

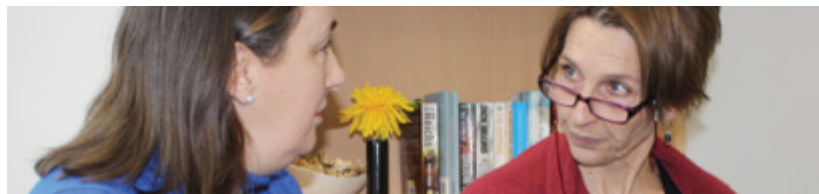


Royal College  
of Nursing

# Assessing, managing and monitoring biologic therapies for inflammatory arthritis

RCN guidance for rheumatology practitioners  
Third edition





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# Assessing, managing and monitoring biologic therapies for inflammatory arthritis

RCN guidance for rheumatology practitioners (Third edition)

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# Foreword

Welcome to this third edition of the RCN's guidance on assessing, managing and monitoring biologic therapies for inflammatory arthritis which provides a best practice framework for rheumatology specialist practitioners and the wider health care team involved in supporting the administration, monitoring and delivery of care to patients in a variety of settings.

Since the second edition of this guidance was published in 2009, significant developments have impacted this sphere of practice. These include:

- the availability of several new licensed treatments
- the development of biosimilars and their impact on access to biologics
- updated clinical guidelines and pathways to improve the management of conditions in adults and children issued by the National Institute for Health and Care Excellence (NICE)
- new commissioning arrangements resulting from the enactment of the Health and Social Care Act 2012, which aims to liberate the NHS (England) by giving patients more choice and clinicians more control
- the expansion of the British Society of Rheumatology Biologics Register (BSRBR) to create dedicated ankylosing spondylitis (AS) and rheumatoid arthritis (RA) registers to track the progress of patients taking biologic therapies and the long-term safety profile of biologic agents
- the NICE multiple technology appraisal (due for completion in October 2015 at the time of writing), includes the following:
  - review of TA 130, 186, 224, and part review of 225 and 247 (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis) – completion date to be confirmed

- review of TA 195 (adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor) completion date to be confirmed
- review of TA 143 and TA 233 (adalimumab, etanercept, infliximab and golimumab for treating ankylosing spondylitis and axial spondyloarthritis (non-radiographic) which is currently in progress – proposed completion date July 2015
- at the time of writing NICE was in the process of scoping an MTA for juvenile idiopathic arthritis – abatacept, adalimumab, etanercept and tocilizumab (GID-TAG465) – anticipated publication February 2016.

Relevant for physicians, rheumatology specialists practitioners, and health professionals who support patients who have been prescribed biologic therapies, this publication provides guidance for practice, signposts core documents and resources, and highlights the key issues for practitioners working in a variety of settings. Some sections may also be useful for patients making decisions, alongside their health professionals, regarding their treatment.

**Editorial Team, RCN Rheumatology Forum**

# Introduction

The role of biologic therapies in the treatment and management of patients with inflammatory joint diseases has continued to evolve and is an area that has significant implications for all practitioners. Biologic agents are generally effective, well tolerated and safe in most patients, however they can increase the risk of complications, including infection. As the safety of patients is paramount, this risk can be reduced by careful assessment and monitoring.

This guidance has been developed to support practitioners in the safe and effective assessment, screening and management of patients when biologic therapies are being considered. It provides practitioners with practical information to help them care for patients with different forms of inflammatory arthritis, in all care settings.

Note: the term practitioner is used throughout this document and relates to nurses or allied practitioners who have been trained in assessing, managing and monitoring biologic therapies for inflammatory arthritis.

The aim of this document is to provide practitioners with an outline of current biologic therapies, both licensed and unlicensed, and refers the reader to additional key documents and resources that will support practitioners in the UK to develop a standardised approach to caring for patients receiving biologic therapies.

**PART ONE** of this document deals with the management of biologic therapy in adults, focusing on three main treatment indications covered by NICE/SIGN:

- rheumatoid arthritis (RA)
- psoriatic arthritis (PsA)
- ankylosing spondylitis (AS).

**PART TWO** of this document covers specific issues relating to the care of children and young people, including transition of care to adult services.

Unless otherwise specified, the guidance refers to all of the listed biologics.

## The guidance

This document should not be regarded as definitive on all issues related to biologic therapy, but should be read alongside the following key texts:

- the British Society of Rheumatology and British Health Professionals in Rheumatology (BSR and BHPR) resources and guidelines
- guidelines issued by the British Society for Paediatric and Adolescent Rheumatology (BSPAR)
- National Institute for Health and Care Excellence (NICE) technology appraisals and clinical guidelines
- National Patient Safety Agency (NPSA) publications guidelines
- the Scottish Intercollegiate Guidelines Network (SIGN) guidelines relevant to those working in Scotland
- Nursing and Midwifery Council (NMC) professional regulations or similar bodies for those practitioners where nursing is not their primary professional registration
- the summary of product characteristics (SPC) for all relevant drugs, including drugs prescribed alongside biologics – found in the Electronic Medicines Compendium (eMC) which contains up-to-date and easily accessible SPCs for all medicines licensed for use in the UK (see [www.medicines.org.uk](http://www.medicines.org.uk))
- local protocols, policies and guidelines for infusions, including sharps (RCN, 2013; HSE/EU, 2014)



- local governance arrangements, including home care delivery services policies.

A full and comprehensive listing of these and additional advisory documents, alongside core documents produced by national regulatory bodies, can be found at [Appendix 1](#).

## Biologic therapies

The term 'biologic' describes treatments developed and produced in live cell systems (biologically active systems). There are a number of biologic therapies for different indications used in the field of rheumatology. Those currently licensed target the pro-inflammatory cytokines tumour necrosis factor alpha (anti-TNF $\alpha$  alpha agents), interleukin 1 (IL-1 receptor antagonist agents), interleukin 6 (anti-IL-6 receptor antibody agents), or are B cell depleting, or T cell co-stimulant inhibitors.

## NICE/SIGN and Innovation in Health

NICE/SIGN technology appraisals are recommendations on the use of new and existing medicines and treatments within the NHS, and are based on a review of:

- clinical evidence – how well the medicine or treatment works, and
- health economic evidence – how well the medicine or treatment works and how much it costs the NHS. In other words, does it represent value for money?

Health care professionals are expected to take the above fully into account when exercising their clinical judgement. However, this guidance does not override the individual responsibility of health care professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

NICE/SIGN aim to standardise access to health care and the NHS is legally obliged to fund and resource the

medicines and treatments recommended by NICE's technology appraisals. The technology appraisals outlined in this guidance define the criteria for treatment with biologic therapy for specific conditions. In addition, there are a number of NICE publications, such as the Quality Standards (QS33, NICE 2013) for rheumatoid arthritis, which provide a framework for the measurement of service provision. QS33, for example, requires that patients with RA are offered monthly treatment escalation to an agreed low disease activity score.

In the current economic climate there is a strong drive to improve outcomes and quality of life for patients through innovation. Innovation Health and Wealth (IHW) is a Department of Health initiative (DH, 2012; DH, 2013) which aims to drive the adoption and diffusion of innovation at pace and scale within the NHS, including ensuring the effective implementation of NICE technology appraisals.

There is an expectation for clinical commissioning groups (CCGs) and the NHS England to promote innovation and a direct link between innovation and financial incentives to support Commissioning for Quality and Innovation (CQUIN) has been established.

In essence IHW fosters a view that if a medicine – such as a biologic drug – is approved by NICE as part of a technology appraisal, then it should be automatically added to local formularies and be available for those who need it, within 90 days of the publication.

Innovation in treatment regimens are progressing, not only in relation to the way biologic therapies are utilised. For example, the early use of non-biologic disease modifying drugs (DMARDs) as a first-line treatment for patients with rheumatoid arthritis, ideally within three months of the onset of persistent symptoms, has been recommended to reduce disease progression and long-term disability in relation to the condition. There is good evidence that this early treatment and support can reduce joint damage and enable people with arthritis to live as active a life as possible, and reduce the need for biologic therapies (NICE CG79). These innovations benefit both the patient and the health economy.

## Biosimilars

Also known as follow-on biologics or subsequent entry biologics, biosimilars are biologic medical products with an active drug substance made or derived from a living organism by means of recombinant DNA or controlled gene expression methods.

These officially approved subsequent versions of innovator biologics are made by a different sponsor following patent and exclusivity expiry on the innovator product. Biologics are highly complex molecules, and may be sensitive to changes in manufacturing processes. Follow-on manufacturers do not have access to the originator's molecular clone and original cell bank, nor to the exact fermentation and purification process, nor to the active drug substance. They do, however, have access to the commercialised innovator product. Differences in impurities and/or breakdown products can have serious health implications. This has created a concern that copies of biologics might perform differently than the original branded version of the product, resulting in reduced efficacy or safety.

