Policy Analysis Centre

A Common Disease with Uncommon treatment

European Guideline Variations and access to innovative therapies for Rheumatoid Arthritis

Tony Hockley & Joan Costa-Font

With a Foreword by

Professor Alistair McGuire
London School of Economics & Political Science

June 2012

Policy Analysis Centre
Kings Hyde House
Kings Hyde, Lymington
England SO41 8LT

Tel: +44 15 90 68 10 44
Email: info@policy-centre.com

Policy Analysis Centre Limited
Registered in England & Wales Company No: 3467629
VAT: GB 769 7112 93

Contents

Acknowledgements

This research would not have been possible without the hard work of a team of talented researchers able to gather, translate and analyse the guidelines of the sample countries. These included Sean Boyle, Aureliano Finch, Cecilia Minelli, Max Schlueter, Sotiris Vandoros, Bernard van den Berg, Olivier Wouters, Lada Leyens, Anna Sagan, and Marta Vilella Vila. This team produced data of the highest quality within a very short timescale, for which we are extremely grateful. They do not, of course, share any responsibility for any errors in the final document.

Tony Hockley & Joan Costa-Font

Funding

This research was commissioned and funded by Merck Sharp & Dohme Ltd. MSD reviewed the report prior to publication in line with the ABPI Code of Practice. The authors had full editorial control of the content.

Terminology & Abbreviations

Some of the main abbreviations use in this paper are listed below. Readers should note that the terms *"Anti-TNFs"* and *"biologics"* may be used interchangeably, often relating to the referenced data. *"Guidelines"* and *"Guidance"* are also used in the same way, although in certain jurisdictions they have very different meanings; in England, for example, NICE guidance in its *"Technology Appraisals"* impose a high degree of compulsion on the health system, and therefore constitute much more than an indicative *"guideline"* on best practice. Although the terms are not, of course, the same we have sought to use them as most appropriate in each situation rather than seek to clarify the exact use on each occasion. Our intention is that the loss of accuracy is more than offset by the accessibility of the text. Where precision is required we have, however, sought to ensure that it is provided.

Anti-TNF	Biologic agents that reduce the effect of the tumour necrosis factor (TNF) protein in triggering inflammation: At present these are: etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab
Biologics	Drugs that are developed through biological processes rather than being chemically synthesized. At present there are eight biologics for rheumatoid arthritis, five of which target the TNF protein (Anti-TNFs).
DAS-28	A system for scoring disease activity, including an assessment of the number of swollen or tender joints out of a total of 28. Score thresholds include: <2.6 Remission; <3.2 Well controlled; >5.1 Active disease
DMARDs	Disease-Modifying Anti-Rheumatic Drugs. Slow acting drugs that lessen the activity of Rheumatoid Arthritis by reducing swelling and stiffness. DMARDs can reduce the effects of the body's immune system. In addition to the Anti-TNFs and other biologics DMARDs include methotrexate, sulfasalazine, azathioprine, gold, cyclophosphamide, ciclosporin and anti-malarial drugs
EULAR	European League Against Rheumatism
GCs	Glucocorticoids: Steroids used in treating RA
LEF	Leflunomide: the newest standard DMARD
MTX	Methotrexate: A standard DMARD
NICE	National Institute for Health and Clinical Excellence, London
RA	Rheumatoid Arthritis
SSZ	Sulfasazaline: A standard DMARD
Sources: Arthritis Care factsheets (www.arthritiscare.org.uk) National Rheumatoid Arthritis Society (www.nras.org.uk)	

About the Authors

Tony Hockley is a public policy economist, and Director of the Policy Analysis Centre. He has served as Special Adviser to two Secretaries of State for Health, and as a senior policy analyst within a range of industries. He currently teaches on Masters Degrees at the London School of Economics and Political Science (LSE), where he is also conducting doctoral research

Dr Joan Costa-Font is a Senior Lecturer and Reader in Political Economy in the Department of Social Policy at the London School of Economics and Political Science (LSE), specialising in the economic analysis of European welfare systems. He is also a Professor of Applied Economics at the University of Barcelona

Professor Alistair McGuire is Professor in Health Economics at the London School of Economics and Political Science (LSE). Recent publications include *The LSE Companion to Health Policy* (Edward Elgar. 2012), which he co-edited with Dr Costa-Font, and *Does Competition improve Public Hospital efficiency? Evidence from a quasi-experiment in the English National Health Service* (LSE. 2012)

Foreword

Professor Alistair McGuire (LSE)

This Report usefully documents the variation in treatment across 12 European countries in the treatment of Rheumatoid Arthritis (RA). It notes the large cost imposed on societies by this disease. Given that it can strike individuals when young there are considerable associated losses in productive working years, in addition to the treatment costs imposed on health care systems. This burden could be reduced by ensuring individuals have access to effective, specialist care.

The Report highlights that there is however, wide medical practice variation in this disease area. This variation, as documented by the Report, seems most acute in the access to specialist care. This may in part be due to the fact that primary care physicians see a low number of new cases each year leading to misdiagnosis and delays in referral. It also seems to be the case that patients themselves delay seeking treatment. It also reflects the case that, as the Report notes, the number of practicing rheumatologists not only varies across different health care systems, but may well fall below optimal levels in a number of countries. Where specialist care is sought the clinical guidance across countries varies and there is a lack of consent over appropriate levels of monitoring and optimal management of this disease.

Rheumatoid Arthritis is a debilitating disease. For those it affects it is life changing. Yet there remains considerable variation in treatment advice. This is partly as the disease is progressive and appears to progress at different rates across individuals. Yet even accounting for variation in individual disease progression there appears to be remaining unaccountable variation in medical practice.

There is a general consensus that unwanted treatment variation is driven by at least three factors. First there may be disagreement over effective care. There may be simply a poor understanding of the disease. Clinical evidence over the range of effective treatments may simply be lacking. This will be particularly true when there is rapid technological development within the disease area. It may be that clinical trial evidence does not provide adequate information over the timing of treatment in disease progression, or provides little information on specific disease sub-groups. Or it may be that the disease is sufficiently heterogeneous in its impact, that it is difficult to extrapolate clinical trial findings to the general patient population. There may be a wide range of disease complications.

All these factors seem to apply to RA, where individual progression and treatment reaction does appear to vary across countries, and most likely within countries also. Of course in these circumstances more information should be sought on disease progression and treatment effect. Clinical guidelines can help here, but where there is a lack of clarity in guidance this merely confuses further. Clear statements on clinical guidance, as this Report states, are an important way forward.

Second, patient preferences may simply vary. Given that chronic disease treatment choice should be based on an informed choice arrived at by both the providers of health care and the patient, the role of patient preferences is critical. Not least as this will improve treatment compliance. Of course the expression of patient preferences relies on an ability to make such informed choices. Once again the evidence base becomes crucial. If the expression of patient preferences is merely a further expression of ignorance over effective care then obviously it is not warranted. Additionally, the availability of adequate resource to meet patient preferences is required. Obviously different health systems have different funding mechanisms and levels of funding that will lead to variations in medical practice. But the variation may not simply reflect the level of resource demanded for effective treatment. In optimally treating RA there is general agreement that multidisciplinary clinical teams are important. This requires, as a first step, access to specialist care supported by effective complementary care. As the Report documents the access to specialists varies significantly across Europe. Indeed the level of access to multidisciplinary teams also varies considerably.

Of course it is important that treatment is not led solely by the availability of supply. This is the third reason why medical practice can vary to an unwanted extent. In absence of good clinical information, clinical practice may be led by a notion that more treatment is always better. This is not always going to be the case, and uninformed supply of care will lead to unwanted practice variation.
So in a disease area where clinical understanding and information is poor, where the treatment up-take is sensitive to patient preferences and where there is treatment sensitivity to resource supply there will be medical practice variation. All three aspects appear to affect the treatment of RA.

Not all medical practice variation is bad. Particularly where there is rapid improvement in treatment, or where the range of treatment options has been enhanced the diffusion and up-take pattern of these new interventions will lead to practice variation. This complicates the interpretation of practice variation as, undoubtedly some of the variation will reflect the movement from older treatment practices to new practices. This in itself emphasizes the need for increased information on the disease. Over recent years the treatment of RA has seen the introduction of a range of new, effective biological treatments. The complementary role of these treatments has led to wide variation in practice as their diffusion has spread. In most cases treatment guidelines have aided practice, highlighting their proper place in the treatment package for this chronic disease. Yet as this Report states the role of guidance on treatment is not consistent, and may be contributing to unwanted variation in practice.

This Report is timely. For while knowledge is advancing over the natural history of RA, the Report highlights much more information is required as considerable variation in practice remains. The Report gives indications of where such information would be most beneficial.

Given the incidence of RA, first contact with the health service may lead to slow diagnosis or even misdiagnosis given that a range of conditions can resemble RA symptoms. It would seem appropriate then, given the high burden imposed on individuals, for clear diagnostic information to be made widely available to non-specialists. Treatment adoption would benefit from more information concerning the

natural history of RA and, particularly on the impact new treatments have on disease progression. There are, however, few natural history studies or even follow-up, longitudinal databases in this area. Consensus over treatment guidance would also help, not just to establish the appropriate placement of effective clinical treatment but also to clearly define the role of complementary services, including physiotherapy.
I recommend this Report therefore as a means of helping to establish why medical practice variation exists in the treatment of RA in Europe and where we might look to reduce unwanted variation.

Executive Summary

This paper draws on a review of existing literature on Rheumatoid Arthritis in Europe and variations in clinical guidelines for its treatment, and compares current guidelines across 12 Member States of the European Union.

It finds significant differences affecting patients' access to the biological agents that have transformed the treatment of RA since the 1990s.

