently, clinical researchers recommended that work functioning instruments include a full psychometric assessment in the development phase, and that these findings be reported together with the tool questions to ensure the reliability and validity of the instrument (Alheresh, Vaughan, LaValley, Coster, & Keysor, 2016).

Table 4 is a compilation of factors that require consideration when measuring presenteeism, based on the tools identified in this systematic review (and previously identified by presenteeism researchers cited in this report). Presenteeism requires attention to context, as drug intervention benefits can be undermined by any negative influences in the workplace, such as the environment or work relationships. Randomized controlled trials are helpful in this regard, as they are better able to isolate the impact of the drug on the outcome. Units of measurement are an added consideration. Seven units of measurement (days, hours, percent, monetary unit, rate, scale or score, and odds ratio) were noted in the included papers. Because existing tools are problematic for researchers, two recent investigators used their own measures of presenteeism, collected their

own data, and used large population samples to avoid past measurement issues and advance our understanding of presenteeism (Arnold, 2015; Quazi, 2013).

PICO Question 3

What is the impact of the drug interventions on sickness presenteeism? Have the DMARD drug interventions reduced sickness presenteeism and/or increased work productivity?

The results of the drug interventions in the reviewed studies were overwhelmingly positive, with almost all data comparisons indicating improved work productivity in working age adults living with rheumatoid arthritis. Statistically significant differences were attained in practically all instances. Although health outcomes were not reported at the endpoint, health had been incorporated into the analysis through the minimal clinically important difference (MCID), defined as the smallest change in an outcome that a patient would consider important (Table 5). The MCIDs create binary outcomes (e.g., responder-nonresponder, continuer-noncontinuer, completer-noncompleter, remitter-non-remitter) to divide the sample into participants with desirable outcomes and without desirable outcomes. Proponents of dichotomization emphasize the value of basing outcome reporting on health criteria and of introducing two types of significance, clinical and statistical (Page, 2014). The Pharmaceutical Research and Manufacturers of America issued a position paper to explain the rationale underlying dichotomization (Uryniak et al., 2012).

Much has been written about how presenteeism is a more pervasive problem than absenteeism (Bierla et al., 2013; Cooper & Dewe, 2008), but quantitative data are rarely reported. To determine the presenteeism-absenteeism relationship with regard to rheumatoid arthritis, I mapped presenteeism-absenteeism pairs from the included studies. Next, I inspected pairs for the use of time (hours, days, weeks, months) and reduced the 206 pairs to 63 pairs that had adequate data to calculate a presenteeism-to-absenteeism ratio. The ratio was 1.7 at baseline and 3.11 after treatment (Table 6), meaning that presenteeism and absenteeism were at more similar levels before treatment (as expected) than after treatment (when the drug had improved health and thereby reduced

presenteeism and improved work productivity). The baseline ratio is similar to the range of 1.7 to 2.0 proposed by Sainsbury Center for Mental Health. The post-drug intervention ratio of 3.11 indicates that the drug improved presenteeism to a greater extent than absenteeism. Comparison of parallel sets of presenteeism and absenteeism findings using ratios circumvents many measurement issues. The ratios in this report are simply ratios depicting an overall trend until this issue is better understood. Possibly, the ratio is part of the answer in developing a method to measure presenteeism. Such ratios are not usually reported in published articles, but are shown in Table 6 to encourage further analysis and discussion.

When inspecting the actual amount of presenteeism and absenteeism (in units of hours or days) in the reviewed articles, two observations can be made. First, the actual amount of presenteeism exceeds absenteeism as measured in units of time. Second, the amount of improvement in presenteeism and absenteeism (also measured in units of time) and attributed to DMARDs tends to be higher for presenteeism than absenteeism, but not consistently higher. It should be noted that only six of the 15 included studies reported units of time such as days and hours. Other authors used non-time measures of presenteeism such as percentages or MCID, which were not readily compared. It was a concrete measure (i.e., time) that made the calculation of a ratio possible in this study. The ratio of presenteesim-to-absenteeism is useful to indicate the actual hours of each and the relative amount of each *before* an intervention, *afte*r an intervention, and with regard to the *amount of change* resulting from the intervention (e.g., drug, workplace wellness, social change, or other type of intervention). Clearly, ratios based on units of time measuring presenteeism and absenteeism do not indicate associated costs, such as replacement employees, recruitment of new employees, overtime payments, etc., but possible ratios based on real time units are a starting point. Experienced human resource specialists are familiar with the associated non-labour costs.

When conducting this review, I found that the literature does not really address the topic of

analysis, including the range of dichotomous analyses (based on MCIDs) now used to incorporate health considerations into work productivity studies. This represents another major challenge in presenteeism measurement. The authors of the pharmaceutical industry position paper had to be contacted to understand responder analysis and apply the basic concept to other papers using dichotomous analysis of responders versus non-responders. Only statistical publications addressed dichotomy, and only the OMERACT Handbook made brief mention of MCID and PASS (Patient Acceptable Symptom State) from a methodological perspective (Boers et al., 2017). In my review of the literature, I could not find any peer-reviewed discussions linking presenteeism measurement, dichotomous analysis (with health variables like HAQ, FAS, VAS, SF-36, etc.; see Table 5), and the subsequent reporting of presenteeism data for use in human resources, economic analysis, or rheumatology research. In sum, more methodological work is required to move presenteeism from theory to application (Kigozi et al., 2017).