Biosimilars are regulated in the same way as the original biologic therapies, by the European Medicines Agency (EMA) under whose guidelines, manufacturers of biosimilars are required to demonstrate there are no clinically meaningful differences between the biosimilars and the originator biologic therapy in terms of quality, safety and efficacy.

The first monoclonal antibody biosimilar has recently been licensed for use in the UK. Manufactured by Celltrion, it has two brand names – Inflectra (marketed by Hospira) and Remsima (marketed by Napp). It is similar to the original product Remicade® (infliximab), made by Johnson & Johnson and has been approved by the EMA for the treatment of inflammatory conditions including rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

Although inflectra and remsima have been approved, a last minute extension of the original patent on Remicade® (Infliximab) means that these are now unlikely to be available in the UK before February 2015;

Inflectra and Remsima are predicted to be around 30 per cent cheaper than the original drug. Several other biosimilars are also currently in late stage clinical trials.

Biologic therapies have progressed greatly in the last 20 years, and research is leading us towards better performing, safer, more specific drugs. The reduced costs of biosimilars also have potential for improving access to biologic therapies in years to come.

## Patient choice and involvement

The Government's ambition is to achieve health care outcomes that are amongst the best in the world and in its white paper *Equity and excellence: Liberating the NHS* (DH, 2010) it sets out its vision of an NHS that puts patients and the public first, giving everyone more say over their care and treatment.

Making the concept of 'no decision about me, without me' a reality for everyone along the patient pathway – in primary care, before a diagnosis, at referral and after a diagnosis – means involving patients fully in their own care, with decisions being made in partnership with clinicians rather than by clinicians alone. The widespread adoption of shared decision-making is central to empowering and involving patients fully in their own care and treatment.

The Shared decision making programme, part of the Quality, Innovation, Productivity and Prevention (QIPP) Right care programme which ended on 31 March 2013, has now become the responsibility of NHS England which has stated its objective to embed shared decision-making in NHS care.

The shared decision-making process makes it possible for patients reaching a decision crossroads in their health care to explore all the treatment options available to them, work through any questions they may have and select a treatment route which best suits their needs and preferences – all in consultation with their health care professional.

This approach requires the development of new therapeutic relationships between patients, carers and

clinicians in which everyone works together, in equal partnership, to make decisions and agree a care plan. The shared decision-making approach is also being embedded at the strategic and commissioning level, and as a result patients are increasingly involved in the co-design, co-commissioning and co-production of health care.

### The key messages for patients and those who support them are:

- shared decision-making allows you, the patient, to be an equal partner in your health care, working with your doctor, nurse or other health professional to make an informed decision about your treatment
- whilst clinicians may be treatment experts, you, as the patient, are ‘an expert in yourself’
- always remember to ‘ask three questions’:
  1. what are my options?
  2. what are the pros and cons of each option for me?
  3. how do I get support to help me make a decision that is right for me?

### Key messages for provider organisations and the voluntary sector:

- there is enormous potential to be realised when patients are joint decision-makers in their own treatment options
- patients are more likely to be satisfied with their health care experience
- patients are more likely to adhere to their chosen treatment
- clinical outcomes and safety are improved
- shared decision-making helps to break down the barriers of jargon, experience and the perceived hierarchical relationship between patients and their health care advisors.

The Health Foundation, in conjunction with Cardiff and Newcastle Universities, has been working with frontline health professionals to embed best practice

and support the culture shift from a traditional ‘passive patient’ and ‘expert health professional’ care model towards a more equal partnership. Its training programme – MAGIC (making good decisions in collaboration) – supports clinical teams to embed shared decision making with patients into everyday practice.

### Patient and shared decision-making resources

Patient decision aids for biologic therapy are available at: [www.musculoskeletal.cochrane.org/decision-aids](http://www.musculoskeletal.cochrane.org/decision-aids)

Shared decision making resources can be found at: <http://personcentredcare.health.org.uk/person-centred-care/shared-decision-making>

Measuring shared decision making (sure score): [www.rightcare.nhs.uk](http://www.rightcare.nhs.uk)

Improving patient experience – ‘ask three questions’ available at the e-learning resource for shared decision making: Advancing Quality Alliance [www.aquanw.nhs.uk](http://www.aquanw.nhs.uk)

Quality statements from the NICE clinical guidelines on patient experience in adult NHS services (NICE CG138) specify that patients should be:

- actively involved in shared decision-making and supported by practitioners to make fully informed choices about investigations, treatment and care that reflect what is important to them
- supported by practitioners to understand relevant treatment options, including benefits, risks and potential consequences.

Ultimately, the decision about whether to prescribe a NICE approved medicine should be arrived at between the prescriber and the patient.

## Service provision

The rheumatology service’s primary responsibility for patients receiving biologic therapies is to deliver safe and effective care using a robust management pathways that assure the safe administration and monitoring of

biologic therapies, and that all eligible patients have access to timely and cost-effective treatment.

Other rheumatology service responsibilities include:

- reporting and acting on any adverse effects, errors or near misses to the Yellow Card Scheme (see [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)) and the BSRBR (yellow card reporting is a requirement under the Black Triangle medicines pharmacovigilance scheme, which indicates the requirement for intensive monitoring through the use of an inverted black triangle symbol after the trade name of a British medicine or vaccine). For biosimilars it is important to report by the product name not the substance e.g. Remsima not infliximab (MHRA 2008) and also the batch number (MHRA 2012)
- support for on-going monitoring and management
- providing a high quality multidisciplinary patient-centred approach where all members of the health care team, including patients, are valued and have a voice (Francis Inquiry Report, 2013)
- managing risk is an essential part of running a safe service; practitioners should consult their own local policies and ensure that all potential risk areas have been addressed
- any untoward incidents and near misses should be reported following local policy and guidelines
- locally agreed pathways must ensure that diagnostic and eligibility criteria have been addressed and adhered to as outlined by NICE/BSR/SIGN guidance
- ensuring the shared decision-making process is tailored to the patient, carer or family's needs and wishes, taking into account any capacity issues which should be clearly recorded and audited (Mental Capacity Act, 2007)
- record evidence that shared decision-making has been utilised in the provision and delivery of biologic therapies in line with commissioning requirements, for example using the *Sure Score to support shared decision-making* (Legare, 2010)

- provide appropriate training and educational resources to support patients with the self-administration of subcutaneous injections
- undertake integrated working with community service providers such as home care companies and primary shared care providers
- exception reporting processes should be in place where patients are considered to be likely to benefit but do not fit locally agreed criteria; processes may differ locally, but in essence the reasons for exceptional consideration should be clearly documented and supporting evidence provided.

For guidance on specifying a service for people who need biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology see [www.nice.org.uk](http://www.nice.org.uk)

- time should be allowed for consent and observational data collection documentation for BSRBR studies. Funding is available to support teams if needed, the registers continue to grow and provide essential information used to support safe and effective treatment for patients.

The BSRBR-RA study team can be contacted at: [biologics.register@manchester.ac.uk](mailto:biologics.register@manchester.ac.uk)

The BSRBR-AS study team can be contacted at: [bsrbr-as@abdn.ac.uk](mailto:bsrbr-as@abdn.ac.uk)

- undertake the collection of data and reporting to support effective local commissioning and the management of patients on biologic therapies.

For further information see the NICE 'into practice' online guidance, *Specifying a service for people who need biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology*, available at [www.nice.org.uk](http://www.nice.org.uk).

### Francis report summary

Published in February 2013, the final report of the Francis Inquiry into failures of care at Mid Staffordshire NHS Foundation Trust has profound implications for the whole of the NHS. Its key recommendations are summarised here:

- a 'duty of candour' requires all NHS staff to be honest, open and truthful in all their dealings with patients and the public
- a single regulator for financial and care quality, with patient safety and quality standards for all trusts
- powers to suspend or prosecute boards and individuals with criminal liability, where serious harm or death has resulted to a patient due to a breach of standards
- banning gagging clauses in relation to public interest issues of patient safety and care
- only registered people should provide direct care for patients in a hospital or care home setting; a registration system should be created
- reinstatement of lead clinician identification so that patients and their supporters are clear who is in overall charge of a patient's care
- the fit and proper person test for directors should be subject to a new test, which should include a requirement to comply with a prescribed code of conduct for directors
- complaints should be published on hospital websites, alongside the trust's response
- GPs need to undertake a monitoring role on behalf of patients who receive acute hospital and other specialist services
- local authorities should be required to pass over the centrally provided funds allocated to its local Healthwatch, while requiring the latter to account to it for its stewardship of the money.