The authors compare national guidelines against the consensus recommendations from the European League Against Rheumatism (EULAR). The main findings are that:

- Variations in treatment thresholds are particularly worrying. Getting thresholds right is fundamental to high quality care.
- Stringent guidelines are imposing limits on clinical freedom and undermining the care of specific patient groups: Biologics are known to be effective in treating both moderate and severe RA. Some guidelines continue to restrict their use to severe cases alone.
- Health systems are failing to balance the direct costs of treatment against the healthcare and productivity costs of poor treatment
- The EULAR goal of achieving remission or a state of low disease activity is not reflected in several national guidelines, which are more focused on means rather than ends.
- Eliminating delays to initial treatment are an important factor in tackling RA, yet current guidelines provide for delays ranging from weeks to months
- Several countries continue to apply restrictions on access to biologics, either individually or as a group, that fall well short of best practice established by EULAR

Notable outliers include:

- Swedish and German guidelines offer specialists a significant degree of flexibility in their shared decision-making with individual patients
- A four month delay from diagnosis to treatment is provided for in the Polish guidelines
- England & Wales, Belgium, Germany and Sweden generally require that treatment needs to fail with *two* standard DMARDs before a biologic agent is used. In the Belgian case this delay before use of a biological agent is set at a minimum of six months. Spanish guidance recommends a switch to another DMARD, including Anti-TNFs, if goals are not achieved within three months.
- English & Welsh guidance continues to require a state of *severe* disease (DAS-28 >5.1) before biologic agents are used, despite widespread

acceptance of effectiveness in tackling moderate disease (3.2>DAS-28 <5.1)

- Access to rituximab and its place in the care pathway is subject to particularly wide variation.
- France, Spain, Poland and Greece make some provision for first-line use of biologics in treating early or aggressive disease, whereas England and Belgium specifically exclude this possibility for all patients.

Most national guidelines are still far removed from the goals-based approach recommended by EULAR. This is, of course, largely because they are at present unable to take into account anything but the direct treatment costs of the disease, rather than its wider health system and economic consequences. In the current economic environment the wider impacts of ill-health are particular important. Finding ways to ensure that health systems can support productivity and target avoidable disability whilst maintaining their own financial sustainability will be at the heart of the health policy debate. The effective treatment of RA with the goal of the rapid achievement of remission or low disease activity is a particular case for careful consideration by policy makers.

Introduction

Rheumatoid Arthritis (RA) is a highly damaging and all-too-common disease, with the prospect of dramatic personal and economic consequences for those affected by it. Pharmaceutical advances in recent decades have, however, helped clinicians provide therapies that can actually halt the progression of this disease. How health systems adapt to the arrival of modern biological therapies is a central challenge facing them, balancing the costs of fully tackling a disease against the wider costs of failing to do so. This cross-country comparison offers a snapshot of how they are meeting this challenge.

The challenge of RA is particularly pertinent at a time of low economic growth and fiscal austerity. The working population of Europe is expected to raise its productivity, work longer before retirement, with reduced recourse to disability benefits than its predecessors. RA and other diseases that afflict working people can dramatically affect these expectations. The indirect costs of RA are a multiple of the direct costs of treatment. For England alone the most recent estimate of annual productivity losses due to RA is some £6.6 billion (NRAS 2010). These are losses that no European economy can afford.

In this research we have endeavoured to gather the latest guidelines from our sample of 12 European countries, and to assess these against the most recent international recommendations from EULAR. It is important to note that guidelines do not have a common status. In some countries, such as England, they can be compulsory, whereas in many they are little more than advisory. Whether they are followed in practice is, therefore, an entirely different topic, whatever the degree of official compulsion. Whilst we have tried to include insights into adherence to guidelines where this is available, this would require a very different research method.

Given the effort and expertise expended on the EULAR recommendations individual countries, agencies, or expert societies would need to make a very strong case in support of clear local variations. We have found little evidence to support the differences in patient access to biologic therapies for RA.

Unlike the EULAR recommendations, there is little evidence that the costs of the disease, including productivity costs, are being considered in decisions on treatment protocols. For patients who require biologic therapies there are huge variations in their access to them according to where in Europe they live. The fastest possible adoption of an appropriate therapy is of huge importance in RA, yet many countries persist in their insistence that conventional therapies are used in the most severe cases for several months before access to a biologic agent is permitted.

Prescriptive guidelines can also fail specific groups of patients. Some may focus on the most severe cases, and be particularly clear on the cessation or reduction of treatment for patients with low disease activity or in remission. In doing so they can too easily neglect those who fall between these two extremes.

Treating Rheumatoid Arthritis in Europe: A Review of the Literature

Since the 1990s anti–tumour necrosis factor (TNF) and other biologic agents have revolutionised the treatment of rheumatoid arthritis (RA). Before this previous milestones had been the introduction of cortisone in the 1950s, and towards the end of the 20th Century the use of methotrexate (MTX) and other disease modifying anti-rheumatic drugs (DMARDs) to slow the disease process. The introduction of TNF-inhibitors ("Anti-TNFs"), however, has been a significant breakthrough in treating this widespread disease. The Anti-TNFs brought the potential not only to control inflammation, but also to prevent or slow irreversible joint erosion. There are now five Anti-TNFs available to tackle RA: infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab[1].

Table 1
Date of EU Licence for Biologics for Rheumatoid Arthritis

Rituximab	June 1998
Infliximab	August 1999
Etanercept	February 2000
Anakinra	March 2002
Adalimumab	September 2003
Abatacept	May 2007
Tocilizumab	January 2009
Certolizumab pegol	October 2009
Golimumab	October 2009

Source: European Medicines Agency www..ema.europa.eu

The first three were launched in fairly quick succession and still dominate the biologic management of RA. Early treatment with an Anti-TNF in combination with methotrexate (MTX) has been shown to slow disease activity or achieve remission in a considerable percentage of patients (Emery et al, 2008), and this is reflected in the 2009 clinical recommendations produced by the European League Against Rheumatism (Smolen, 2010).

Common Prevalence, Variable Treatment

The global prevalence of RA within the population has been estimated at about 0.5–1.0% worldwide, rising to around 2% among the population aged over 60 years (Lundkvist et al, 2008). It is normally two times more common in women than in men and its diagnosis tends to peak amongst middle-aged individuals (Bone and Joint Decade, 2005).

Some estimates suggest that between 7% and 16% of the diagnosed adult patient population are being treated with biologics. However, the variability in access to these therapies is large, ranging for example from 5% in Austria to almost 30% in Norway (Kobelt and Kasteng, 2008). Across the World an estimated 1,136,000 patients have been treated with Infliximab, 500,000 patients with etanercept, and 370,000 with adalimumab since these products became commercially available (Tak and Kalden, 2011). Hoebert et al (2011) have observed a general

[1] Additional biological drugs that are licensed for use include: rituximab, a chimeric monoclonal antibody that depletes B-cells; abatacept, a selective T-cell co-stimulation modulator that blocks a key co-stimulatory signal required for T-cell activation; and tocilizumab which is a humanised monoclonal antibody that inhibits cytokine interleukin-6 (IL-6).

trend in all the countries surveyed of increasing biologic treatment, but with wide variations. They found, for example, an almost six-fold difference between the low level of usage in Portugal and patients' access to these therapies in Norway.

Barriers to Treatment

Delayed diagnosis.
Rheumatologists diagnose the vast majority of patients identified as suffering from RA. Hence, the speed and ease of patient access to specialist care is closely associated with the speed of access to anti-TNFs.

Waiting times to diagnosis vary from country to country. Evidence suggests, for example, that waiting times are around six months in France, but much longer in Germany, Italy and Spain (Innobus, 2009). Whilst national treatment guidelines produced by the relevant scientific groups in many European countries focus on rapid diagnosis and early treatment, other features of health systems may prevent the achievement of this goal. A study by the National Audit Office in the UK (NAO. 2009) suggests that better coordination between services is a key to the early detection of RA and the rapid prescription of anti-TNFs.

Budgetary restrictions
Earlier intervention would, of course, increase the number of patients put forward for treatment. The ongoing growth in the range of biologic therapies, by increasing the sequential treatment options available, has the potential to increase the duration of biologic treatment. (Kobelt and Kasteng, 2009). The potential increase in demand will, of course, be a cause for concern in cash-constrained health systems.

Budgetary caps at the national level, as in Italy, or the office level, as in Germany have a significant influence on the capacity of physicians to prescribe biologics (Innobus, 2009). An estimate by Kobelt et al (2009) suggested that the average treatment cost per patient with RA in Europe was €12,900; ranging from an average of €15,000 in Western Europe to €3,750 in the countries of Central and Eastern Europe. Table 2 shows some of the significant variations in treatment spending between countries, and the dramatic variations in spending on biologic treatment[2], which bear little obvious relation to the levels of either the direct or wider total costs of managing RA.

Alongside this it is also important to consider that the non-medical costs of RA far exceed its medical costs. These wider costs also vary between countries, although to a lesser degree than the medical costs.

The relationship between Anti-TNF prices and treatment levels is not clear, and cost does not appear to be the main driver of uptake. Germany is reported to

[2] Variability measured by the coefficient of variation is 0.36 for total cost, but 0.53 for biologics. This is calculated by dividing the standard error by the mean, to provide a statistical measure of dispersion.

have had the highest ex-factory price in Europe, and Italy one of the lowest. Both, however, show some of the lowest rates of use of biologics in Western Europe. The presence of prescribing budgets can be a limitation. In Italy, biologics can only be prescribed in the hospital setting, and hospital drugs are limited to 2.4% of total spending (Kobelt and Kasteng, 2008).