CHAPTER 5: DISCUSSION

The main PICO question – *"In persons living with rheumatoid arthritis, can sickness presenteeism be reduced more by drug interventions using biological disease-modifying antirheumatic drugs than by comparator drugs?"* – was answered in the affirmative. Control-experimental designs, almost without exception, demonstrated better outcomes for the biologic than the comparator DMARDs. Newer analyses using binary designs tied to health outcomes indicate that DMARDs improve outcomes for responders but do not produce desired outcomes for non-responders. As advances are made in personalized medicine, and the pathogenesis of rheumatoid is better understood, it may be possible to improve care for persons who are now non-responders.

With biologics improving work productivity for persons living with rheumatoid arthritis, it

is important to assess the extent of improvement. Examination of the included articles indicates the level of improvement in presenteeism in the workplace, household, or social/leisure spheres of life. On an individual variable basis, it is possible to determine whether the biologics are associated with better or worse outcomes for presenteeism and absenteeism, and assess the level of improvement for individual measures, but not on a trial basis or group basis (i.e., summary basis). A more detailed comparison is challenging (even impossible) due to the wide range of presenteeism measures, the diverse units of measurement, and the varying time recall and reporting periods (e.g., one day, one week, or one month), unless assumptions are made. Therefore, the conceptualization and quantification of presenteeism and absenteeism require urgent attention, which will take time and advanced expertise (Alheresh et al., 2016; Koopmans et al., 2011, Lenssinck et al., 2012; Verstappen et al., 2012). Meanwhile, to better understand the issues involved in measuring the two key variables in this study, presenteeism and absenteeism, I calculated a presenteeism-to-absenteeism ratio, using parallel sets of presenteeism and absenteeism measures based on actual time. This ratio was independent of units of measurement. I propose that such a ratio could be reported as standard practice (when appropriate). This could be done at baseline or at endpoint, or for the difference between the two, as depicted in Table 6.

Examination of the included articles and their measurement tools suggests that it is necessary to clearly define the purpose of the study and to understand the tools in advance ofdoing a systematic review. I spent much time studying the tools that purportedly measure presenteeism before I was able to determine that many of the measures were noise, given the purpose of this project. Instead, it is more important to focus on the hard measure of presenteeism and absenteeism (time in hours or days) rather than soft measures (time as percentages, or as described by ordinal / interval scales with descriptive responses). In this regard, the articles that reported baseline, endpoint, and change between baseline and endpoint allowed me to compare baseline to endpoint

for presenteeism and absenteeism using actual amounts of time. Overall, however, measurement challenges in this area persist. Some of those challenges, including those posed by different definitions of presenteeism, different ways of expressing results, different recall intervals, and different units of measurement, have recently been summarized and updated by Suter et al. (2016).

Earlier work on the significance of presenteeism in relation to losses in work productivity (Goetzel et al., 2004) highlighted the need for research in this area, but researchers only started studying the impact of biologics on presenteeism many years later, due to a more pressing need to understand other aspects of biologics, such as the relative impact of specific biologics, the importance of early intervention, the definition of remission, the economic aspects of biologics, and patient preference for symptom control medications over aggressive remission biologics (Verstappen et al., 2012). As a result, relatively few studies have measured the impact of biologics on presenteeism or, more broadly, employment and work productivity. The studies that do report the impact of biologics must be read with care, to avoid misinterpretation. The paradigm shift in the management of rheumatoid arthritis with biologics (from "low and slow" to "strong and aggressive"), the wide range of rheumatoid arthritis disease activity that may appear in some trials, and the date of publication are some cues to help interpret this paper and the relevant literature (Dale, 2015; Verstappen et al., 2012).

All but one of the included studies of presenteeism were published in rheumatology journals. The longstanding issues with presenteeism measurement suggest that organizational management and business research methods expertise may be of help (Marion & Balfe, 2011). Interdisciplinary collaboration can advance the study of presenteeism and work productivity and help quantify presenteeism. Moreover, the trend toward patient involvement is critical. Work is of high importance to patients dependent on income and retirement savings, so their personal experience is vital in informing rheumatoid arthritis and presenteeism researches about relevant priorities. The

importance of this point is illustrated by OMERACT's commitment to patient participation in working groups, the inclusion of work as a core patient indicator, and the search for tools that accurately measure presenteeism. Finally, presenteeism is not yet recognized as an economic phenomenon, is not widely accepted to have an economic value exceeding that of absenteeism, and is not generally controlled or managed, except through workplace wellness programs (Standard Insurance Company, 2012). Advances in measuring presenteeism for related diseases may provide insights into the measurement of presenteeism for rheumatoid arthritis (Lensberg, Drummond, Danchenko, Despiegel, & François, 2013).

Conclusion

With presenteeism representing greater economic value than absenteeism, and with global economic activity becoming increasingly competitive, it is important to consider untapped sources of productivity gain. Presenteeism and absenteeism are two possible ways of increasing work productivity and an organization's competitive position, be it for rheumatoid arthritis or another workplace malady (especially workplace stress and mental health). Attempts should be made by human resource professionals to capture and better manage this important source of work productivity.