Also see: *The Andrews report 'Trusted to care'* (2014), the independent review into the care of older patients at the Princess of Wales and Neath Talbot Hospitals in Wales, which contains highly specific recommendations regarding aspects of care and of frail older people and patients with dementia which is of particular relevance when shared treatment decisions are being made.



# PART ONE: ADULT PATIENTS

## Section 1: Assessment and monitoring of biologic therapies

NICE guidance continues to stipulate the eligibility criteria for biologic therapies. To support a patient starting biologic therapy, practitioners need to understand NICE eligibility criteria as well as the main diagnostic criteria, safety, monitoring and management issues for each condition.

**Rheumatoid arthritis (RA)** is a chronic and progressive disabling condition characterised by inflammation of the synovial tissue of the joints. It may cause tenderness, swelling and stiffness of joints and their progressive destruction, and symptoms including pain and fatigue. Rheumatoid arthritis affects three times as many women as men and has a peak age of onset of 40–70 years. It is estimated that 580,000 people in England and Wales, approximately 1 per cent of the population, have rheumatoid arthritis. Of these, approximately 15 per cent have severe disease making them eligible for biologic therapy (NICE TA195, 2010)

**Psoriatic arthritis (PsA)** is an inflammatory arthritis affecting bone, tendon and joints and is associated with psoriasis of the skin or nails. The prevalence of psoriasis in the general population has been estimated between 2 per cent and 3 per cent. The estimated number of those diagnosed with PsA and eligible for biologic therapies has been calculated by NICE in a costing template as 2.4 per cent (NICE TA199, 2010).

**Ankylosing Spondylitis (AS)** is a multisystem disease characterised by inflammatory back pain which can

also have non-skeletal manifestations (including iritis and inflammatory bowel disease) that can be severe. The condition is a type of spondyloarthropathy with prevalence estimate of 0.1-2 per cent of the UK population. Peak onset is between 15-25 years of age; the male: female ratio is 3:1. Women tend to have milder or subclinical disease. Many patients with mild disease may remain undiagnosed. Estimates of suitability for biologic therapies vary between 14-38 per cent (NICE TA143 2008).

**Juvenile idiopathic arthritis (JIA)** is a relatively rare disease. Management of this condition is currently commissioned as a specialised service by NHSE. Available data suggest that the number of children aged 4-17 years with JIA eligible for and receiving treatment with biologic therapies is 0.015 per cent, or 15 per 100,000 children per year. Older individuals over the age of 16 years, who continue to experience JIA as adults, are treated with the same options used for children and young people but individual funding may need to be requested (NICE TA238, 2012). For more information, see PART TWO: CHILDREN AND YOUNG PEOPLE of this document.

Rarer musculoskeletal conditions, such as systemic lupus erythematosus (SLE) and systemic vasculitis (SV), are treated with biologic drug therapies – some of which are as yet not licensed: in England, specialised commissioning has produced approved protocols for access to rituximab for SLE and SV. There is increasing evidence for the benefit of B-cell depleting drugs such as rituximab rather than the anti-TNF $\alpha$  drugs. There are also on-going clinical trials exploring the therapeutic potential of costimulatory blockage, such as abatacept, in the management of SLE. Belimumab is licenced as an adjunctive therapy for SLE high disease activity, although not NICE approved.

Other long term conditions treated with biologic therapies include skin conditions such as psoriasis, and inflammatory bowel conditions such as Crohn's disease (CD) and ulcerative colitis (UC).



Table 1 outlines the current biologic therapy options licensed and available for adults with RA, PsA and AS, along with related information on mode of action, current NICE approval, and administration method.

**Table 1: Biologic therapy options for adults\***

Generic drug and (brand name)	Manufacturer	Mode of action	Current NICE approval (by condition)	Licence	Mode of administration
Adalimumab (Humira®)	Abbvie	Anti TNF $\alpha$ Human monoclonal antibody	RA TA130 & TA195 PsA TA199 AS TA143#	RA AS (also AS without radiographic evidence, but signs of inflammation (elevated CRP and/or MRI) JIA Also: Psoriasis Crohn's Disease Ulcerative colitis	40mg every other week by subcutaneous injection Prefilled pen or syringe
Certolizumab pegol (Cimzia®)	UCB Pharma limited	Anti TNF $\alpha$ PEGylated Fab' fragment of a humanised monoclonal antibody	RA TA186	RA AS PsA	400mg at weeks 0, 2 and 4 (given as two injections of 200mg), and then 200mg every other week thereafter by subcutaneous injection Prefilled syringe
Etanercept (Enbrel®)	Pfizer (formerly Wyeth)	Anti TNF $\alpha$ Human receptor fusion protein is a dimer of chimeric protein	RA TA130 & TA195 PsA TA199 AS TA143#	RA JIA PsA AS Also: Psoriasis	25mg twice a week, or 50mg weekly by subcutaneous injection Prefilled syringe or MyClic pen (50mg dose only) or vial and diluent
Infliximab (Remicade®)	MSD (formerly Schering Plough)	Anti TNF $\alpha$ Chimeric human-murine IgG1 monoclonal antibody	RA TA130 & TA195 PsA TA199	RA (with MTX) PsA Also: Psoriasis Crohn's Disease Ulcerative colitis	3-5mg per kg of body weight. Intravenous infusion repeated 2 weeks and 6 weeks after the first infusion, then every 8 weeks (can be 6-weekly in AS)

**Table 1: Biologic therapy options for adults\* continued**

Golimumab (Simponi®)	Schering Plough (MSD)	Anti TNFα Human monoclonal antibody	RA TA225 PsA TA220 AS TA233#	RA (with MTX) PsA AS Also: ulcerative colitis	50mg monthly by subcutaneous injection (100mg can be considered if over 100kg and no response after 3-4 injections) Prefilled pen and syringe Caution: as this treatment comes in two strengths – care should be taken to provide the right strength to ensure that patients are not under or overdosed
Abatacept (Orencia®)	Bristol-Myers Squibb	T-Cell co-stimulation inhibitor Fusion protein	RA TA280	RA (with MTX)	500mg, 750mg or 1000mg (depending on weight) at week 0, 2, 4 then monthly by intravenous infusion eg weight <60kg = 500mg; ≥60kg = 750mg and ≥100kg = 1000mg OR 125mg weekly subcutaneously prefilled syringe (may be preceded by one infusion)
Rituximab (MabThera®)	Roche Products Ltd	B-cell depletor Chimeric mouse/human antibody IgG1 monoclonal antibody	RA TA195	RA (with MTX) Also: NHL CLL GPA/MPA +different dose	1g at week 0, 2 then repeated no more than every 6 months by intravenous infusion (some patients go much longer between infusions, based on clinical need)
Tocilizumab (RoActemra®)	Roche/Chugai Products Ltd	IL-6 receptor Humanised monoclonal antibody	RA TA247	RA sJIA pJIA	8mg per kilogram of body weight once every 4 weeks – by intravenous infusion (maximum dose 800mg) OR 162mg weekly subcutaneously prefilled syringe

\*Accurate as of November 2014

# Under review by NICE MTA

Assessment, management and monitoring of biologic therapies may be provided in secondary care settings, or community settings including in patients' homes.

The role of rheumatology practitioners is to support and guide the person considering biologic therapy and their family through diagnosis and treatment options, and provide on-going access to support and information, safe monitoring and follow up.

### Specialist rheumatology practitioners should:

- have specialist skills and knowledge in the management of rheumatological conditions
- be able to use the principles of shared decision-making in patient education and support, ensuring patients have enough information to make an informed choice, including the route of drug administration
- utilise specialist knowledge of current NICE eligibility criteria, assessment requirements and use of outcome measures in daily practice.
- be competent in the management and administration of biologic therapies by infusion or subcutaneous route, and in the treatment of adverse reactions including knowledge of cautions and contra-indications of biologic therapies and use of current reference resources where needed, such as SPCs
- be competent in the education and training of patients in the self-administration of subcutaneous injections and equipment disposal (this training may need to be supported by a local protocol or guideline).

A competency example can be found at [Appendix 2](#).

## 1.1 Before treatment starts

Practitioners should ensure that patients fulfil the eligibility criteria for biologic therapy as defined by NICE/SIGN, and have made a choice of treatment options available based on a discussion about the risks and benefits of each option.

Patients should be assessed and diagnosed according to validated diagnostic criteria RA, PsA and AS; these are summarised in [Appendix 3](#).

Severity of disease is a key component for defining eligibility. Outcome measures specified in NICE technology appraisals are:

- DAS (Disease Activity Score) 28 for RA
- PsARC (Psoriatic Arthritis Response Criteria) for psoriatic arthritis,
- BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and spinal pain VAS (Visual Analogue Scale) for AS.