Table 2
Biologics' share of health system RA spending (2008)
€/patient

	Total	Direct	Biologics	Biologic /Total %
Greece	11,460	5,551	1,952	17.0
Sweden	13,063	3,543	2,158	16.5
Ireland	16,844	5,645	2,716	16.1
Spain	9,944	5,383	1,443	14.5
Belgium	15,770	3,959	2,222	14.1
Neths	18,047	7,847	1,543	8.5
Slovenia	7,888	3,797	648	8.2
UK	11,997	5,265	888	7.4
France	20,522	10,252	1,475	7.2
Germany	18,791	7,261	1,284	6.8
Italy	11,546	4,552	731	6.3
Poland	3,720	1,922	88	2.3

Kobelt & Kasteng (2009)

A 2009 study by the National Audit Office (NAO) in England estimated that RA costs the English NHS £560 million annually, and that approximately 580,000 adults in England currently have the disease, with a further 26,000 new cases diagnosed each year. The NAO also put the additional costs to the English economy due to sickness absence from work and aspects of work-related disability at some £1.8 billion a year. Total cost estimates from the National Institute for Health and Clinical Excellence are even higher, at between £3.8 - 4.75 billion per year (NICE 2009), and from NRAS at £6.6 billion (NRAS (2010).

Diagnostic Variations

At present there is no single European or international method of diagnosing rheumatoid arthritis and no single diagnostic test to detect it. Diagnosis is, therefore, very much still subject to physicians' own knowledge and methods (NAO, 2009).

Reimbursement limitations and delays

Using data from 13 countries Pease et al (2011) suggest that regional reimbursement policies may be influencing initiation of anti-TNF therapy alongside variations in physicians' preferences. *Cost-effectiveness thresholds*, differ between countries due to differences in the costs and epidemiology of the condition, leading to differing decisions. Access to these medicines after they have obtained a licence can be slow, running to around 100 days in Ireland, 300 in Slovenia and 400 in Belgium (Kobelt and Kasteng, 2008).

Safety concerns
In RA the body's immune system acts to harm joints. Suppressing the immune system to tackle this can obviously increase the risk of infection and studies have borne this out with the use of biologics, to varying degrees (Dixon et al, 2010). Nevertheless, these drugs may prove to be safer than originally anticipated (Dixon and Felson, 2012), but it is important that clinicians and patients remain alert to the risks inherent in immune system suppression. (Antoni and Braun, 2012; Galloway et al, 2011).

Shortages of rheumatologists.
There is wide variation in access to specialists across European countries (Innobus 2009, NAO 2009). The limited availability of specialists and lengthy specialist referral processes can be important factors leading to late diagnosis and treatment (Kobelt and Kasteng, 2008) with harmful consequences. Kobelt and Kasteng cast doubt on the existence of a direct link between the number of specialists and the prescription levels of biologics, as countries with similar specialist densities, exhibit different levels of use of biologics. Whilst the availability of specialists may affect rapid access to diagnosis and appropriate treatment, other factors are evidently more important to the choice of treatment.

Table 3
Number of Rheumatologists

Country	Density
France	1/2514
Sweden	1/4512
Netherlands	1/8015
England	1/10011
Wales	1/10611
Scotland	1/11311
Spain	1/14017
Germany	1/14213
Ireland	1/22716
Poland	1/38460
Slovenia	1/125000

Physician training
Levels of physician education on RA appear to be an important factor in patient access to Anti-TNFs. Limited knowledge in primary care of the early symptoms of inflammatory arthritis has ramifications on early referral to rheumatologists for diagnosis and treatment (Tak & Kalden, 2011). Due to simpler diagnosis patients with severe and active disease are more likely to have good access to treatment (Innobus, 2009). Understanding of RA in the wider population is, of course, also an important factor, which should lead patients to present with the disease to a physician for diagnosis. (Pease et al, 2011)

Geography
Interviews used in the course of the Innobus (2009) study led the authors to identify significant regional differences *within* countries, attributed to differences in the density of specialists and to geographic economic inequalities. Areas around academic research hospitals appeared to offer access to the best quality of treatment within a country. This geographic inequity was also apparent from comments by some local experts made during the interviews that formed part of our own research.

Prosperity
Sokka et al. (2009) correlated clinical status of patients with RA with the national GDP, to suggest that the burden of rheumatoid arthritis was higher in countries with lower GDP levels.

Discussion
Access to specialists is the key to early diagnosis. In the UK and Spain, the existence of a "gatekeeping" primary care system creates the need for referral prior to a specialist consultation. Much, therefore, rests on the ease and speed of referral. The Spanish Society of Rheumatology (SER) recommends a maximum waiting time between consultation with the primary care physician and access to a specialist in rheumatology not exceeding two weeks (SER, 2005). Patients with suspected septic arthritis should be referred immediately.

In other countries that do not have a gatekeeping system such as France, Poland and Belgium, ease of access to aspecialist is, of course, less of an issue but heavily reliant on the patient taking the initiative to present to a physician.

Countries differ in the extent to which the healthcare system reimburses RA costs. For instance, in France, all RA-related healthcare costs (including biologic DMARDs) are reimbursed for the majority of payments as it is categorised as a life threatening condition.

Studies looking at guidelines to ensure appropriate access to biologic therapies (e.g., Deighton and Hyrich, 2008) find that access varies considerably between different nations. More specifically, in some countries patients are denied access to therapies that would be available in others. Evidence suggests that the use of Anti-TNF drugs has been found to vary considerably across Europe (Jonsson *et al*, 2008), in part due to variations in guidelines, but also due to administrative and reimbursement restrictions. It is not uncommon for national health technology agencies (HTA) and medical organisations to adopt very different judgements as to whether and when to use Anti-TNFs, as described below. Perhaps one of the main standardisation drivers includes the blueprint role of the recommendations of the European League Against Rheumatism (EULAR) generally considered a benchmark for RA treatment guidelines (Combe *et al,* 2007, Landewe et al, 2009).

Jönsson et al. (2008) examined variations across 30 countries in the use of several TNF inhibitors and standard DMARDs They found relatively high usage of Anti-TNFs, when compared to other EU member states, in Norway, Sweden and the Netherlands.

Emery et al (2009) and the Innobus (2009) study examined diagnosis and treatment patterns in the late 1990s and early 2000s. They found that national guidelines, and Italian regional guidelines, exhibited some notable differences to EULAR recommendations. In particular, these guidelines stipulated more specific treatment recommendations, and they recommended widely varying diagnosis and monitoring practices. The UK, in particular, had notably restrictive guidance.

Furthermore, the Innobus (2009) study found marked differences across national guidelines in their approaches to biologic therapies. In France and Spain, national guidelines indicate that biologic treatment should be started after failure of initial MTX treatment, or, in severe cases, as first-line treatment, whilst in other countries, biologics are only recommended after failure of MTX and at least one other DMARD.

An NAO (2009) study using data from 2007 revealed that the percentage of patients on Anti-TNFs was 4% in Germany, 6% in the UK, 8% in Spain and France, 11% in the Netherlands, and 12% in Sweden.

Pease et al (2011) undertook a cross-country study comparing Anti-TNF treatment. Their findings indicated that a lower disease severity was noted in databases from countries with less restrictive Anti-TNF coverage. More generally, results suggest that regional variation exists between the 13 countries analysed in the initiation of treatment with anti-TNF agents among RA patients and suggest that in some cases this variation may be increasing.

Some explanation for cross-country variation in the use of anti-TNFs may, of course, relate to differences in need. Generally, with some exceptions there is a North-South dimension with a higher prevalence in the North (Alamanos and Drosos, 2005). However, the latter might not be a stable trend due to migration as well the relative ageing of southern societies. Some variation in prevalence can also emerge due to different demographic profiles, as prevalence of RA will be higher in countries with more highly-aged population profiles. Whilst these differences may account for variations in absolute treatment and service provision levels they cannot, however, account for variations in treatment protocols.

Guideline Variations: A twelve-Country Survey

During January and February 2012 the Policy Analysis Centre gathered clinical guidelines for the use of biologics in the treatment of RA across a sample of 12 European countries[3]. The sample countries cover a broad range of European Union member states, from a population of two million to 82 million, and a more than three-fold difference in total (public and private) per capita health spending. Once this data had been collected our researchers then conducted a telephone interview with one or more national experts in each country, primarily in order to verify that the guidelines were the most relevant for the purposes of our comparative study. The summary reports for the 12 countries are available online as a separate document (PAC 2012).

Table 4
Survey Country Characteristics

	Population (m)	GDP/capita €000s	Total health spend $/capita($PPP)	Government Debt %GDP
Belgium	10.7	31.0	3946	96.2
England	52.2	25.3	3487	68.2
France	64.3	29.6	3978	78.1
Germany	82.0	29.3	4218	73.4
Greece	11.2	20.7	2724	126.8
Ireland	4.5	35.7	3781	65.5
Italy	60.0	25.2	3137	116.0
Netherlands	16.4	34.6	4914	60.8
Poland	38.1	15.8	1394	50.9
Spain	45.8	22.9	3722	53.2
Slovenia	2.0	17.3	2579	35.4
Sweden	9.2	31.3	3722	41.9

Sources: European Commission; OECD; UK Office for National Statistics

Financial data for "England" relates to United Kingdom. Financial data for all countries relates to 2009, except for health spending figure for Greece (2007).

In a fast-moving area of pharmaceutical innovation the selection of a benchmark against which to compare guidelines is fraught with difficulty. At the time of writing the EULAR recommendations (Smolen 2010) themselves were already more than two years old, having been developed in the Autumn of 2009. Given their provenance, however, and their status as a widely-accepted standard of care amongst rheumatologists they do present a valuable basis for comparison. The table of "overarching principles" and recommendations from EULAR is included as Annexe 2.