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Table 1

Profile of publications describing interventions to improve work productivity

Design[1]	#	Lead Author	Year	Drug Trial	Sample	Data Collection Tools [2]	Intervention	Comparator
RCT	1	Anis	2009	COMET	542	WLQ, WPAI, PQ	ETN+MTX	MTX only
	2	Emery	2016	OPTIMA & PROWD	1,180	RA-WIS, WPAI	ADA+MTX	PBO+MTX
	3	Fleischmann[3]	2016	AMPLE	646	WPAI-RA	ABA+MTX	ADA+MTX
	4	Hazes	2010	RAPID 1&2	1,601[4]	WPS-RA	CZP+MTX	PBO+MTX
	5	Kavanaugh	2009	RAPID 1&2	1,601	WPS-RA	CZP+MTX	PBO+MTX
	6	Li	2011	AIM & ATTAI	1,043	APaQ	ABA+PBO	PBO
	7	Smolen	2014	CERTAIN	194	WPAI-RA	CZP	PBO
	8	Smolen	2016	PRESERVE	763	WPAI-RA	ETN+MTX	N/A[3]
	9	Van Vollenhoven	2010	PREMIER	664	PQ	MTX+ABA; MTX	PBO+MTX
OS	10	Hone	2013	OPERA	204	WPAI-RA, DAQ, cost losses	ETN50	None
	11	Hoving	2009	Jan van Breemen	59	VBBA, WAI, cost losses	ADA 40	None
	12	Hussain	2015	AWARDS	63	WPAI; HAQ-DI; FSS; VAS-F	ADA	None
	13	Zhang	2008	CanAct	467	HLQ-DA, cost losses	ADA40	None
	14	Zhang	2015	PRIZE	196	VOLP	ETN50+MTX	None
RCT/ OS	15	Zhang	2016	PRIZE	120	VOLP	ETN25+MTX	MTX&PBO
Total	14	9 unique leads		16 unique trials	7,742	13 unique tools (11 were published in the literature)	5 drugs	4 types

[1] RCT=randomized controlled trial; OS=observational study.

[2] PQ refers to patient questionnaires and is listed if mentioned in the published article.

[3] Fleischmann (2016) was a head-to-head study comparing two bDMARDs, ABA and ADA. Head-to-head studies are recommended to compare two good drug options. Although relatively rare, head-to-head studies of bDMARDs are gradually increasing in the literature.

[4] RAPID 1 & RAPID 2 samples (1,601) were counted once because Hazes and Kavanaugh trials used the same RAPID samples.

Table 2

Health status and disease activity outcomes presented in study baseline data

Category	**Measure**	**Scale / Unit**	**Studies[1]**		**Min to Max[2, 3]**
			Number of Studies	Study # (See Notes)	
Health Status					
General Health Status	Patient general health Visual Analogue Scale (VAS)	0-100	1	#8	VAS=40.9-47.8
General Health	Patient General Health Score	0-100 mm.	2	#14 & 15	#14= 52.5 #15= 7.3-13.1
Quality of Life	EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)	0-1	1	#1	0.36-0.44
	EQ-5D index	0-1	2	#14 & 15	#14= 0.49 #15=0.86-0.90
	EQ-5D-VAS	0-100	3	#1, 14, & 15	#1 & 14= 42.9-65.0 #15=84.2-92.0
Lifestyle	Body mass index (BMI)	Mean (kg/m^3)	4	#7, 12, 14, & 15	BMI=25.1-28.9
	Overweight or obese	Percent	1	#12	37.3%
	Smoking status, non-smoker	Percent	2	#14 & 15	46.9-59.4%
	Smoking status, has stopped	Percent	2	#14 & 15	15.4-28.1%
	Smoking status, smoker	Percent	3	#8, 14, & 15	12.5%-28.1%
	Alcohol use	Percent	3	#8, 14, & 15	#8= 11.1-11.6%; #14 &15=43.6-50.0%
Co-morbidity	Number of diseases	Mean	2	#14 & 15	1.9-2.5
	Hypertension	Percent	1	#12	20%
	Osteoarthritis	Percent	1	#12	12.3%
	Diabetes	Percent	1	#12	10.8%
	Osteoporosis	Percent	1	#12	7.7%
Patient Global Assessment	Patient Global Assessment of Disease Activity	0-100 mm.	1	#6	63-69
	Patient Global Assessment	0-10 cm.	1	#8	4.6-5.5
	Patient Global Assessment score	Not stated (defined as 0-10 cm./0-100 mm.)	3	#13, 14, & 15	#13, #14=58.4-65.6; #15=4.8-10.4
Physician Global Assessment	Physician Global Assessment	0-10	1	#8	4.0-5.2
	Physician Global Assessment score	Scores suggest a 0-100 scale	3	#13, 14, & 15	#13, #14 = 56.4-64.4; #15 = 3.5-5.4
Functional Disability Level *[Only #10 did not report HAQ.]*	Health Assessment Questionnaire – Disability Index (HAQ-DI)	*0-3 (mean):*	14/15:		
		0 to 1 (mild difficulties to moderate disability)	2	#7 & 15	#7=0.5-1.2 #15=0.16-0.27
		1 to 2 (disability moderate to severe)	12	#1 to 6, 8, 9, & 11 to 14	1.1-1.8 (majority)
		2 to 3 (severe to very severe disability).	0	N/A	N/A
Fatigue	Functional Assessment of Chronic Illness Therapy (FACIT)	0-52	3	#8, 14, & 15	#8,14= 29.5-33.7 #15= 42.7-44.7
	Fatigue Assessment Score (FAS)	0-10	2	#4 & 7	4.3-6.5
	Visual Analogue Score – Fatigue (VAS-F)	0-100 mm.	2	#3 & 6	60-73
	Patient Acceptable Symptom State (PASS)	N/S	2	#14 & 15	#14= 48; #15=30-49
Rheumatoid Factor	Rheumatoid Factor (RF^+)	Percent	5	#2, 4, 7, 8, & 11	#2, 8 & 11=61.1%-91.9% #4 & 7=67.3-100%
Morning Stiffness	Morning stiffness duration	Minutes	1	#8	158-227
Short Form-36 Questions	SF-36 Mental Component Score (SF-36 MCS)	51.7 is norm for all ages (Hopman et al., 2000)	5	#1, 6, 7, 14, & 15	40.7-45.1 except for #15=52.2-54.1
	SF-36 Physical Component Score (SF-36 PCS)	50.5 is norm for all ages (Hopman et al., 2000)	6	#1, 4, 6, 7, 14, & 15	27.5-36.9 except for #15=48.7-51.7
	SF-36 Physical Function Domain (SF-36 PF)	0-100 using mean score; SF-36 PF is 85.8 for	1	#4	32.3-32.9