When using outcome measures practitioners should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses and make any adjustments they consider appropriate to suit the patients circumstances and secure equality of access to treatments.

As well as diagnosis, disease severity and the duration of the DMARD trial, you should also consider:

- methotrexate (MTX) tolerance – to support plan for co-prescription if needed (see the HACA section below for more information)
- suitability for self-injection
- patient choice
- other health conditions including pregnancy
- extra-articular manifestations of disease (for example, ocular/skin involvement).

If the patient declines treatment, or does not fulfil eligibility criteria, you should provide guidance on

their treatment options and act as the patient's advocate.

Biologic therapy should normally be started with the most cost-effective medicine (taking into account drug administration costs, required dose and product-price-per-dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules. Always refer to local protocol/policy.

### 1.1.1 Assessment

Practitioners frequently have to assess patients for biologic therapy, and a full history is essential to ensure safe prescribing. Check lists are a useful tool to ensure nothing is missed.

The NICE and SIGN guidance algorithms for RA, PSA and AS can be found at [www.rheumatology.oxfordjournals.org](http://www.rheumatology.oxfordjournals.org) and [www.medicines.org.uk](http://www.medicines.org.uk). See also the BSR guideline (2011) for rituximab and the BSR guidelines (2014) for tocilizumab.

The following sections contain check lists based upon recommendations in RA safety guidelines for anti-TNF therapies BSR/BHPR (2010) and the SPCs of current biologic therapies, and apply to all drugs, unless stated otherwise.

#### Contra-indications, special warnings and precautions

Biologic therapy should not be considered for patients with:

- infection (including skin), sepsis or risk of sepsis, serious active infection – for example, TB, hepatitis, HIV
- hypersensitivity to the active substances or to any of the excipients, severely immunocompromised state, for example, hypogammaglobulinaemia or where levels of CD4 or CD8 are very low (rituximab)
- hepatic impairment and where baseline ALT or AST is  $> 5 \times \text{ULN}$  (upper limit of normal) (tocilizumab and infliximab)

- significant haematological abnormalities, for example, reduced WBC, neutrophil or platelet count
- an absolute neutrophil count (ANC) below  $2 \times 10^9/\text{l}$  (tocilizumab and infliximab)
- a clear history of multiple sclerosis (MS)
- lupus diagnosis/symptoms/strongly positive ANA (antinuclear antibodies) and positive double-stranded DNA (anti-ds DNA) as +ANA and anti-ds DNA antibodies development may occur with etanercept, adalimumab, certolizumab pegol and infliximab – is also listed in the SPC as an adverse drug reaction for golimumab
- moderate/severe congestive cardiac failure (CCF) (New York Heart Association class/grade III/IV) (NYHA) or severe, uncontrolled cardiac disease – all anti-TNF $\alpha$  agents list moderate/severe CCF as a special warning/contraindication
- history of having received a recent live vaccine; it is recommended that a period of at least four weeks is allowed, prior to commencement of any biologic therapy, following the administration of a live vaccine (Butler, 2008; updated 2012)
- hereditary problems of fructose intolerance (golimumab).

### 1.1.2 Precautions and screening

#### History of infection

There is an increased risk of infection for all patients receiving biologic therapy with or without MTX, particularly in the first six months of therapy with anti-TNF $\alpha$ . Therefore patients should be asked:

- if they have any infection (including skin infections such as cellulitis) or history of recurrent infection.
- any TB contact or exposure or a family or personal history (check BCG scar) (BTS, 2005) – also ask about work history particularly in rural areas as anecdotally there is an increased risk of latent TB

for individuals working with cattle or pigs, or individuals involved in the slaughter of these animals.

- you should also check the patient's hepatitis and varicella history, and any HIV risk factors.

(NICE, 2011; MHRA, December 2013; Dixon et al., 2010; Singh et al., 2010 (a&b); Galloway et al., 2011a; Galloway et al., 2011(c); Galloway et al., 2013).

### Current health conditions

Patients should also be asked about any current conditions, in particular:

- auto immune conditions such as lupus
- diabetes
- neurological disorders such as MS
- malignancies (including skin)
- cardiac disorders such as heart failure (CCF), hypertension / hyperlipidaemia, ischaemic heart disease, arrhythmias
- haematological disease, disorders – such as neutropenia, thrombocytopenia, leucopenia, pancytopenia and/or, aplastic anaemia
- hepatic impairment, disease such as hepatitis
- pulmonary/lung disease – such as interstitial lung disease, COPD
- uveitis
- any planned surgery
- current or planned pregnancy/ breastfeeding/ contraception plans
- diverticulitis and hyperlipidaemia (tocilizumab).

In addition you should check for:

- any allergies including latex
- risks of malignancy such as ulcerative colitis, history of smoking, Barrett's oesophagus, cervical

dysplasia and/or large bowel polyps or family history of malignancy

- for anti-TNF $\alpha$  agents : a medical history of psoriasis, prolonged PUVA or immunosuppressive therapy needs to be considered, as a significant number of reports of psoriasis developing in patients treated with these agents specifically have emerged (Collamer et al., 2008; Harrison et al., 2009 – BSPBR; Ko et al., 2009)
- MS family history
- vaccination history – such as flu and pneumonia and chicken pox/shingles, measles, mumps and rubella (MMR), as per local guidelines, and BCG scar
- anti-coagulation treatment (certolizumab pegol may cause erroneously elevated activated partial thromboplastin time – aPPT)
- sodium controlled diet as tocilizumab (IV only), abatacept and infliximab all contain sodium.

### Investigations checklist

Your investigations checklist should include:

- IgG and (before rituximab cycles, as can become depleted and increase infection risk)
- if indicated exclude possible infection, such as swabs, MSU, sputum
- pre-treatment chest X ray
- hepatitis B and C serology for all biologic indications (MHRA, 2013)
- HIV screening and testing if risk factors identified via initial screening
- liver enzyme parameters – ALT and AST (and in particular for tocilizumab and infliximab) when administered concomitantly with MTX; treatment to be initiated and continued in caution if ALT or AST >1.5 x ULN
- FBC – neutrophil, leucocyte and platelet count

- ANA – if positive, suggest repeat test and order extractable nuclear antigen (ENA) and double stranded DNA (ds-DNA) to help exclude lupus, as some patients have developed positive ANA and anti-ds DNA antibodies following treatment with some biologic therapies, hence the reason for pre-treatment positive ANA testing
- MMR screening (as per local policy)
- varicella zoster serology (varicella IgG levels) – see separate section for further information
- lipids before tocilizumab and Cimzia® as can cause hyperlipidaemia
- check current APPT status if on heparin anti-coagulants and ensure this is recorded
- pre-treatment blood pressure check is advised
- suspected malignancy should be investigated.

### TB/TB screening

There is evidence from the BSRBR (Dixon et al., 2010a&b) to suggest that the rate of TB in patients with RA treated with anti-TNF $\alpha$  therapy was three-to-four fold higher in patients receiving infliximab and adalimumab than those receiving etanercept. A study by Burmester et al., (2012) has found that the use of appropriate pre-treatment screening and prophylaxis for latent TB resulted in a significant reduction in the risk of active TB in adalimumab clinical trials.

However, even though only some biologics have been identified to increase both the risk of and reactivation of TB, it is recommended (all SPCs; BTS, 2005; BSR/ BHPR, 2010) that all patients are screened for TB prior to the commencement of biologic therapy.

TB screening should include:

- the establishment of a patient's TB history/contact/ previous treatment
- clinical examination and a chest x-ray and if appropriate
- TB testing (for example, Quantiferon or T-spot) in all patients (local recommendations may apply)
- results should be recorded in the patient's medical record and alert card.

Prescribers are reminded of the risk of false negative tuberculin skin and Interferon-gamma TB blood test results, especially in patients who are severely ill or immune compromised.

Any patient with an abnormal chest x-ray or previous history of TB should be referred for assessment by a specialist with an interest in TB, as any patient with evidence of active or potential latent TB or at high risk of TB should be treated with standard anti-mycobacterial therapy (supervised by an appropriate specialist) before biologic therapy is initiated. (BTS, 2005; Butler, 2008 – updated 2012; NICE (CG117) 2011; RCN, 2012).

### 11.3 Vaccinations

The following section is designed as a resource to support the practitioner in providing vaccination advice to the patient or carer – or a health professional providing vaccination (such as the practice nurse). It is not intended to support the provision of vaccination itself, as this is outside the remit of rheumatology services.