[3] Belgium, England, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Spain, Slovenia, Sweden

The foundation stone of the EULAR recommendations is set, perhaps, in the sense of treatment urgency: that ***treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made***, and that it should be aimed at **reaching a target of remission or low disease activity as soon as possible in every patient**; as long as the target has not been reached, treatment should be adjusted by frequent and strict monitoring

They also recommended that changes in therapy be made at least every three months when the disease is active, and that these changes should be made on the basis of composite measures of disease activity, which include joint assessment, but not necessarily inflammatory markers. Such measures included the DAS with a 28-joint count (DAS28)[8] and the Simplified or Clinical Disease Activity Index (SDAI or CDAI).

Finally, they recommend a "new" diagnostic classification criteria that establishes a point value between zero and 10. Every patient with a point total of six or higher is unequivocally classified as an RA patient.

National and Regional Guidelines
Countries differ in whether they have general guidelines for RA treatment, and in whether they provide specific guidance on the use of biological agents.

In **Poland** a team of experts has published recommendations although these do not act as formal standards of care. In France national guidelines specific to the use of biologics, are issued by the national health authority (Haute Autorité de la Santé; HAS) which links guidelines adherence to funding. The French guidelines were in issued in 2007 but were suspended in 2011 due to issues of *"transparency"* and *"conflicts of interest".* However, physicians can continue to use them until replacements are published.

As is the case in **Belgium**, some European countries may have no clinical guidelines. However, the reimbursement criteria for biologics partly fill this gap, and notably rely heavily upon guidelines from NICE and EULAR.

In **Spain** , the first version of the guidelines (GUIPCAR) was published in 2001, most recently updated in 2011. In Spain, as elsewhere, regional authorities and agencies may publish their own recommendations. In March 2011, for example, Catalan guidance was produced to cover RA and biologic therapies in this region of Spain. In Germany, clinical guidelines are published by the German Society for Rheumatology (DGRh), and the latest revision took place in 2011.

Clinical guidelines for **Sweden** produced by the Swedish Society for Rheumatology (SRF) were published in November 1998. They are non-binding; and are reviewed on an annual basis. Updates from 2004 and 2011 are available online (SRF, 2004)

In **Slovenia**, EULAR 2010 guidelines are adopted by the Slovenian Society of Rheumatologists. They cannot be fully implemented in practice, however, due to the very low number of rheumatologists in Slovenia relative to other European

countries. Additionally, the Health Insurance Institute of Slovenia, which provides compulsory health insurance for Slovenians, works on a fixed annual budget for biologics.

In **Ireland** there are no statutory guidelines in place. Whilst there is some expectation that guidelines will be introduced, at the time of writing there has been no confirmation of any intention to do so. However, the Irish Society for Rheumatology published its own guidelines in 2005.

In 2009 in **The Netherlands** specialist RA professionals developed clinical guidelines; clinical practice can depart from these, but only in consultation with the individual patient and with documentation of the reasoning.

Comparison of the 12 countries against the EULAR principles and recommendations

EULAR "overarching principles" A-C:
Specialist-led care, shared decision-making, and consideration of disease and productivity costs alongside treatment costs

The **Spanish** Society for Rheumatology's standards of care recommend that all cases of arthritis lasting more than four weeks should be referred to a specialist, regardless of the suspected diagnosis

Swedish guidelines show some flexibility in decision-making, particularly in making assessments of levels of disease activity. Swedish physicians can, for example, take into account the patient's general well-being as well as a DAS-28 or other disease activity score, so that patients with "low" scores may still have access to biologic therapies if considered appropriate.

There is little evidence from the survey of guidelines that wider healthcare and productivity costs are taken into account in treatment decisions, although the Swedish health system, as mentioned above, does provide support for clinician flexibility to go beyond DAS-28 or other rigid scoring systems in their decisions. Both the direct treatment costs of RA, and its wider costs are significant. In the UK, the National Audit Office (NAO) estimated that the NHS spends £560 million on RA each year (of which £160 million is spent on biologics), and that the wider cost to society in terms of sick leave and work-related disability is £1.8 billion a year. They put the approximate NHS cost per annum per patient for conventional DMARDs at £300, compared with £10,000 for biologics (NAO 2009). More recent data from the NHS Information Centre revealed that in 2010, hospital-prescribing expenditure on the four main biologics (for all uses) came to £557 million, out of total expenditure on hospital prescribing of £4.1 billion, and that it was growing at an annual rate of between 13-19%. The lack of any consideration by NICE of wider economic consequences is a cause for concern that has been expressed by the National RA Society in the United Kingdom.

Rapid diagnosis and treatment – EULAR Recommendation 1
Early recognition of RA is important. Left untreated it can result in substantial damage to the joints which may otherwise be avoided. The sense of urgency is well reflected in national guidelines, although the speed of referral and treatment initiation can vary in practice for a variety of reasons. Where a direct approach to a specialist is possible without going through a primary care "gatekeeper", as in France, a more rapid process might be expected. However, some evidence suggests that those patients who make a direct approach to a specialist actually wait considerably longer than those who seek a referral from primary care (Innobus 2009).

Since 2005 the **Spanish** Society for Rheumatology has required that waits for referral to a specialist should not be more than two weeks, and that treatment should commence immediately upon diagnosis. New guidelines in **Sweden** in 2011 put increased emphasis on the importance on rapid and aggressive action on untreated RA, although the focus on quick action had already featured heavily in guidelines from 1998 that had been developed jointly between experts in Norway and Sweden (Swedish guidance is now updated annually). In **England** the 2009 Guidelines from the National Institute for Health and Clinical Excellence establish a standard of "urgent" specialist referral for a patient whose hand or feet joints are affected, or have more than one joint affected, or who have left more than three months before seeking medical advice.

In **Germany** the guideline issued by the national society for rheumatology is focused on "Early RA", given concerns over continued delays in initiating treatment. German guidelines establish a preface that the aim is to provide all new cases of RA in Germany with specialised care within 12 weeks – a goal that is currently only achieved in less than 25% of all new RA cases.

Italian guidance from the Associazone Patologie Internazionali Autoimmuni, however, recommends that treatment is initiated within three months of the first manifestation of disease, subject to drug availability. **Polish** guidance from 2008 provides for first-line DMARD treatment by the fourth month after diagnosis.

Whilst most countries try to match the EULAR recommendations, for some this can be a high aspiration. In **Slovenia**, for example, the low number of rheumatologists makes it impossible for the health system to provide patient consultations with a specialist at least once every three months. Rheumatology is a new specialty within Slovenia, so that the first doctors with this specialist training graduated in 2010. Patient care for RA has been provided by specialists in internal medicine.

A Goal of achieving and Maintaining Low Disease Activity – EULAR Recommendation 2
The EULAR recommends a goal-based approach to the management of RA, with the focus on the rapid achievement of remission or "at least" low-disease activity. This is most commonly taken to be a DAS-28 score of less than 3.2 for low

disease activity and less than 2.6 for remission, and is widely reflected in national guidelines.

In **France** monthly disease monitoring is recommended until remission is achieved, and thereafter, on a three-monthly basis. Every six to 12 months, structural damage is assessed by X-ray, and a functional assessment is used to complement disease activity and structural damage. The **Greek** National Organisation for Medicines states very clearly that the treatment objective is to put the patient into remission or into low disease activity as soon as possible, meaning within three to six months. Monitoring under the **Swedish** guidance is on a three-monthly basis.

Adoption of an Anti-TNF - EULAR Recommendations 7, 8
In **France** patients can access biologic DMARDs as second line treatment after unsuccessful treatment with a single synthetic DMARD for at least three months; while other countries including **England, Belgium,** and **Sweden** require patients to have received two previous synthetic DMARD treatments, although the Swedish guidelines do make provision for use of a biologic after a single DMARD in cases of rapid disease activity progression. In **Ireland**, the HSE emphasises that there are many conventional DMARDs available for use. The **Netherlands** also stipulates a three-month use of conventional DMARDs prior to use of a biologic, although in **Belgium** this requirement is much longer at six months.

In **France** etanercept and adalimumab are the most frequently used biologics, in 80% of cases used in combination with MTX, and as monotherapy for the remainder. Safety and tolerability are important criteria for this choice of drugs. Subsequent biologic use: infliximab is usually reserved as second line biologic treatment due to the higher incidence of side effects observed; infliximab is not recommended as monotherapy. Cycling of etanercept and adalimumab also occurs. Additionally, rituximab and abatacept are used as a strategy after unsuccessful treatment with adalimumab or etanercept (or infliximab), with a preference for rituximab due to its lesser frequency of administration.

The **Italian** Society of Rheumatology offers a prescriptive definition of failure in MTX treatment, after which an Anti-TNF may be adopted:

- High disease activity measured through DAS28 lasts for at least one month;
- DAS28 registers a moderate disease activity in concomitance with unfavourable prognostic factors i.e. immunological and serological factors, clinical markers, imaging markers, joint damage progression.

The presence of progressive joint damage (new erosions), regardless of disease activity, is documented by plain radiographs; In Italy, Anti-TNF biologic treatments are usually given in case of failure of DMARDs with active disease. At present, Anakinra and Anti-TNFs should be used after the failure of DMARDs,

NICE in **England** has found that in patients with established active disease, the addition of a biologic agent adds significant benefits in terms of symptom control, function and quality of life. In addition there was some evidence that in direct comparisons of biologics against conventional DMARDs, biologics were

superior (NCCCC 2009, p156). Over the last ten years NICE has produced a series of Technology Appraisals (TAs) regarding the use of various non-conventional RA drug therapies. In some cases later publications have overridden the findings of earlier ones.