Category	Measure	Scale / Unit	Studies[1]		Min to Max[2, 3]
		population)			
	SF-36 Vitality Domain Score (SF-36 VT)	0-100 using mean score; SF-36 VT is 65.8 for population	1	#4	35.3-37.0
Pain	SF-36 Bodily Pain (SF-36 BP)	0-100 mm. using mean score; mean is 75.6 for population	1	#4	29.5-30.2
	Patient Pain Assessment Score (Pain-VAS)	0-100 (lower score is better score)	8	#1, 3, 4, 6, 7, 13, 14, & 15	60.9-71.0 except for #7=36.8-36.9 #15=5.78-10.9
	Brief Pain Inventory (BPI)	0-10 (0 is no pain and 10 is pain as bad as you can imagine). Low scores are better scores.	1	#8	3.7-4.7
Other disease-specific symptoms	Extra-articular Rheumatoid Arthritis manifestations	percent of participants (lower is better)	1	#12	9.2%
Disease Activity					
DAS *[Only #10 and #12 did not have a DAS of some type]*	Disease Activity Score (DAS28)	0-10	9	#1, 2, 6, 8, 9, 11, 13, 14, & 15	5.0-6.6 except for #15 which is 1.69-1.93
	Disease Activity Score Erythrocyte Sedimentation Rate (DAS28ESR)	Mean	4	#4, 5, 7, & 8	#4, 5, & 7=4.4-7.0; #8=20.2-22.9 mm/h
	Disease Activity Score28 C-Reactive Protein (DAS28CRP)	Mean	1	#3	5.5
	Patient Global Assessment of Disease Activity	0-100	1	#7	35.6-36.7
	Physician Global Assessment of Disease Activity	0-100	1	#7	26.9-27.2
ESR	ESR	mm/h	2	#7 & 13	25.7-37.0
	ESR	mean, min-max	1	#7	28.0-43.0
CRP	CRP	mean, mg/L or mg/dl	4	#7, 8, & 13	4.5-13.4 (mg/L); 16.6-40.3 (mg/dl)
	CRP	Median, mg/L	2	#7 & 8	4.5-13.4 (mg/L)
mTSS	Modified Total Sharp Score (mTSS)		1	#5	38.3-46.7
	Total Sharp Score (TSS)		1	#9	17.5-22.0
Joint Assessment	Joint erosion score		2	#5 & 9	10.8-23.1
	Erosive disease	Percent	1	#11	79.7%
	Joint space narrowing score		2	#5 & 9	6.7-25.1
	Swollen Joint Count (SJC, 0-68)	Mean	4	#1, 2, 7, & 9	2.7-22.8
	Swollen Joint Count (SJC, 0-28)	Mean	4	#8, 13, 14, & 15	= 3.5-12.6 except #15=0.3-0.8
	Tender Joint Count (TJC, 0-71)	Mean	4	#1, 2, 7, & 9	3.7-32.1
	Tender Joint Count (TJC, 0-28)	Mean	4	#8, 13, 14, & 15	=5.0-14.6 except #15=0.31-0.50
	Clinical Disease Activity Index (CDAI)	Mean	2	#7 & 8	13.0-21.2
	Simplified Disease Activity Index (SDAI)	Mean	2	#7 & 8	14.2-22.0

1 The article numbers correspond to the lead author as follows: #1=Anis (2009); #2=Emery (2016); #3=Fleischmann (2016); #4=Hazes (2010); #5=Kavanaugh (2009); #6=Li (2011); #7=Smolen (2014), #8=Smolen (2016); #9=vanVollenhoven (2010); #10=Hone (2013); #11=Hoving (2009); #12=Hussain (2015); #13=Zhang (2008), #14=Zhang (2015); and #15=Zhang (2016).

2 This summary table is based on scores reported in included articles, and considers means (single score) and ranges of scores (minimum-maximum) when compiling minimum-maximum scores which is an approach similar to Clarke, Higgins, & Adeli, (2016). Where outcomes were obviously different, the studies were reported separately (this occurred with regard to article #15 where bDMARD dosing occurred to induce remission, as reflected in responder scores). The purpose of the table is to portray the range of outcome reports, the relative frequency with which each outcome was reported, the most common measures, and the tendency to report outcomes at baseline rather than endpoint.