Practitioners should identify the patient's immune status whilst planning their care pathway. This will mean patients are adequately prepared before starting treatment and do not have to wait to start biologic therapies (Saag et al., 2008)

Unless contraindicated, it is recommended that all patients requiring biologic therapy be up-to-date with all clinically indicated vaccinations such as:

- influenza and pneumococcal immunisation
- varicella zoster (VZ) (check or agree a local policy as children in the UK are not routinely given VZ vaccine, and adults are only vaccinated for shingles)
- hepatitis B
- measles, mumps and rubella (MMR).



Note: you should check when it is effective and safe to start treatment (the period of time that should elapse between vaccine administration and first treatment) but on the understanding that this should not result in significant delay in starting such treatment, as this would be contrary to the ‘treatment-to-target model’ (Harpaz et al., 2008; Saag et al., 2008; BSR, 2011, Butler, 2008 - reviewed 2012; Nisar and Oster, 2013, Galloway et al., 2013; SPCs)

### Live vaccines

Live vaccines should not be given to immunocompromised patients or concurrently with biologics therapies (EULAR, 2012 – Chap 10 pp. 223-253; BSR, 2013; WG, 2013; SPCs) without first seeking the appropriate specialist practitioner’s advice. There is no contraindication for the administration of live vaccines to relatives or friends of patients having biologic therapies. Individuals who are changing the nappies of young children who have just received the MMR vaccine should be advised to wear gloves. Handlers of pets who have received live vaccines should also wear gloves.

Please refer to [The Green Book](#) for the latest information on vaccines and vaccination procedures.

Immunocompromised status:

- receiving systemic high dose steroids (>40mg/day) for more than one week
- treated with a combination of DMARD’s including azathioprine, ciclosporin, MTX, cyclophosphamide, leflunomide and biologics (consider long half-life of leflunomide) until at least six months after treatment stops.

For more information, see the ‘Shingles (Zostavax®) vaccination’ section of this document.

If a vaccination is indicated before treatment starts this should be given four weeks prior to commencing treatment, as response after starting treatment is thought to be poor (Butler, 2008 – reviewed 2012; Harpaz et al., 2008 – ACIP in Nisar & Oster, 2013).

See [Appendix 4](#) for a list of live vaccines currently available in the UK.

If vaccination is required with a live preparation, the determination of the appropriate time elapsed from discontinuing a biologic drug before a live vaccine can be given is drug specific and is based on at least three cycles of the drug treatment half-life (see Table 2). This time frame ensures that the drug has effectively cleared from the body. The half-life of drugs are documented in the SPC (DH, 2006 – chapter updated 2013). Further advice can be sought from a pharmacist, local medicines information unit and separate section on half-life and elimination.

**Table 2. Elapsed time before giving live vaccines after treatment**

Abatacept	3 months
Adalimumab	3 months
Etanercept	4 weeks
Infliximab	6 months
Rituximab	Not whilst on treatment or whilst peripheral b-cells are depleted
Tocilizumab	Not whilst on treatment
Golimumab	Not whilst on treatment
Certolizumab pegol	Not whilst on treatment

### Varicella zoster immune status/vaccination

Checking varicella immune/herpes zoster status has been identified as an important aspect of patient care, especially in those who have autoimmune inflammatory disease and require immunosuppressant medication. This group of patients are at greater risk of infection and/or reactivation of latent disease/shingles (Butler, 2008 – reviewed 2012; McCarthy et al., 2011; DH, 2006 – Chapter 34, updated 2013; Galloway et al., 2013; RCN, 2013) fatal varicella in patients on immune-suppressive therapies, (McCarthy et al., 2011).

If varicella (chicken pox or shingles) history or antibody status is unknown or uncertain, varicella zoster (varicella zoster IgG (VZIG)) blood test screening is recommended prior to vaccination and if clinically indicated, at least two weeks (preferably four weeks) before the commencement of biologic therapy (McCarthy et al., 2011; DH, 2006 –chapter 34, updated 2012; RCN, 2013; Harpaz et al., 2008; BSR, 2011; Galloway et al., BSRBR, 2011).

VZ vaccination of all RA patients prior to starting biologic therapy is not thought to be indicated (Nisar & Oster, 2013).

As live vaccines are contraindicated in immunocompromised patients, varicella zoster immunoglobulin (VZIG) can be given instead, if such patients have:

- had significant exposure to chicken pox or herpes zoster
- a condition that increases the risk of severe varicella (including immunosuppressed patients)
- lack of antibodies to VZ virus
- exposure that warrants evaluation of status.

Please see section 1.1.6 **Safety monitoring** of this document for more information on varicella treatment.

In September 2013, the DH and BSR published reports relating to the immunisation against shingles in people with inflammatory rheumatic disease, informing practitioners of an immunisation programme against shingles (herpes zoster) for older adults (using a live vaccine named Zostavax®) under which the vaccine is to be offered to adults aged 70, with an additional catch up programme for 79 year olds in 2013. The vaccine is authorised for use in patients over the age of 50, but the targeting of people over 70 is felt to be the most cost-effective way of using this vaccine.

Zostavax® is a live vaccine, and caution needs to be exercised in the use of any live vaccines in people who may be immunosuppressed. In general, live vaccines are contra-indicated in patients on potent immunosuppressants – such as cyclophosphamide and biologic therapies (BSR, 2013).

The DH (2013) guidelines for the use of Zostavax® state:

“Therapy with low-doses of MTX (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6 mercaptopurine (<1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are not considered sufficiently immunosuppressive and are **not contra-indications** for administration of zoster vaccine.”

While the guidelines do not clarify the situation for individuals on more than one immune suppressive treatment, we have assumed this equates to more intensive immuno-suppression.

‘Low-dose’ corticosteroids are also **not a contra-indication** (‘low-dose’ is not defined, but doses of prednisolone 10mg daily or less in an adult would usually be considered to be low dose and a dose of 7.5mg is considered to be physiologically equivalent. See SPC for details).

Most rheumatology teams will be aware that the use of biologic therapies and other powerful immunosuppressants is not always documented appropriately in primary care medical records – since these drugs are invariably prescribed in secondary care.

The rheumatological community therefore need to be aware that Zostavax® may be offered by GPs to patients on biologic therapies and other potent immunosuppressants. It is therefore appropriate to warn patients aged 70 and over (and/or their GPs) on biologic therapies and other potent immunosuppressants that they should not receive zostavax. If there is doubt about the balance between the risk of shingles and the risk of immunisation then advice should be sought from an appropriate specialist (such as an immunologist or infectious diseases physician).

### Inactivated vaccines

Although influenza and pneumococcal vaccines do not offer complete protection (70-80 per cent influenza and 50-70 per cent pneumococcal) these should be offered to all patients receiving immunosuppressant therapy. Pneumococcal vaccine should preferably be given before starting therapy, but if not it should be repeated at five-yearly intervals (rather than 10).

Non-live vaccines may be given to patients receiving biologics. However, the immunological response may be inadequate and a repeat dose should be considered at three months if the response titre is low.

Patients should receive influenza vaccination four to six weeks before rituximab treatment and annually (before

rituximab re-treatment if possible) at a time when B cells are likely to be returning. In order to increase the chance of developing protective antibody titres, it has also been suggested that pneumococcal immunisation should be considered before starting MTX in combination with adalimumab.

Hepatitis B vaccination has very few contra-indications to administration. In the adult population 10-15 per cent fails to respond to three doses of vaccine. Immunocompromised patients may achieve only a suboptimal response to immunisation. Refer to immunisation guidance from the Department of Health or seek local specialist advice if required (DH, 2006). See [Appendix 5](#) for a list of non-live vaccines currently available in the UK.

### Pregnancy exposure and infant vaccination

There is limited evidence regarding live vaccination of infants exposed to biologic therapy agents in the womb. Table 3 outlines the guidance in the SPCs where this exists. Where there is no guidance each situation should be considered individually. The administration of live vaccines before these time periods should only be considered where benefits outweigh the risks. Always follow local guidance. Close liaison with the patients (and infants) GP is essential and the relevant risks to the infant highlighted.

**Table 3. Time elapsed before giving live vaccines to infants exposed to biologic therapy in utero**

Abatacept	No guidance
Adalimumab	5 months
Etanercept	16 weeks
Infliximab	6 months
Rituximab	No guidance
Tocilizumab	No guidance
Golimumab	6 months
Certolizumab pegol	Minimum 5 months

For more detailed information on immunisation and contra-indications refer to the Department of Health [The Green Book website](#) and the SPCs.

### 1.1.4 Patient advice

Patients and their carers need adequate resources to enable them to learn about the nature of their condition, treatment options, benefits and risks of treatment, and likelihood of those risks and benefits.

They need to understand the NICE eligibility, screening and monitoring requirements for biologic therapy, the choices they can make in relation to the preferred route of drug administration and the personal implications of this choice.