The British Society of Rheumatology (BSR) produced guidelines in 2000 relating to eligibility for Anti-TNFs which were adopted within NICE TA36 (2002)[4] and became part of the NICE guidelines in 2009. NICE's TA36 had retained the BSR eligibility criteria, but tightened the response criterion by requiring six-monthly assessments to demonstrate maintenance of response. These guidelines as discussed above were that an adult patient would be eligible for the use of biological therapies only if the following criteria were satisfied:

- DAS-28 > 5.1 on two occasions one month apart;
- Failure to respond to two DMARDs one of which is MTX
- A successful response is demonstrated, by a drop in the DAS-28 score of 1.2 points.

In **Germany**, guidelines generally recommend initiating therapy with MTX, and state that biologics are said to be monotherapeutically not superior to MTX, but should be reserved for combination use with MTX following failure of a standard DMARD monotherapy.

In **Ireland** in order to be eligible for Anti-TNFs patients should have already been treated with MTX at the highest possible dosage (20mg/week) without registering a significant reduction in their disease activity, or be intolerant to MTX treatments. In this latter case Anti-TNFs should be adopted only after use of a DMARD for at least three months at the optimal dosage. Information for patients on the Arthritis Ireland website suggests that etanercept, infliximab and adalimumab are the most widely used biologics in Ireland, for people with severe RA for whom conventional DMARDs failed (Arthritis Ireland. Undated)

In **The Netherlands** the choice for the first biological is mainly determined based on clinical experience. The guideline notes that the first three Anti-TNFs (infliximab, etanercept and adalimumab) had been in use for 10 years in cases of first-line DMARD failure, so that this experience can guide decisions given that a significant level of data is now available.

Biologics for moderate disease activity

In 2010 the British Society for Rheumatology and BHPR (British Health Professionals in Rheumatology) published a new set of recommendations which made an important change to the recommended eligibility criteria. Deighton *et al.* (2010) quote several studies that show conventional DMARD treatment strategies do not suppress disease progression in patients with DAS-28 < 5.1 but > 3.2, and concluded that such patients would benefit from a more aggressive therapy regime. Moreover they claim greater efficacy for biologics in patients with moderate compared with severe baseline disease activity, in terms of decreased disease activity and radiological outcomes. Finally they note that the

[4] Subsequently replaced by NICE TA130 (2007)

EULAR consensus guidelines, Swedish, Dutch and Spanish guidelines all use a threshold of 3.2. Kiely et al (2012) argue for a change in the NICE guidelines to reflect this: *"common consensus that a biologic should be started in patients who fail to achieve a 28-joint DAS (DAS-28) <3.2 after treatment with traditional DMARDS.*

Switching Anti-TNF or other biologic – EULAR Recommendation 9
In the presence of a range of biologics and *"high level evidence"* the EULAR recommendations are very clear in their support to try more than one biologic in the search for the best treatment for each patient if a first Anti-TNF fails to achieve the treatment goals.

NICE guidance for **England** is prescriptive on the switching of biologics. It recommends the use of rituximab in combination with MTX for adults with severe RA (DAS-28 > 5.1) who have an inadequate response to, or are intolerant to, other DMARDs including at least one Anti-TNF. This was based on the estimated cost-effectiveness of rituximab (NICE 2010b). Etanercept, adalimumab, abatacept, infliximab, and golimumab are each recommended in combination with MTX only for adults with severe RA (DAS-28 > 5.1) who have an inadequate response to, or are intolerant to, other DMARDs including at least one Anti-TNF, and who cannot take rituximab either because of a contra-indication or an adverse event. NICE found rituximab to be more cost-effective, but for people who are unable to take either rituximab or methotrexate, then biological therapies are more cost-effective than other conventional DMARDs (NICE 2010b).

Kiely et al (2012) criticise NICE for this prescriptive range of choices between biologics, arguing that tocilizumab should be available as the first-choice biologic for MTX-intolerant patients, and that abatacept and tocilizumab should be allowed for patients intolerant to Anti-TNFs, and that rituximab should be more readily available (Tocilizumab was, in fact, later recommended by NICE in February 2012 following a reduction in its unit costs by the manufacturer).

In **Ireland** rituximab and abatacept are available only if other DMARDs including Anti-TNFs have not been successful. Rituximab is given with MTX; abatacept can be given as a monotherapy. Finally, tocilizumab is described as a "new biological drug" prescribed for treatment of moderate to severe RA that has not responded to other treatments. It can be given as a monotherapy or in conjunction with MTX.

In **Italy** rituximab and abatacept are administered in case of ineffectiveness of the first line biological treatment (Montecucco, 2011) Clinical experience in Italy suggests that a lot of patients do not sustain a response to Anti-TNF therapy: as a consequence clinicians often choose to switch to a different drug or escalate the dose. Drug discontinuations are particularly worrisome and usually arise because of poor or absent tolerability for biologics. A recent observational study (Punzi. 2011) carried out in 23 centres (nine in the North, four in the South, 10 in the centre) has highlighted a high rate of discontinuation and dose adjustment over a 36-month period.

In **Greece**, treatment with biological factors in RA should be continued only if there is evidence of satisfactory response of the disease after six months of continuous treatment. If the response is not satisfactory, treatment should be ceased and substituted by another biological factor or any other treatment that is considered necessary. In Greece, abatacept and tocilizumab have indications as the first biological treatment.

In **Poland** treatment with rituximab and abatacept is reserved for patients in whom the combined therapy involving anticytokine drugs is ineffective. A survey of rheumatologists has suggested that biological agents are considered to be effective in RA treatment, and the most commonly used biologics are adalimumab (47% of doctors), etanercept (99%), infliximab (81%) and rituximab (64%). Abatacept and anakinra are used the least frequently (12 and 1% respectively).

In **France**, biologics are used in patients with severe RA or those who fail to sufficiently respond to DMARDs (some 40–60% of patients initially treated with MTX.)

In **Belgium,** for the treatment of patients suffering from severe RA, the guidelines state that they cannot decide between NICE and EULAR recommendations, therefore doctors are advised to consider the reimbursement policies from INAMI when making a decision. Should it be the third treatment on a patient with severe RA, the introduction of an Anti-TNF (in combination with MTX) is allowed. Other biologic compounds, such as abatacept or tocilizumab (having the same reimbursement conditions as Anti-TNFs), can be used. If the treatment with the first biologic is not successful another Anti-TNF or alternative biologic DMARD can be used. The use of rituximab is allowed if the disease progression is not stopped by at least one treatment round with a biologic DMARD compound.

In **Spain** if a satisfactory response is not obtained in three months or if DMARD-related toxicity occurs, the physician should evaluate the possibility of changing treatment by adding a new drug or modifying the dosage. It is essential that a patient with RA who has not responded to a particular DMARD treatment in monotherapy or combination therapy has the option of other treatments of proven efficacy as quickly as possible. If response to MTX is unsatisfactory after reaching the maximum dosage and assuring the bioavailability of the agent, the panel recommends the use of LEF or SSZ or an Anti-TNF agent as the second step in the treatment ladder, either replacing or in addition to MTX. If MTX toxicity is such as to oblige its withdrawal, the panel recommends using LEF or SSZ or an Anti-TNF agent as the second step on the treatment ladder.

In **Sweden**, The 2004 guidelines do not include any explicit restrictions on the administering of biologic treatments (e.g. no economic criteria). The guidelines also do not specify which biologic agents should be used or when a switch between agents is advisable, although they mention a few available options at the time (e.g. adalimumab, etanercept and infliximab); they do not specify when

dosages or prescription frequencies should be adjusted. The treatment response measures are defined on an individual basis and should include evaluation of disease activity (DAS28 scores, physical examination of joints) and records of side-effects; patient response should be measured after two to three months. The guidelines discuss the use of surgery in extreme cases where pharmacological treatment is unsuccessful. Finally, the document highlights the importance of holistic care of patients, which includes improved patient-information to encourage an environment of patient concordance and also to stress the impact of lifestyle factors (e.g. smoking) and rehabilitative medicine on the successful treatment of the disease.

The Swedish guidelines provide data on the various Anti-TNFs which have been approved for combination therapy: Adalimumab, etanercept, infliximab and golimumab have been approved for use with MTX, while SSZ, LEF and azathioprine can be used alongside other DMARDs. The guidelines offer clinical evidence on the drugs to be used in the case of drug-resistance or unsatisfactory patient response to other treatment (abatacept, rituximab or tocilizumab). It remains at the doctor's discretion when dosages can be adjusted if a patient responds (e.g. enters remission) and some evidence suggests that continued low-doses of adalimumab or infliximab is beneficial. In addition, the document highlights the necessary precautions to ensure patient safety during the pharmacological treatment.

Intensive medication strategies to be considered in every patient – EULAR Recommendation 11
EULAR recommend consideration of an intensive strategy, including the combination of MTX with a biologic or GC, in all patients, and particularly in those with a severe and progressive disease course who are least likely to respond well to DMARD monotherapy.

Consideration of an intensive initial therapy including a biologic appears to be rarely considered, even in patients with a poor prognosis.

Biologics as first line treatment?
Some guidelines now include the possibility of using a biologic as first line treatment in certain cases, although others specifically exclude this option

In **Spain**, in cases of early RA that are expected to be especially incapacitating due to characteristics of the disease, an initial combination therapy of MTX and an Anti-TNF agent may be indicated; the objective of this treatment is to induce rapid remission and try to withdraw the Anti-TNF agent and maintain RA remission with MTX in monotherapy. In the Spanish region of Catalonia, however, doctors are recommended not to initiate biologic treatment until other DMARDs have been tried. In **Poland** etanercept is currently the initiating therapy drug in the programme for treatment of aggressive RA, with rituximab as second-line therapy. Anticytokine drugs (such as infliximab, etanercept, adalimumab, etc.) should be used in combination with full doses of MTX or, in exceptional cases, with another first-line drug.