3 Paper #15 reflects outcomes immediately after dosing for remission (Phase I), and entering the dose reduction or fading phase (Phase II). Therefore, the scores reflect remission or low disease activity unlike other scores describing persons living with rheumatoid arthritis, which may reflect active, established, refractory, or other aspects of rheumatoid arthritis.

Table 3

Concepts in questions/items used to measure presenteeism, absenteeism, and related concepts

Tool	Presenteeism	Absenteeism	Other Related Concepts
APaQ	*how often able to perform usual activities	*days unable to do usual activities	None.
DAQ[1]	*degree affected housework (0=nil;100= full)	*days missed from domestic activities *hours missed from domestic activities *hours spent on domestic activities.	*satisfaction with domestic productivity
HLQ-DA[2]	*hindered by health problems at paid work *how often had seven work loss issues *extra hours required to catch up on work	*days unable to perform work (2 weeks) * date illness started	*have paid employment? *net income from paid work *your situation if no paid work (5 choices) *hours spent on 4 types of unpaid work *if others took over household (5 choices) *activities did/did not do due to health *general questions (6 demographics)
PQ1 Anis	*formula estimate (using HAQ, WPAI, & WPS)	*days missed from work due to health *hours cut down on work due to health *if stopped work due to health.	*employment status (10 choices) *work productivity loss (days x rate of pay)
PQ2[3] *Van Vollenhoven*	*degree paid work was affected by RA (0-100) *degree house work affected by RA (0-100)	*days of paid work missed due to RA *days unfit to work at home due to RA	**employment status (~7 options) **favorable/unfavorable job status
VAS[4]	Scale 0-100		
VBBA	*questions asked to explain presenteeism (not a question about presenteeism per se)	*contract hours a week before RA onset *changed work tasks due to RA *changed work hours due to RA *task modifications due to RA	*pace and amount of work (11 items) *independence in your work (11 items) *relationships with colleagues (9 items) *relationship with your superior (9 items)
VOLP	*at work during past seven days *do same work in less time if not ill *time taken when have health issues *time taken if no health issues *multiplier (teamwork, co-workers usually work with, your importance to teamwork) *substitutability (others able to do your work, hire temporary staff to do your work, can temporary workers do your work)	**days absent from work due to health	**employment status (9 options) *change in employment status (5 choices) *change due to RA or not *hours spent on four types of unpaid work *hours spent on unpaid work activities *help in household due to health status
WA5[4]	**current work ability vs. lifetime best (0-10)		
WIS	*Number of difficulties encountered (stress, pace, effort, etc.) with work instability score being degree of mismatch of self vs. job		
WLQ-25[6]	*Time Management (TM) – 5 items *Physical Demands (PD) – 6 items *Mental-Interpersonal (MI) – 9 items *Output Demands (OD) – 5 items N.B.: Does not tell hours of presenteeism		
WPAI-GH	*WPAI-RA reads health problems (not RA)		
WPAI-RA[7]	*how much RA affected work (0-10) *how much RA affected daily activities (0-10)	*hours missed from work due to RA *hours missed for other reason *hours worked in past seven days	*currently employed
WPS-RA[8]	*days RA reduced work productivity by half *how much arthritis interfered with work *days productivity at home reduced by half *how much arthritis interfered with home	*days did work because of arthritis *days did not do house work due to RA *days missed family/social due to arthritis *days hired outside help due to arthritis	*currently employed outside home *occupation *job function *work status if not paid work (6 choices)
	Costs are derived variables.		
Costs	*cost of lost workdays due to presenteeism (minimum and maximum) (Anis)	*cost of total absenteeism (min and max) *cost of missed workdays	*cost, reduced working time *cost, stopped workdays, maximum *cost, stopped workdays, minimum *cost, total work productivity loss, min *cost, total work productivity loss, max
	*presenteeism, annual economic gain/person (Hone)	*absenteeism, annual economic gain/person	*total, annual economic gain/person *net annual economic gain (savings)
	*indirect costs – presenteeism (Hoving)	*indirect costs – absenteeism	INDIRECT COSTS *production loss paid work *costs for paid work loss

Tool	Presenteeism	Absenteeism	Other Related Concepts
			*production loss unpaid work *reduction of leisure time DIRECT HEALTHCARE COSTS *treatment (TNF inhibitor) *medication (other) *specialist and outpatient care DIRECT NON-HEALTHCARE COSTS *(medical) aids *professional home care *other (transport) costs
	Module 4b: lost productivity (Zhang, 2008) *presenteeism in past 2 of 12 weeks *presenteeism by A20 responder status *presenteeism by HAQ MCID	Module 4a: lost productivity costs *absenteeism in past 2 of 12 weeks; *absenteeism by A20 responder status *absenteeism by HAQ MCID	Module 4c: lost productivity costs *unpaid work in past 2 of 12 weeks *unpaid work by A20 responder status *unpaid work by HAQ MCID *plus: *total lost productivity cost (past 2 weeks) *total costs (1+2+3) by A20 Responder *total costs by HAQ MCID
	Nil (Zhang, 2015)	Nil	In the past 3 months: *total costs of lost productivity; any costs? *total costs of lost productivity; total costs? *paid work productivity loss (hours) *any costs of lost productivity (%) *total costs of lost productivity

[1] Domestic Activity Questionnaire – The overall domestic productivity score was calculated in terms of responses to questions 1 through 4 using a formula [(Q3 – Q2) × Q4]/Q3 × 100] expressed as a percentage, where higher percentages indicate a) fewer hours missed from domestic activities and/or b) increased productivity during domestic activities.