A major concern with biologic therapy is the risk of infection. Patients on any biologic should be advised to avoid exposure to potential risk factors for infection, given information on the signs and symptoms of infection to watch for, and advised:

- to report symptoms promptly to their GP, so that advice can be given
- STOP any biologic agent if in any doubt (until specialist advice has been obtained)
- complete antibiotics (if prescribed) and
- NOT to restart biologic therapy until appropriately reassessed by the GP and/or specialist practitioner team.

As the reactivation of TB is a particular concern with anti TNF, patients must report any TB warning signs – such as persistent productive cough, haemoptysis, weight loss or fever.

Other considerations.

- All patients and parent/caregivers should be advised to promptly report any development of any new or worsening symptoms – such as neurological, cardiac, pulmonary, skin, uveitis disorders/ symptoms and/or malignancies to their medical and/or specialist practitioner for advice and to stop any biologic treatment until their symptoms have been appropriately evaluated.
- All patients and parents/caregivers should be informed of the signs and symptoms of blood dyscrasias (persistent fever, bruising, bleeding,

pallor whilst on the treatment) and advised to seek immediate medical and/or specialist practitioner advice and STOP any biologic therapy until their symptoms have been appropriately evaluated and treated.

- Prior to surgery patients should be advised about the length of time their biologic therapy should be stopped pre-operatively (see following section) and that they should contact their specialist practitioner regarding the recommencement date of biologic therapy post operatively.
- Carry a Patient Alert Card and show it to health professionals before any new treatment or intervention (Arthritis Research UK also provides a free Biological therapy alert card which patients can order at [www.arthritisresearchuk.org](http://www.arthritisresearchuk.org)).
- Patients on rituximab must be given an alert card with each infusion, which includes information about the very rare but serious complication of progressive multi-focal leucoencephalopathy (PML). PML has also been identified with other immunosuppressive treatments, such as abatacept and leflunomide.
- Patients with diabetes should be warned of the possibility of hypoglycaemia with etanercept.
- It is recommended that patients are advised to ensure they are up-to-date with all appropriate (inactivated) vaccinations, for example, pneumococcal vaccination, hepatitis B.
- Patients should be advised NOT to receive any LIVE (attenuated) vaccines concurrently with biologic therapies and to seek the appropriate specialist practitioner advice.
- If live vaccines are required these should be administered at least four weeks prior to commencing any biologic therapy.
- Contraception advice (as appropriate) should be provided to both male and female patients and precaution against pregnancy should be advised.

- Patients should also be encouraged to inform their GP of the commencement of any biologic therapy.

Appendix 6 contains a sample information sheet for patients or carers administering injections of biologic therapies at home.

### Travel advice

Primary care teams are usually responsible for giving vaccinations and specific advice. As prescribers and rheumatology specialists we have a duty of care to ensure relevant specific advice is available, usually under shared care arrangements. The following general advice should be given and patients should be advised to discuss fully with the person providing vaccination.

- All non-live vaccines should be given as appropriate.
- The parenteral typhoid vaccine offers only 70-80 per cent protection, so personal, food and water hygiene must be emphasised to travellers in endemic areas.
- Immunisation with the oral cholera vaccine (Dukoral®) does not provide complete protection. Scrupulous attention to food, water, and personal hygiene is essential when travelling to areas where cholera exists.
- Yellow fever vaccine is contra-indicated making travel to endemic areas, including tropical Africa and South America inadvisable. A certificate saying yellow fever vaccine cannot be given on medical grounds may be acceptable to some immigration authorities in special circumstances.
- Malaria prophylaxis is essential when travelling to countries where there is a risk of developing malaria. Prophylaxis is not absolute and personal protection against being bitten is very important. Patients taking hydroxychloroquine alongside their biologic therapy should not take chloroquine as part of their malaria prophylaxis regime.



Patient and carer fact sheets and booklets can be found at many websites, including:

[www.arthritis.org.uk](http://www.arthritis.org.uk) (includes information in different languages)

[www.nras.org.uk](http://www.nras.org.uk) (RA specific information on biologics including 'the story so far' published in April 2014)

[www.arthritisresearchuk.org](http://www.arthritisresearchuk.org) (a broad range of condition specific leaflets).

- 'patient global' visual analogue scale (PG-VAS) (Van der Heijde et al., 1992).

Treatment should be monitored, with assessment of DAS-28, at least every six months (BSR/BHPR, 2010; NICE CG79, 2013).

For further information on carrying out the DAS28 score, the National Rheumatoid Arthritis Society (NRAS) has produced a DAS28 quick reference guide for health professionals, which is available at [www.nras.org.uk](http://www.nras.org.uk).

An adequate response is defined as an improvement in DAS of  $\geq 1.2$  points – 'moderate or good response'.

Treatment should be withdrawn if an adequate response (as defined above), is not achieved or maintained. Note: exceptions for withdrawal may be made in certain circumstances – such as patients experiencing a reduction in disease activity but chronic pain inflating DAS, or those being treated for ocular diseases.

An alternative anti-TNF $\alpha$  may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.

See NICE TA130, TA186, TA195, TA225, TA247 and TA280 for more information. Please also see section [1.1.5 Other outcome measures in PART ONE](#) of this document.

### 1.1.5 Monitoring efficacy

Patients on biologic therapies should be monitored (routine blood tests and outcome measures) initially every three months to evaluate their response to treatment. Please refer to the NICE TA guidance documents (as mentioned above).

Patients on monotherapy (not taking an additional DMARD) should then be monitored every six months.

Appropriate monitoring data should be submitted to the BSRBR for patients who have consented and been registered. This monitoring for efficacy should be reviewed in conjunction with safety monitoring and patient support. The following section outlines response criteria.

#### Rheumatoid arthritis

NICE recommend that biologic therapy should be continued only if there is an adequate response six months after initiation of therapy and if an adequate response is maintained.

DAS-28 is a key outcome measure to evaluate the response to therapies and is commonly used in clinical trials and treat-to-target strategies.

It is a composite index of four process variables:

- 28 tender joint count
- 28 swollen joint count
- a measure of inflammatory arthritis the consistent usage of either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)

#### Psoriatic arthritis

Assessing the outcomes of the effectiveness of treatments for psoriatic arthritis are based on measures of the anti-inflammatory response and relies on outcome measures that accurately and sensitively measure disease activity.

Biologic therapy response criteria for PsA assessment (used in line with NICE) include the Psoriatic Arthritis Response Criteria (PsARC). This is the key disease activity measure of response to biologic therapy for patients with psoriatic arthritis.

An adequate response to treatment has been defined as

an improvement in at least two of the four PsARC criteria (one of which has to be a joint tenderness or swelling score) with no worsening in any of the four criteria.

The four PsARC criteria are:

1. patient global self-assessment (0-5 Likert scale)
2. physician global assessment (0-5 Likert scale)
3. 68 Tender joint count
4. 66 Swollen joint count.

The improvement criteria are:

- 0-5 Likert scale = a decrease of 1 category; or 20 per cent or greater improvement in patient assessment of disease activity
- 0-5 Likert scale = a decrease of 1 category; or 20 per cent or greater improvement in physician global assessment of disease
- 30 per cent or greater improvement in tenderness
- 30 per cent or greater in swollen joint count.

NICE recommend that treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response, using PsARC, at 12 weeks. However, NICE states that people whose skin disease has a PASI 75 response at 12 weeks, but whose PsARC response does not justify continuation of treatment, should be assessed by a dermatologist to determine whether continuation of treatment is appropriate, on the basis of the skin response alone.

For more information see NICE TA199 and TA 220; BSR (2012) and SIGN's *Guidelines for the treatment of psoriatic arthritis with biologics* (SIGN, 2010); Please also see section [1.1.5 Other outcome measures in PART ONE](#) of this document.

## Ankylosing spondylitis

Response criteria to biologic therapies for patients with AS response includes:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- spinal pain VAS (0-10).

BASDAI measures the extent of five domains: fatigue, spinal pain, joint pain or swelling, areas of localised tenderness (enthesitis) and morning stiffness of spine.

An adequate initial response to biologic therapy defined as:

- a reduction of BASDAI to 50 per cent of the pre-treatment value or by  $\geq 2$ ,

AND

- reduction in spinal pain VAS by  $\geq 2$ cm.

Response to be first measured at 12 weeks and then at 12 weekly intervals. If an adequate response to treatment is achieved and treatment is tolerated, patients should continue on treatment. If the response to treatment (as defined above) is not maintained, a repeat assessment should be made after a further six weeks. If, at this six-week assessment, the above response has not been achieved or maintained, treatment should be discontinued.