The 2008 Guidelines of the Hellenic Society for Rheumatology in **Greece** state that in Early RA initial treatment can involve Anti-TNFs with MTX in cases with a DAS-28 score >5.1, or with more than six swollen or tender joints, or where two out of five adverse prognostic factors are present.

In **England** NICE excludes the possibility of using a biological therapy before treatment with MTX has been tried (NCCCC 2009). In **Belgium,** biologics are not accepted as first line treatment. The guideline argues that *"there is insufficient scientific proof that the use of biologics in combination with synthetic DMARDs at this early stage is more beneficial than the use of synthetic DMARDs + GC"*. It should be noted, however, that the early use of synthetic DMARD combination therapies is widespread in Belgium and the Netherlands. The Belgian guideline states that the use of a biological DMARD is reserved for patients with active and advanced forms of RA, having had insufficient response to two alternative classical DMARD treatment (one of them MTX).

Care of patients in persistent remission – EULAR Recommendations 12, 13
The main goal for RA treatment should be remission, which was defined as the absence of signs/symptoms of inflammatory disease activity.

In **Poland**, survey evidence suggests that most biological therapy lasts 12 months to 24 months, but longer than this in a quarter of cases. Some doctors continue to administer biological therapy after remission since discontinuation of the therapy may lead to disease exacerbation. Under the Polish system, if biological therapy has to be restarted a new eligibility application has to be made.

In **Belgium**, progressive and slow treatment termination is recommended only if long and stable remission is observed (more than six months) and after consultation between the rheumatologist and the patient.

In **Germany**, the guidelines suggest using the Disease Activity Score (DAS28) or the ACR remission criteria (ACR50) to identify remission. DAS28 values less than 2.6 reflect a well-controlled disease activity, while values greater than 3.2 indicate insufficient control.

The **Irish** Society for Rheumotology concludes that: "*Some patients who have responded well to anti-TNF therapy may be able to remain in remission with a reduced dose or reduced frequency of treatment*…….[but]…..*each patient needs to have their regime tailored individually"* (ISR. 2005)

Recent Changes and next reviews

In England NICE has published clinical guidelines for the treatment of RA (NICE 2009) as well as a series of technology appraisals (TAs 130 (NICE 2007), 186 (NICE 2010a), 195 (NICE 2010b), 198 (NICE 2010c), 225 (NICE 2011c) and 234

(NICE 2011a)) which are intended to determine the use of biological therapies in England and Wales. These are not without controversy and have been the subject of recent criticism by the British Society for Rheumatology (Deighton et al. 2010) as well as some leading rheumatologists.

NICE is committed to review its guidelines on a regular basis. Thus the guidelines issued in February 2009 are subject to a 3-year review: hence 2012. In November 2011 NICE issued a consultation document recommending that there should be no change in the current guideline recommendations (NCCP 2011). In 2012 NICE duly announced that the result of the review was that there would be no changes (NCCP 2012), and the 2009 guidelines stand.

More recently, an article in Rheumatology by Kiely *et al.* (2012) has also stressed the need to change the NICE guidelines. Kiely and colleagues make two main points:

Firstly they argue there is: "*a common consensus that a biologic should be started in patients who fail to achieve a 28-joint DAS (DAS-28) <3.2 after treatment with traditional DMARDs.*". They point to the fact that the use of a threshold of 5.1 for use of biologics sets England and Wales at odds with many published guidelines and standards

Secondly they state that the current NICE guidelines restrict the choices of biologics available especially for MTX-intolerant patients who are confined to Anti-TNFs alone, and for serial DMARD-IR (DMARD inadequate responders) where no switching is allowed between Anti-TNFs, and the use of abatacept is prevented.

There are two significant factors that may impact on the use of biological drugs in the NHS in England in the future:

- In 2012 tocilizumab was allowed by NICE as an alternative biologic to Anti-TNFs, brought about by a reduction in the unit cost to the NHS of this drug (NICE 2012).
- a new drug, tofacitinib, has been developed that can be delivered in tablet form (not infusion) and which will act as an JAK3 inhibitor. It was suggested to us by one leading rheumatologist that this form of therapy could be much cheaper, making its immediate use possible once it is licensed if its cost means that it does not warrant a NICE appraisal. At the time of writing, however, there is considerable speculation over the possible pricing of tofacitinib, as the manufacturer may seek a "convenience" premium over injectables (Silverman 2012, Hirschler 2011). NICE issued a draft scope for an appraisal of the drug in November 2011 (NICE 2011d).

In **Poland,** from 2010, patients need to formally qualify for biologic therapy in a system affiliated with the Rheumatology Institute in Warsaw, which also performs a therapy monitoring role. Patients for whom therapy is terminated following remission, need to repeat the qualification process if therapy needs to begin again following new disease progression.

In **France** guidelines were suspended in 2011 and they are being discussed at the time of writing although, as mentioned earlier, clinicians should still followed the "suspended" guidelines until replacements are published.

In **Germany**, The German Institute for Quality and Efficiency in Health Care (IQWIG) published a preliminary report plan in May 2011, titled "*Biotechnologically produced pharmaceuticals in second line therapy for Rheumatoid Arthritis. Report plan*". Commissioned by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. Patient relevant endpoints used for the study will be: Remission; pathology of RA; structural joint deformity; bodily functional status, including daily activities; social functional level (participation in professional and social life); health related quality of life; overall mortality; adverse drug reactions (ADR).

Methodologically, the IQWIG study will collect data through systematic literature research on primary RCT studies. In addition, relevant secondary publications from systematic overviews and HTAs will be included. Finally, the study will also draw on available data from pharmaceutical companies, publicly accessible study registers, publicly accessible documents of licensing authorities, and information from selected authors as well as feedback provided on the hearing and preliminary report.

In a comment on the IQWIG report plan, the DGRh has criticised the choice of clinical endpoints and requested a review of selected criteria (Braun *et al* 2011). More specifically, by drawing solely on randomised clinical trials the sample sizes and follow-up periods will be insufficient to validly measure endpoints such as overall mortality and structural joint deformity. Other selected endpoints such as pain, fatigue and morning stiffness are said to lack sufficient specificity, for which reason DGRh rather advises use of response criteria such as ACR50 or DAS28. Finally, the authors criticise a lack of patient relevant endpoints and a formulation of statistical methods for evaluation of results, which increases the risk of misinterpretations. IQWIG is currently in the process of redesigning the research methodology following DGRh comments.

An algorithm guideline for RA therapy stratification in Germany is also currently in development. This will provide a hierarchical structure for medicinal treatment options, and is planned for publication in autumn 2012

In **Sweden,** new guidelines were published in 2011 and introduced several important changes. The new guidelines heavily stress the importance of rapid action by physicians to quickly and aggressively counter the serious effects of untreated RA. Prognostic indicators are an important tool to identify patients more likely to require biological treatment. Combination treatment with adalimumab, certolizumab, etanercept, golimumab or infliximab (all drugs in this guideline are listed alphabetically, not according to priority) is established as second line therapy; in patients demonstrating contraindications to the use of anti-TNF treatment or have other pre-existing conditions, doctors should consider the use of abatacept, rituximab or tocilizumab. If these are unsuccessful,

doctors should consider the use of monotherapy Anti-TNFs (adalimumab, certolizumab or etanercept). If none of these treatments are successful in curtailing disease progression, step three is the use of alternative biologics (abatacept, rituximab or tocilizumab).

Until 2010 decisions for financing biological drugs in **Slovenia** were taken by the Ministry of Health through a special commission, whilst all the other drugs were evaluated by the Health Insurance Institute of Slovenia (HIIS). Since 2010 this unusual treatment of biologics has changed, so that they now also fall within the remit of the HIIS. Guidelines on the prescription of biologics were published in January 2011 and updated in July 2011 and will now be updated on a regular basis.

Conclusions

This short survey of 12 European countries reveals significant variations in patient access to the best care for RA. Given the debilitating nature of this disease, its onset commonly in middle-age, and the potential to achieve its control using the full range of therapeutic options available, guideline variations must be a cause for concern.

As Professor McGuire explains in his Foreword to the report, there is nothing intrinsically bad in variations in guidelines and practices particularly during periods of innovation. Rapid innovation is undoubtedly the case for RA, with a succession of new developments in biologic therapies since the 1990s. At the time of writing, however, some biologic therapies have now been licensed within the European Union for almost 15 years, and health systems have substantial experience in their use. Yet, our study reveals wide variations with regard to access to these older biologics, as well as to the more recent arrivals. Furthermore, the presence of highly-regarded pan-European guidelines on the treatment of RA provides a very useful yardstick of best practice that does not exist in many other areas of clinical practice.

Very limited regard seems to be given in guidelines and their development to the personal and societal costs of the disease, to set against the direct medical costs of its treatment.

RA is, thankfully, a disease for which a wide range of treatment options, including combination therapies, is available in order to tailor treatment to achieve the most effective personal care for each patient. Yet overly prescriptive guidelines serve to restrain these clinical options. An approach, as recommended by EULAR, focused more wholeheartedly on goals rather than tactics would ensure that more people with RA receive the best possible care and lead the best possible lives with their disease under control.

For the purposes of headline comparison we have endeavoured to give each country an overall mark out of ten in terms of how well it meets the ambitions of

the EULAR recommendations based on the data that we have gathered. This is depicted in the table below.