[2] Health and Labor Questionnaire (Hakkaart-van Roijen & Essink-Bot, 2000) – The HLQ 2000 version consists of four modules, specifically: 1) absence from work, 2) reduced productivity, 3) unpaid labor production, and 4) labor-related problems. Later versions consist of three modules (e.g., HLQ 2010 version contains only three modules). Dr. Hakkaart-van Roijen of the Institute for Medical Technology Assessment in the Netherlands confirmed that the Impediment Score for Unpaid Work is part of the fourth module of the Health and Labour Questionnaire in the 2000 version (personal communication, December 4, 2013). An updated version of the HLQ questionnaire and manual were produced in 2013.

[3] Patient Questionnaire 2 by van Vollenhoven et al. (2010) asked the presenteeism and absenteeism questions to employed patients and homemaker patients. Among patients who self-identified as being both an employed person and a homemaker, the amount of absenteeism and presenteeism was assessed separately for their employed work and their household work.

[4] Visual Analogue Scale is not listed, as it was not described in the study. It is a generic tool used by many fields, with a scale (ruler) of 0 to 100 or, less often, 0 to 10.

[5] Work Ability Score (WAS) is the first item of the Work Ability Index (WAI), which is regarded as the central item of the WAI. Regardless of the name assigned, the single-item WAS or WAI is the worker's self-assessment of their present ability in comparison to their lifetime best. The scale's range is 0-10, where 0-5 is "poor," 6-7 is "moderate," 8-9 is "good," and 9-10 is "excellent" (Fassi et al., 2013; Tuomi et al., 2006).

[6] Work Limitation Questionnaire (WLQ) - Self-administered Long Version (1998; updated 2011) (The Health Institute, Tufts Medical Center; Debra Lerner, PhD; Benjamin Amick III, PhD; and Glaxo Wellcome, Inc.).

[7] Work Productivity and Activity Impairment (WPAI-RA) asks six questions that assess ability to work and perform regular activities during past seven days. The tool produces four scores, specifically: 1) absenteeism (work time missed), 2) presenteeism (impairment at work), 3) work productivity loss (overall work impairment or OWI), and 4) activity impairment (AI). The four WPAI-RA subscale scores are expressed as percentages (higher percentage indicating greater impairment and less productivity).

[8] Work Productivity Scale-Rheumatoid Arthritis (WPS-RA) was provided by Union Chimique Belge (UCB) Pharma, where the tool is used under a copyright license from Pharmacia/Pfizer.

Table 4

Measurement considerations incorporated into presenteeism tools

Descriptor	Specific Considerations
Employment status	currently (with no time horizon); full-time, part-time, reduced time; stopped work (disability); cessation (permanent); change in work to accommodate disease; function; role
Amount of time lost	days or hours per measurement interval
Level of impairment	% time reduced one-half or more; % usual capacity for work
Measurement interval	7 days (1 week); 14 days (2 weeks); 30 days (month or 4 weeks); 90 days (12 weeks or 3 months)
Recall time	past 2 weeks; past month (of any measurement interval listed above)
Unit of measurement	time (hours or days); monetary; rate; scale; score; MCID
Aspect of work	paid work; household work; family/social/leisure activities; usual activities
Participant type	employee only; homemaker only; employee-homemaker; all persons
Reason time missed	rheumatoid arthritis; arthritis; health reason; non-health reason
Health status	level of health; specific health condition(s) suffered
Disease severity	duration of RA; time since diagnosis; clinical measure (ACR, EULAR)
Duration (time horizon)	permanent; temporary
Workplace setting	workplace characteristics (as in VBBA, WAI, VOLP, WLQ25)
Score interpretation	categorical classifications; scoring standards or cut-offs
Employee intervention	based on score, specified course of action is taken
Research design	randomized controlled trial or long-term observational study, depending on the stage of drug testing and circumstances
Usability of outcome for purpose of study	measurement addresses purpose of data collection (e.g., amount of lost productivity, cause of productivity loss, condition amenable to intervention, etc.)
Type of number/metric	actual; estimate; projection (may be at point in time or over time)