Alternative anti-TNF $\alpha$  is not recommended in patients who have either NOT:

- achieved an 'adequate initial response' to treatment

OR

- who experience loss of efficacy of the initially adequate response during treatment.

However, for patients who have been shown to be intolerant of one particular biologic therapy, before the end of the 12-week initial assessment period, an alternative anti-TNF $\alpha$  treatment is recommended (note: this is currently under a NICE MTA review as there is increasing evidence to suggest that switching can be effective). Please also see section [1.1.5 Other outcome measures in PART ONE](#) of this document.



## Other outcome measures

Additional functional and quality of life measures are helpful in measuring responses that are important to patients, and can provide important self-monitoring information. There are far too many to include in this document, however the most commonly used include:

- the Health Assessment Questionnaire (HAQ); an annual review is recommended by NICE (NICE CG79, 2009 – updated 2013; NICE QS33, 2013)
- the Short Form (36) health survey (SF-36); a patient-reported 26 item questionnaire which measures quality of life
- EQ5D.

Relevant to psoriatic arthritis:

- Psoriatic Arthropathy Quality of Life Index (PsARCQOL)
- Total Sharp Score – radiological (x-ray) assessments of disease progression
- Psoriasis Area Severity Index (PASI) – a tool for the measurement of psoriatic skin lesions.
- Dermatology Life Quality index (DLQI).

Other assessments used in ankylosing spondylitis can include:

- Bath Ankylosing Spondylitis Functional Index (BASFI) – measures the impact of AS on ability to perform everyday tasks
- Bath Ankylosing Spondylitis Global wellbeing (BAS-G) – assesses the effect of AS on health over the last week and previous six months
- Bath Ankylosing Spondylitis Metrology Index (BASMI) – measures the impact of AS on spinal mobility and physical ability (NICE, 2008; NASS, 2013).

## 1.1.6 Safety monitoring

A safety monitoring summary can be found at [Appendix 8](#) of this document.

### Infection

Patients should be assessed before each infusion (or self-assess before each injection) for evidence of infection. The early recognition of atypical presentations of serious infections or rare and unusual infections is critical in order to minimise delays in diagnosis and treatment. Vigilance is needed before, during and after treatment (please see the patient education section of this document for further information).

Practitioners should also have a high index of suspicion for atypical and opportunistic infections. Biologic therapy should be promptly stopped in suspected cases. Patients should have rapid access to specialist care for consideration of early anti-bacterial/anti-fungal/anti-viral treatment.

### Varicella/shingles

Patients on biologic therapy have a higher rate of varicella zoster (VZV) reactivation due to both the immunosuppressive activity of biologic therapy and if taking additional MTX or steroids (Galloway et al., 2010). If VZV is reactivated, the risk of disseminated infection is higher – this includes systemic infection such as pneumonia or encephalitis. Immunity should be checked, even if previously documented as 'immune', as biologic therapy may adversely affect the patient's immunity status.

It is important to be aware of the incubation period of varicella/shingles (VZV) infection. If a person has been in contact with an infectious source and goes on to develop symptoms of infection themselves, these are likely to develop between 7–21 days after exposure.

### Definition of VZV contact

Contact is defined as being in the same room as someone with VZV for at least 15 minutes or a face-to-face contact – for example, having a conversation. This particularly applies if the source has:

- chickenpox of any distribution (exposure to chickenpox is of greater clinical significance than shingles)

OR

- shingles with facial nerve involvement (uncovered lesions)

OR

- disseminated shingles (> 1 dermatome involved)

OR

- if the source is also immunosuppressed.

Source: *The Green Book* (DH)

Chickenpox infectivity is approximately up to eight days. Sources with chickenpox excrete plentiful amounts of virus from the nasopharynx from two days before the appearance of the rash, and then in these cutaneous vesicles until all the lesions have crusted over.

Sources with shingles do not excrete significant amounts of vaporised virus from the nasopharynx if not immunocompromised. Infectivity period is approximately seven days from the time the rash appears until all lesions are crusted over and no new lesions appearing. If skin lesions are also covered then the infectivity risk is minimal. However, exposure should be taken into clinical consideration.

Note: if the source is also immunosuppressed then the infectivity period may vary. Shingles pain in the dermatomal distribution of affected nerve precedes fever and malaise by a few days.

### Varicella treatment

If a patient taking biologic therapy is exposed to a household contact who develops primary varicella (chickenpox) and if the risks from infection are

perceived to be significant, the patient should be considered for varicella zoster immunoglobulin (VZIG) under guidance from a microbiologist.

VZIG can be given up to 10 days post exposure, but is most effective within seven days. If the exposed patient has a firm past history of chickenpox or shingles, administration of VZIG can be delayed up to 10 days whilst awaiting the immune status result for chickenpox or shingles; if positive, VZIG is not indicated.

If, however, there is no or an unclear history, VZIG should be issued within seven days if no immune result is available (DH, 2006 – Chapter updated 2012).

Active varicella infection should promptly receive initial treatment with intravenous acyclovir 10mg/kg iv tds and be further guided by liaison with microbiology.

A break in the biologic therapy treatment should allow 21 days of potential incubation period from the last date of exposure.

Varicella zoster immunoglobulin dose (for adults) is 1g via intramuscular injection. If the patient is unable to receive intramuscular injection (for example, if the patient is on warfarin) then discuss with pharmacy, as normal immunoglobulin can be given by intravenous administration.

If a second exposure occurs more than three weeks after the first dose of VZIG then a repeat dose should be given. Arrange retesting of immune status to check for asymptomatic sero conversion under prior VZIG cover.

If naïve to varicella zoster then 50 per cent may develop chicken pox despite VZIG; infection may be subclinical in 15 per cent of cases. Patient should be monitored for clinical signs of active infection, and caution should be exercised over contacts during the potential infectivity period.

For more detailed information on immunisation and contra-indications refer to the Department of Health [The Green Book website](#)

## Tuberculosis (TB)

Whilst appropriate pre-treatment screening for latent TB results in a significant reduction in the risk of active TB (Burmester, 2012), it has been recommended that for patients on anti TNF therapy a chest x-ray should be undertaken after three months of treatment and thereafter annually, and that patient reported symptoms of TB should be sought at each follow-up.

If a patient develops a productive cough or haemoptysis, or experiences weight loss, advice should be sought from a TB specialist. Treatment with full anti-mycobacterial chemotherapy is advised and treatment with anti TNF can continue if clinically indicated. Monitoring for signs of TB should also continue for six months after stopping treatment.

## Progressive multifocal leukoencephalopathy (PML)

The JC (John Cunningham) virus infection, which results in PML and death, can occur in rituximab treated patients with auto immune diseases. PML is a rare and fatal demyelinating illness with no known treatment. It has also been identified with other immunosuppressive treatments, such as abatacept and leflunomide.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations such as mental state changes, weakness, loss of motor co-ordination, speech or vision changes; patients and practitioners need to be vigilant.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue rituximab (or any other biologic) and consider the reduction of any concomitant immunosuppressive therapy in patients who develop PML (EULAR, 2012; SPCs).

## Blood dyscrasias

This is a rare event in patients on a combination of DMARD and biologic therapies. However, practitioners should ensure that patients are encouraged to report signs suggestive of blood dyscrasias, for example, bruising, bleeding, mouth ulcers, shortness of breath

and persistent fever and ensure that vigilance is applied during routine monitoring.

For patients who also receive methotrexate or sulphasalazine follow local requirements for monitoring. This is usually carried out under shared care arrangements which follow DMARD monitoring guidelines and may differ locally.

Refer to SPCs and the BSRBHPR monitoring guidelines (BSR, 2008) for more information.

## Pulmonary disease/interstitial lung disease (ILD)

There has been a reported increased incidence of ILD; for RA patients, ILD can be severe and life-threatening regardless of the treatment received. However, more data is required before any firm conclusions can be drawn on the risks specifically linked to anti-TNF $\alpha$  therapies. Monitoring for lung function changes are important particularly if pre-existing respiratory problems exist (Ramos-Casals et al., 2007; Dixon et al., 2007; BSR/BHPR, 2010).

## Human anti-chimeric antibodies and human anti-human antibodies

The chimeric biologics for example, infliximab and rituximab – are capable of inducing human anti-chimeric antibodies (HACA) which can:

- increase the risk of allergic or hypersensitivity reactions and/or
- reduce treatment benefits in therapies, such as infliximab and rituximab, used in RA.

Delayed hypersensitivity reactions have also been reported with infliximab when intervals between treatments are increased. This seems to be reduced when MTX is used in combination with biologics; the efficacy of all biologics also seems to improve.