Table 5 **Country Marksheet** **Guidelines and Access to Biologic Therapies**		
Country	**Comments**	Mark
Belgium	Good focus on early and active intervention. Reimbursement criteria the most significant barrier to access	**7**
England	Slow pathway towards biological therapy, and biologic selection restricted.	**4**
France	Flexibility in treatment options and strong focus on achieving remission	**7**
Germany	Interdisciplinary & flexible approach marred by sometimes slow initial access to specialists	**8**
Greece	The most liberal system, albeit with very limited guidance for clinicians	**5**
Ireland	Guidelines not updated since 2005, but evidence of consistent clinical practice	**5**
Italy	Substantial geographic variations in access, and widespread diagnosis delays	**5**
Netherlands	Clinically-led guidelines and payer trust in physician decisions provide treatment flexibility	**8**
Poland	Guidelines have limited impact in practice. A new reimbursement system in 2012 may further restrict treatment choices	**4**
Spain	Substantial regional variations, but widespread access to biologics	**6**
Slovenia	Low number of specialists hampers care. Score-system for access to biologics	**4**
Sweden	Good access for patients with moderate or severe disease activity, and clinical flexibility.	**9**

Focus on thresholds

Aside from all other considerations the most stark contrast in the data is the almost absolute denial of access to biologic therapies to patients whose disease is not under control, but who have not yet reached a state of severe disease activity. Policy makers need to think very carefully about the role of such thresholds alongside their aspirations to deliver more personalised care.

In conclusion, our study reveals no particular logic to explain the huge variations in treating this disease. The postcode lottery of care that confronts patients according to where they live has no clear basis in local economic considerations or in the local burden of disease. The potential to tackle rheumatoid arthritis and limit the burden of the disease is now well established, but the will to do so in

some countries appears to be weak. Of the 12 countries studied this lack of will is most evident in England, where access to modern, biologic therapies is heavily restricted until a patient's burden of disease has become severe. Compared to other European countries this seems to be too little, too late.

The personal and economic burden of rheumatoid arthritis is too significant to permit the persistence of substandard care.

References

Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis*. Autoimmun Rev* 2005;4(3):130-6

American Colleague of Rheumatology (2009), *Position Paper on Biologic Agents for Rheumatic Diseases,* March 2009.

Antoni, C and Braun ,J (2012). Side effects of anti-TNF therapy: Current knowledge. *Clin Exp Rheumatol* 2002; 20 (Suppl. 28): S152-S157

Arthritis Ireland (undated) www.arthritisireland.ie/go/publications/information_booklets/living_with_rheumatoid_arthritis accessed online 28 May 2012

Bone and Joint Decade, 2005. European Action Towards Better Musculoskeletal Health.Sweden: BJD Publication.

Braun J, K Krüger, E Genth (2011), 'Stellungnahme der Deutschen Gesellschaft für Rheumatologie (DGRh) zum Berichtsplan des IQWIG zu biotechnologisch hergestellten Arzneimitteln in der Zweitlinientherapie der rheumatoiden Arthritis', *Zeitschrift für Rheumatologie* 70(10): 882-883.

Combe B, Landewe R, Lukas C, et al (2007). EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66:34-45.

Cots, F (2007). Patient mobility in the European Union. Learning from experience. *J Epidemiol Community Health* 2007;61:1014

Deighton, C & K Hyrich (2008). International guidelines on access to biologic therapy: why the differences and which is best? *Nature Reviews Rheumatology* 4, 520-521 (October 2008) | doi:10.1038/ncprheum0877

Deighton C, Hyrich K, Ding T, Ledingham J *et al.* (2010). BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. *Rheumatology* 2010; 49: 1197-1199.

Dixon, WG and DT Felson (2012), Is Anti-TNF Therapy Safer Than Previously Thought? *JAMA*, in Press.

Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, BSRBR Control Centre Consortium, Symmons DPM, the BSR Biologics Register: Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010, 69:522-528

Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS, Freundlich B: Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008, 372:375-382b.

Emery P, Van Vollenhoven R, Ostergaard M, et al. Guidelines for initiation of antitumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe. *Ann Rheum Dis* 2009; 68:456-459.

Galloway et al (2011). Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* doi:10.1136/ard.2011.152769

Hirschler, B Pfizer must walk the line on arthritis pill price *Reuters* 25 May 2011 http://www.reuters.com/article/2011/05/26/pfizer-arthritis-price-idUSLDE74O27Q20110526 Accessed online 24 April 2012

Hoebert, J.M., Mantel-Teeuwisse, A.K., Dijk, L. van, Laing, R.O., Leufkens, H.G.M. Quality and completeness of tilisation data on biological agents across European countries: tumour necrosis factor alpha inhibitors as a case study. *Pharmacoepidemiology and Drug Safety*: 2011, 20(3), 265-271

Innobus (2009). A Survey of Barriers to Treatment Access in Rheumatoid Arthritis in France, Germany, Italy, Spain and the UK. Innobus, UK.

ISR (Irish Society for Rheumatology) 2005. *Guidelines for Prescribing TNFalpha Blockers in Adults with Rheumatoid Arthritis*. Dublin: ISR.

Jonsson B, Kobelt G, Smolen J. The burden of rheumatoid arthritis and access to treatment: uptake of new therapies. *Eur J Health Econ* 2008; 8 Suppl 2:S61-S86

Kiely DW, Deighton C, Dixey J and Ostor JK 2012. Biologic agents for rheumatoid arthritis – negotiating the NICE technology appraisals. *Rheumatology* 2012; 51: 24-31.

Kobelt, G, Kasteng, F. Access to innovative treatments in rheumatoid arthritis in Europe. Last modified Oct 2009. http://www.comparatorreports.se/Access%20to%20RA%20Treatments%20October%202009.pdf

Landewe RB, Gunther K, Lukas C, et al. EULAR/EFORT Recommendations for the diagnosis and initial management of patients with acute or recent onset swelling of the knee. *Ann Rheum Dis* 2009.

Montecucco, C., R. Caporali, and M. Matucci-Cerinic, (2011) *Updating the Italian Society for Rheumatology recommendations for biologic therapy in adult patients with inflammatory rheumatic diseases.* Clinical and Experimental Rheumatology, 2011. **29**(3 (supp.66)): p. 3-6.

National Audit Office (NAO) (2009). Services for people with rheumatoid arthritis. Published by the NAO, London,15 July 2009. http://www.nao.org.uk/publications/0809/rheumatoid_arthritis.aspx (accessed 30 January 2012)

NCCCC (National Collaborating Centre for Chronic Conditions) 2009. *Rheumatoid arthritis: national clinical guideline for management and treatment in adults*. London: RCP.
http://guidance.nice.org.uk/CG79/Guidance/pdf/English
accessed 15 February 2012

NHS Information Centre 2011. *Hospital prescribing, England: 2010*. Leeds: NHS Information Centre.
http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/hospital-prescribing-england-2010
accessed 15 February 2012

NICE 2001. *Cox-II inhibitors for the treatment of osteoarthritis and rheumatoid arthritis (NICE technology appraisal guidance 27)*. London: NICE.
http://guidance.nice.org.uk/TA27
accessed 15 February 2012

NICE 2002. *The clinical effectiveness and cost effectiveness of etanercept and infliximab for rheumatoid arthritis and juvenile poly-articular idiopathic arthritis*. London: NICE.
http://guidance.nice.org.uk/TA36
accessed 15 February 2012

NICE 2007. *Adalimumab, etanercept and infliximab for the treatment of* r*heumatoid arthritis (NICE technology appraisal guidance 130)*. London: NICE.
http://www.nice.org.uk/guidance/TA130/Guidance/pdf
accessed 15 February 2012

NICE 2009. *Rheumatoid arthritis: the management of rheumatoid arthritis in adults (NICE clinical guideline 79)*. London: NICE.
http://www.nice.org.uk/guidance/CG79/NICEGuidance
accessed 15 February 2012

NICE 2010a. *Certolizumab pegol for the treatment of* r*heumatoid arthritis (NICE technology appraisal guidance 186)*. London: NICE.
http://www.nice.org.uk/guidance/TA186/Guidance/pdf

accessed 15 February 2012

NICE 2010b. *Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (NICE technology appraisal guidance 195)*. London: NICE.
http://www.nice.org.uk/guidance/TA195/Guidance/pdf
accessed 15 February 2012

NICE 2010c. *Tocilizumab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 198)*. London: NICE.
http://www.nice.org.uk/guidance/TA198/Guidance/pdf
accessed 15 February 2012

NICE 2011a. *Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs*. London: NICE.
http://www.nice.org.uk/guidance/TA234/Guidance/pdf
accessed 15 February 2012

NICE 2011b. *Final appraisal determination: Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198)*. London: NICE.
http://guidance.nice.org.uk/TA/Wave18/63/FAD/FinalAppraisalDetermination/pdf/English
accessed 15 February 2012

NICE 2011c Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (TA225). NICE. London. June 2011 http://guidance.nice.org.uk/TA225/Guidance/pdf/English
accessed 24 April 2012

NICE 2011d Proposed Health Technology Appraisal; Tofacitinib for the treatment of moderate to severe active rheumatoid arthritis. London. NICE
http://www.nice.org.uk/media/63B/E5/RheumatoidArthritisDraftScope.pdf
accessed 24 April 2012

NICE 2012. Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). NICE. London. February 2012.
http://www.nice.org.uk/nicemedia/live/13669/58202/58202.pdf

NICE Centre for Clinical Practice (NCCP) 2011. *Review of Clinical Guideline (CG79) – Rheumatoid Arthritis*. London: NICE.
http://www.nice.org.uk/guidance/index.jsp?action=download&o=57054
accessed 15 February 2012

NICE Centre for Clinical Practice (NCCP) 2012. *Review of Clinical Guideline (CG79) – Rheumatoid Arthritis*. London: NICE.
http://guidance.nice.org.uk/CG79/ReviewDecision/pdf/English
accessed 15 February 2012

NICE. Rheumatoid arthritis—drugs for treatment after failure of a TNF inhibitor: final appraisal determination.
http://guidance.nice.org.uk/TA/WaveR/61/FAD/FinalAppraisalDetermination/pdf/English
(accessed 23 December 2011)

NRAS (2010). The Economic Burden of Rheumatoid Arthritis. March 2010. National Rheumatoid Arthritis Society.