Table 5

Types of study designs represented in analysis

Study	DMARD Intervention	Presenteeism Instruments	Times of Reporting	Research Design	Health Dichotomization Variables (except #8 and #10)
RCT					
Anis 2009	ETN+MTX vs. MTX	WLQ; WPAI	Weeks 0 and 52	Control vs. Experimental	
Emery 2016	ADA+MTX vs. PBO+MTX	RA-WIS; WPAI	Weeks 0 and 26	Control vs. Experimental	
Fleisch-mann 2016	ABA+MTX vs. DA+MTX	WPAI-RA	Weeks 0, 24 and 52	Experimental vs. Experimental (head-to-head)	
Hazes 2010	400 mg CZP+MTX; 200 mg CZP+MTX; vs. PBO+MTX	WPS-RA	Week 0 and 12.	Control vs. Experimental	Responder Analysis by: HAQ-DI (MCID≥0.22); FAS (MCID≥1); VAS-Pain (MCID≥10); SF-36 PCS (MCID≥2.5; SF-36 PF (MCID≥5.0); SF-36 VT (MCID≥ 5.0); and SF-36 BP (MCID≥5.0)
Kavan-augh 2009	400 mg CZP+MTX; 200 mg CZP+MTX; vs. PBO+MTX	WPS-RA	Weeks 0, 4, 24, and 52	Control vs. Experimental	
Li 2011	ABA vs. PBO	APaQ	Days 0, 57, 113, 169, 197, and 365		Responder Analysis by: Low Disease Activity (DAS28≤3.2); Remission (DAS28<2.6)
Smolen 2014	CZP vs. PBO	WPAI-RA	Week 0 and 24		Remitter Analysis by: Clinical Disease activity Index ≤2.8
Smolen 2016	ETN+MTX	WPAI-RA	Week 0 and 36		Discordance Analysis by: Global Disease Activity Assessment -Positive (PtGA-PhyGA≥2) -Negative (PtGA-PhyGA≤-2) -Concordance (|PtGA-PhyGA|=0-1)
van Vollen-hoven 2010	MTX+ADA vs. ADA vs. MTX	Clinic tool (presenteeism / absenteeism)	Months 0, 6, 12, 18, and 24 for absenteeism. Weeks 0, 20, 40, 60, 80, 100, and 120 for presenteeism.	Control vs. Experimental	
OS					
Hon e	ETN	WPAI-RA; cost of impairment	0 and 6 months	Observational study	Continuer Analysis by: ETN continuation for 6 months
Hoving 2009	ADA	VBBA; WAI; cost losses	0 and 6 months	Observational study	
Hussain 2015	ADA	WPAI	0 and 6 months	Observational study	
Zhang 2008	ADA	HLQ-DA; cost loss	0 and 12 weeks	Observational study	Responder Analysis by: ACR20 (20% improvement in tender joints or swollen joints, and three of five other measures); HAQ (MCID = 0.22)
Zhang 2015	ETN+MTX	VOLP	Weeks 0, 13, 26, 39, and 52 (retrospective analysis)	Observational study	Responder Analysis by: DAS28≤3.2 at Week 52
RCT / OS					
Zhang 2016	ETN+MTX	VOLP	Phase I (0-52 weeks) dosing; Phase II (52-91 weeks) dose reduction and report at Weeks 52, 64, 76, and 91; Phase III (91-117 weeks) drug withdrawal and report at Week 117	Observational study	Responder Analysis by: DAS28≤3.2 (remission), or DAS<2.6 (low disease activity) at Week 39 in Phase I

Notes: RCT=randomized controlled trial; OS=observational study.

Table 6

Presenteeism-to-absenteeism ratios

Publication	Number of Outcome Measures	Presenteeism/Absenteeism Ratio[1] Column A Smaller dose or control group (baseline)	Column B Larger dosage or experimental group (endpoint)	Column C Difference between baseline and endpoint (Column A-B=C)
Anis (2009)	8	1.38	2.32	0.79
Emery (2016)	1	3.00	2.50	1.75
Hazes (2010)	1	1.82	2.67	2.83
Kavanaugh (2009)	36	1.76	2.11	2.11
Hone (2013)	10	-	8.99	-
Zhang (2008)	1	1.54	2.13	0.60
Zhang (2015)	6	-	0.67	-
Method of Calculation[2]				
#1: Sum, based on number of publications	5-7 max	9.5/5=1.90	21.39/7=3.05	8.08/5=1.62
#2: Sum, based on number of outcome measures	47-63 max	81.1/47=1.72	196.09/63=3.11	87.78/47=1.86

1 The presenteeism-to-absenteeism ratio (P/A ratio) depends on various factors, including 1) the drug dosage or experimental condition (baseline vs. endpoint, or the difference between the two), and 2) the method of calculation. In both methods, the P/A is calculated for the number of outcomes measured in units of time in each publication.

2 In Method #1, the ratios are summed for each publication and divided by the number of outcome measures per publication to derive the average P/A ratio for each publication. In Method #2, all P/A ratios are summed and then divided by the total number of ratios to obtain a single P/A ratio. That is, Method #1 weighs each publication equally (5-7), while Method #2 weighs each time measure equally (47-63). Therefore, Method #2 provides a more representative ratio than Method #1. Further, the seven publications listed reported from 1 (lead authors Emery, Hazes and Zhang) to 36 (lead author Kavanaugh) outcome measures. Therefore, the P/A ratio is more representative for the papers reporting more time outcomes, e.g., Kavanaugh. Further information is available from the author upon request.