PAC (2012) Summary 12-Country Data on Rheumatoid Arthritis Guidelines. June 2012. www.policy-centre.com/projects.html
Pease, C et al (2011). Comparison of Anti-TNF Treatment Initiation in Rheumatoid Arthritis Databases Demonstrates Wide Country Variability in Patient Parameters at Initiation of Anti-TNF Therapy. *Seminars in Arthritis and Rheumatism*, 41(1), 81-89, August 2011

Punzi, L., et al., (2011) *Treatment Patterns of Anti-TNF Agents in Italy: an observational study.* Reumatismo, 2011. **63**(1): p. 18-28.

Saag et al (2008). American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. *Arthritis & Rheumatism (Arthritis Care & Research)* Vol. 59, No. 6, June 15, 2008, pp 762–784.

SER (2005) Los Reumatismos
www.ser.es/publicaciones/Revistas/Revista_Reumatismos/LosReumatismos.php Accessed online 28 May 2012

Sokka T, Kautiainen H, Toloza S, Mäkinen H, Verstappen S, Lund Hetland M, et al. (2007). QUEST-RA -Quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis*2007;66:1491-96

Silverman, E Pfizer's Rheumatoid Arthritis Pill: Not a Slam Dunk *Pharmalot* 20 March 2012 www.pharmalot.com Accessed online 25 April 2012

Smolen, J.S., Landewé, R. et al EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. British Medical Journal, 5 May 2010
http://ard.bmj.com/content/early/2010/05/04/ard.2009.126532.full.pdf

SRF (2004). Guidelines for the care and treatment of patients with rheumatoid arthritis. Basic Document [Swedish]. Svensk Reumatologisk Förening
http://www.svenskreumatologi.se/

Tak, P and Kalden, JR (2011). Advances in rheumatology: new targeted therapeutics
Arthritis Research & Therapy 2011, 13(Suppl 1):S5

Taylor, PC & M Feldmann (2009). Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. *Nature Reviews Rheumatology* 5, 578-582 (October 2009)

The Gallup Organization (2008). Cross-border Health Services in the EU. Analytical Report. Eurobarometer Flash EB No210 [online]. Available at: http://ec.europa.eu/public_opinion/flash/fl_210_en.pdf

Annexe 1

Guideline Recommendations and biologics use criteria: A summary

	Guidelines	EULAR	Preferred treatment	Early Treatment Biologics	Criteria to use biologics
England	Yes	No	A combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) ideally within three months of the onset of persistent symptoms (NCCCC 2009, p128).	NICE thus excludes the possibility of using a biological therapy before treatment with methotrexate has been tried.	Current NICE guidelines only allow the use of biologics for patients where DAS-28 > 5.1 ie patients with high disease activity. However DAS-28 < 3.2 is regarded as the threshold for good disease control.
Poland	Yes – but need for further education and disseminatio n.	Yes	DMARDs, preferred therapy is methotrexate, from the 4th month latest plus glucocorticoids; if DMARD monotherapy not effective, then DMARDs combined therapy.	Guidelines say only if DMARDs are ineffective. In clinical practice, this is currently only 3% of cases.	Guidelines state that treatment with rituximab and abatacept is reserved for patients in whom the combined therapy involving anticytokine drugs is ineffective.
France	Yes, but current suspension of RA guidelines due to issues of transparenc y and conflict of interests. To be used until new guidelines issued.	Yes	In mild/moderate RA, treatment with methotrexate. In severe RA at start, methotrexate + sulphazalazine/ hydroxychloroquine / cortisone Anti-TNFα (+ methotrexate). In severe cases, and if considered necessary, treatment with biologics.	Yes, in severe cases.	As first line treatment in severe cases. Otherwise, as 2nd and 3rd line treatment, if unsuccessful treatment with at least 1 synthetic DMARD or minimum time on previous DMARD treatment of 3 months.
Belgium	No, just reimbursem ent criteria	Yes	Reimbursement criteria considers early treatment with DMARDs as the most important part of RA drug treatment. First treatment choice is methotrexate at high dosage as monotherapy. The first treatment	Not accepted as first treatment for reimbursement. Should the patient be rich and wish to pay the full cost of treatment with biologics, the doctor can decide to prescribe biologic DMARD treatment at any time.	Reserved to patients with active and advanced forms of RA, having had insufficient response to two alternative classical DMARD treatment (one of them methotrexate).

			recommended for severe forms of RA is the combination of synthetic DMARDs with or without GC.		The minimum total time on treatment before being eligible for biologics is 6 months.
Spain	Yes	Yes	DMARD treatment in monotherapy or combination. Initial drug of choice is methotrexate.	Yes, in some cases. In early RA that is expected to be especially incapacitating, initial combination therapy with methotrexate and an anti-TNF agent may be indicated.	When other DMARDs have proven ineffective or in severe early RA in combination with other DMARDs. Regional variations.
Germany	Yes	Yes, but a few differenc es	Methotrexate, usually in combination with a glucocorticoid, recommended as first line therapy for early RA. an early combination therapy is recommended as clinically superior.	The guideline does not make universally binding recommendations about access to treatment with biologics, or contain any provisions about whether these may only be used for second-line or subsequent treatment.	Generally, if DMARD treatment monotherapy or in combination proved ineffective, but guidelines are formulated in general terms to allow flexibility in when to use biologics.
Sweden	Yes	Yes, in some instances	For low-activity RA, methotrexate is the primary recommended DMARD. For moderate-activity, high dose methotrexate and low-dose corticosteroid. Step two is the combination therapy with a biologic agent. For high-activity RA, the first step is methotrexate alongside low-dose corticosteroids (same as step one for moderate-activity). If several indicators of rapid disease progression exist, the use of anti-TNFs (abatacept, rituximab, tocilizumab) should be initiated	Yes, in high-activity RA or methotrexate intolerant patients.	Recommended in moderate- and high-activity RA (or patients with negative prognostic factors), but there is no restriction in the use of biologics, usually at the discretion of the clinician whether a patient is treated with biologics.

			alongside. Methotrexate		
Slovenia	Yes, EULAR recommend ations	Yes	Same than EULAR guidelines	Same than EULAR guidelines	Needs to be approved by a Committee amongst patients who fulfil the certain criteria (DAS 28>4,2, etc.)
Greece	No	No	First choice is treatment with DMARDs (methotrexate) and gluccorticoids. If therapy objectives are not met and there are adverse prognostic factors, biologic agents should then be added.	No	In cases of failure of drugs of the 1st choice + presence of adverse prognostic factors).
Ireland	Not statutory guidelines	No	Recommendations follow the British Society of Rheumatologists.	No formal or statutory guidelines.	No formal or statuto guidelines. The ISR recommendations st certain criteria to be eligible for biologic treatment.
Italy	Yes	Yes	DMARDs (usually methotrexate) as the first response drug in mono dose or combined therapy with palliatives i.e. analgesics. Physicians always have to justify change of treatment. Regions have to implement recommendations, but they can include additional criteria, so regional variations need to be acknowledged.	No	In case of failure of DMARDs with an ongoing, active disease. Patients are eligible anti-TNF treatment if have been treated with methotrexate at the highest possible dosage (20mg/weekwitho ut significant reductionin the DAS28; or are intolerant to MTX treatments. Also, access to biologic therapies varies substantially across regions.
Netherla nds	Yes	Not stated	Atraditional DMARD, preferably methotrexate, (whether or not with glucocorticoïden), for a period of minimum 3 months. In case of	No	In case of insufficient effect, in patients with a bad prognosis, a biological will be considered (TNF-blocker combined with methotrexate or leflunomide).

			insufficient effect, in patients with a bad prognosis, a biological will be considered (TNF-blocker combined with methotrexate or leflunomide). In patients without a bad prognosis, another conventional DMARD will be considered first.		

Source: own elaboration from country reports

Annexe 2

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

Smolen JS, Landewé R, Breedveld FC et al., *Ann Rheum Dis*, 5 May 2010

Overarching principles	
A	Rheumatologists are the specialists who should primarily care for patients with RA
B	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
C	RA is expensive in regards to medical costs and productivity costs, both of which should be considered by the treating rheumatologist
Final set of 15 recommendations for the management of RA	
1	Treatment with synthetic DMARDS should be started as soon as the diagnosis of RA is made
2	Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached treatment should be adjusted by frequent (every 1-3 months) and strict monitoring
3	MTX should be part of the first treatment strategy in patients with active RA
4	When MTX contraindications (or intolerance) are present the following DMARDs should be considered as part of the (first) treatment strategy: leflunomidr, SSZ or injectable gold
5	In DMARD naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied
6	GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term therapy but should be tapered as rapidly as clinically feasible
7	If the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors switching to another synthetic DMARD strategy should be considered
8	In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab) which should be combined with MTX
9	Patients with RA for whom a first TNF inhibitor has failed should receive another TNF inhibitor, abatacept, rituximab, or tocilizumab
10	In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might also be considered, as monotherapy or in combination with some of the above: azathioprine, ciclosporin A (or exceptionally cyclosphamide)
11	Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain
12	If a patient is in persistent remission, after having tapered GCs, one can consider tapering biological DMARDs especially if this treatment is combined with a synthetic DMARD
13	In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between patient and doctor
14	DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent
15	When adjusting treatment factors apart from disease activity, such as progression of structural damage, comorbidities and safety concerns should be taken into account