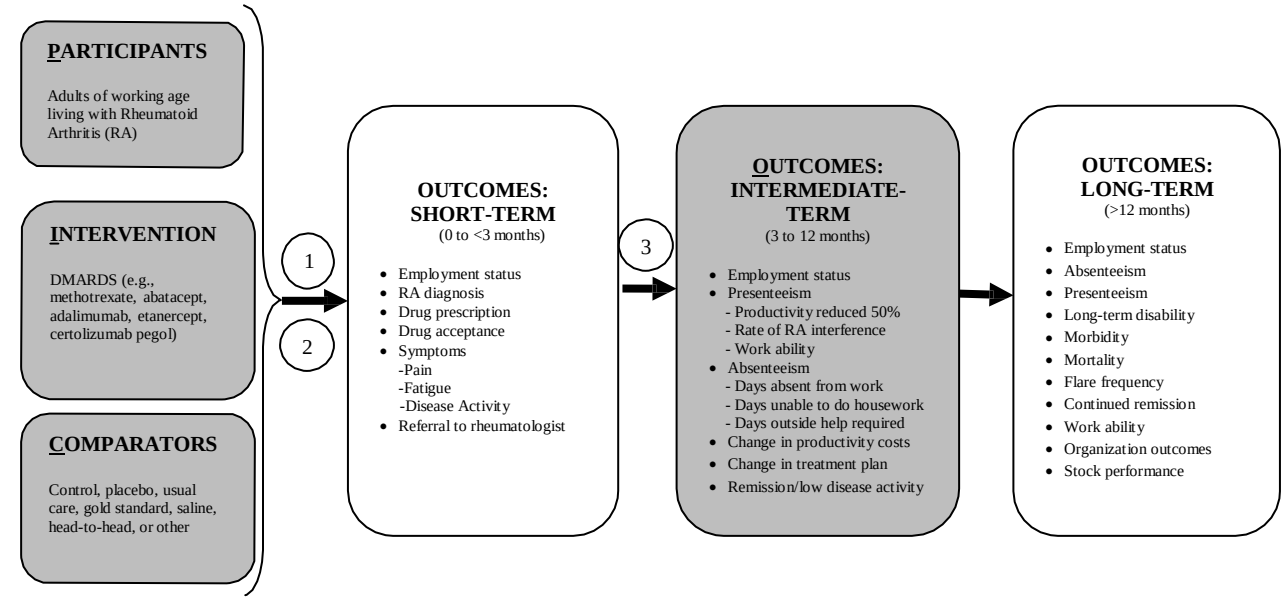

Figure 1. *The PICO analytical framework.*

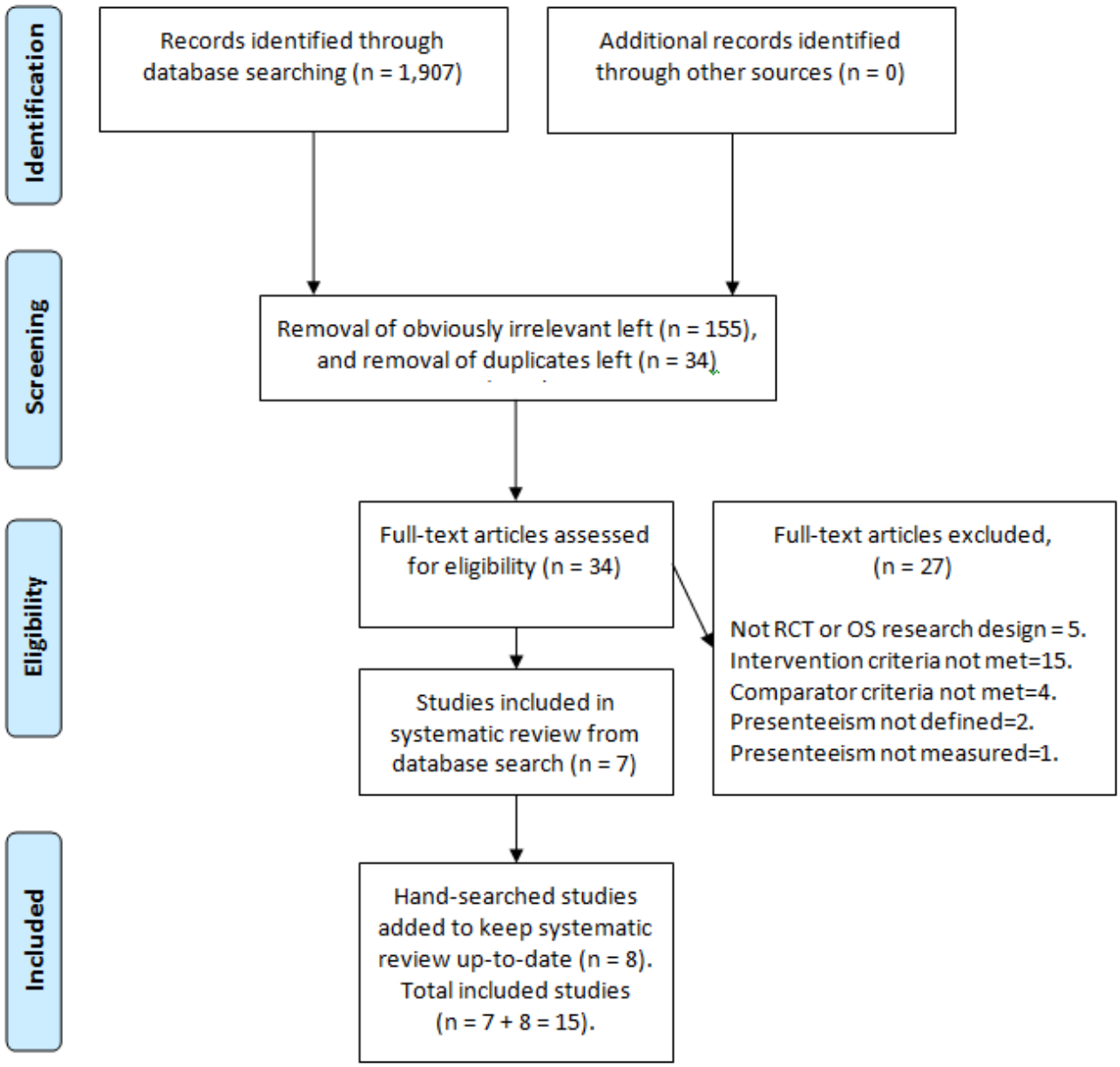

Figure 2. *PRISMA study flow diagram.*