Antibodies may develop in patients against an injected antibody. Biologic therapies are developed from monoclonal antibodies that have been biologically engineered, using technology that combines either fully human or part human proteins to either an immunoglobulin or a receptor.

A patient may, as a result, develop antibodies to the therapy based upon whether the components are made up of human anti-human antibodies (HAHA) or human anti-chimeric antibodies (HACA).

### **Uveitis**

There have been several case reports of uveitis developing in patients treated with anti-TNF $\alpha$  therapy, despite the fact that anti-TNF $\alpha$  has also been reported to successfully treat patients with resistant uveitis.

Most reports of successful treatment of resistant uveitis have been with infliximab (Saurenmann et al., 2006; Tynjala et al., 2007; Braun et al., 2005; Galor et al., 2006 – in BSR/BHPR, 2010).

Most cases of anti-TNF $\alpha$  therapy-associated uveitis have been reported with etanercept (Taban et al., 2006; Wang & Wang, 2009 – in BSR/BHPR 2010).

### **Pregnancy and conception issues**

Patients (of both sexes) and women of child-bearing age should be advised to use appropriate contraception to avoid becoming pregnant and not to breast feed during therapy or for specific time periods following therapy depending on the biologic therapy as follows:

Abatacept	14 weeks
Adalimumab	5 months
Etanercept	3 weeks
Infliximab	6 months
Rituximab	12 months
Tocilizumab	3 months
Golimumab	6 months
Certolizumab	5 months

See SPCs for further information.

Evidence, which assessed the outcomes of 130 pregnancies, concluded that although the results to date had been promising, no firm conclusions could be drawn about the safety of anti-TNF $\alpha$  during pregnancy (Verstappen et al., 2011 – BSRBR). Without further evidence, the guidelines currently in place suggest these drugs should be avoided at the time of conception.

The continuation of anti-TNF $\alpha$  therapy could be considered in patients wishing to conceive/father a child, or if a woman conceives, or if the risks of stopping treatment are perceived to be high. Therefore each case should follow a shared decision making process between the patient and the prescriber where the risk of no treatment or stopping treatment is balanced against the risk of continuing.

The pros and cons of breastfeeding in patients treated with anti-TNF $\alpha$  therapies should be considered on an individual basis, as there is limited evidence on excretion in breast (BSR/BHPR, 2010).

## **1.1.7 Allergic, hypersensitivity and infusion reactions**

Injection site reactions to subcutaneous injections are usually mild and resolve without treatment. Reports of injection site reactions (the most common adverse events reported are bleeding, bruising, erythema, itching, pain and swelling) range from between 6-25 per cent of patients receiving subcutaneous biologic injections.

Common sense suggests that if a patient has any injection site reaction a review of the patients technique is necessary, as poor technique is likely to contribute to this, but there is no research on this topic currently available.

Allergic reactions have been reported to include pruritus, although some serious anaphylactic reactions have also been reported with adalimumab and golimumab (see SPCs for further details).

### **Infusion reactions**

Serious hypersensitivity reactions have been reported in association with:

- tocilizumab — hypersensitivity reactions were generally observed during the second to fifth infusions of tocilizumab. It is reported (see SPC) that such reactions may be more severe, and potentially fatal, in patients who have experienced hypersensitivity reactions during previous infusions even if they have received premedication

with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with tocilizumab. Treatment should be stopped immediately should an anaphylactic/other serious hypersensitivity/serious infusion reaction occur (please see SPC for further details)

- infliximab – acute infusion reactions, including anaphylactic shock and delayed hypersensitivity reactions, have been reported (see SPC). Should this occur the treatment should be stopped immediately and emergency treatment given
- rituximab – is associated with infusion related reactions (IRR). The reactions reported were usually reversible with a reduction in rate, or interruption of rituximab infusion and administration of an anti-pyretic, an antihistamine and occasionally oxygen, IV saline or bronchodilators and glucocorticoids if required. Premedication of an analgesic/antipyretic drug and an antihistamine drug should always be administered before each infusion of rituximab.

### 1.1.8 Hepatitis B and C

The reactivation of hepatitis B and worsening hepatitis C have been reported with virtually all of the biologic therapies (excluding abatacept). Close monitoring of signs and symptoms and of liver function tests should be undertaken for patients receiving biologic therapy (always refer to the SPC).

Screening for hepatitis B and C is recommended in all patients. For those patients who test positive for hepatitis B, consultation with a physician with expertise in the treatment of hepatitis B is required.

However, the BSR/BHPR (2010) also states that a risk/benefit assessment should be undertaken for patients who are hepatitis B positive, as treatment may be safe if appropriate anti-viral treatment is given.

It is recommended that hepatitis serology should be monitored in patients with evidence of past or current B or C infection (BSR/BHPR, 2010).

Recurrence or infection should be reported via the Yellow Card scheme, see [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

### 1.1.9 Malignancy

There is no evidence of increased risk of solid tumours or lymphoproliferative disease for people on biologic therapies, above those expected in the rheumatic arthritis population. There is, however, evidence to suggest that there is an increased risk of some skin cancers such as melanoma with anti-TNF $\alpha$  therapy; consequently, on-going vigilance is required. Preventative skin care and skin surveillance is also recommended (BSR/BHPR, 2010).

New research also suggests that biological therapies do not increase the risk of recurrent cancer compared to conventional disease modifying anti-rheumatic drugs in RA (DMARDs) (BSRBR RA, 2014).

If malignancy occurs while a patient is taking biologic therapies, it may be necessary to stop treatment. This should be discussed with the prescriber and the risks/benefits as these relate to the individual should be taken into account (BSR, 2010).

Note: the advice regarding adverse events for patients taking biologic therapies with psoriatic arthritis is inconclusive. While there is evidence regarding adverse events data from etanercept, adalimumab and infliximab for serious infections, cancer, activation of latent tuberculosis, mortality and withdrawals, the evidence is primarily from people with rheumatoid arthritis or other indications (NICE TA199). There are no studies looking at outcomes from patients with primary malignant disease from precancerous conditions but these should be monitored during treatment, including any skin changes (BSR/BHPR, 2010).



### 1.1.10 Biologics and surgery

The biological half-life of a substance is the time it takes for a substance to lose half its pharmacologic activity. The long half-life of some of the biologic therapies – such as adalimumab, certolizumab pegol, golimumab, infliximab, tocilizumab and rituximab – need to be taken into account if a surgical procedure is planned because of the increased risk of infection.

The half-life of the drug is documented in the respective SPC and the clearance is estimated by multiplying this by five; the washout periods stated in Table 4 reflect this calculation and the frequency of dosing for each agent.

Elimination (washout period) for all biologic therapies = half ( $\frac{1}{2}$ ) life of treatment x 5 times. For example:

- etanercept half-life = three days; therefore the approximate elimination period of treatment = 15 days
- infliximab half-life = 8-9.5 days; therefore the approximate elimination period of treatment = 40-47.5 days (but elimination may take up to six months).

In practice most units recommend a two week gap prior to planned surgery except for infliximab which tends to be continued but with surgery timed for the half-way point between infusions – i.e. around four weeks. In view of the lack of current evidence local guidelines should be followed and planned surgery should always be discussed with the prescriber.

Patients requiring any planned surgery should be advised to stop biologic therapy prior to surgery (as above) and advised not to restart the treatment until all of the following criteria are met:

- antibiotics (if required) have been completed and the wound is not infected
- appropriate clinical advice has been sought from the patient's specialist team.

If emergency surgery is required patients or their carers should be advised to:

- stop biologic therapy immediately
- inform all respective practitioners of the fact they have been on biologic therapy
- show them (if possible) their supplied patient alert card.



**Table 4. Biologic therapy washout and half-life information/calculation\***

Name	Usual dosing interval	Suggested period to stop before surgery	Half life Taken from SPC (available at <a href="http://www.medicines.org.uk">www.medicines.org.uk</a> )	Washout period (5 x half-life)
Etanercept (Enbrel®) SC	25mg dose twice weekly 50mg dose once weekly	2 weeks	3 days	15 days
Adalimumab (Humira®) SC	Fortnightly	70 days (2½ months)	14 days	70 days
Certolizumab pegol (Cimzia®) SC	Fortnightly	70 days (2½ months)	14 days	70 days
Golimumab (Simponi®) SC	Once a month	70 days (2½ months)	9-15 days	45-75 days
Infliximab (Remicade®) IV	Every 4-8 weeks	42 days (1½ months)	8-9.5 days	40-47.5 days
Abatacept (Orencia®) IV	Every 4 weeks	70 days (2½ months)	Half-life = 14.3 days (Range = 8-25 days)	Range 40-125 days Mean 71.5 days
Abatacept (Orencia®) SC	Weekly			
Rituximab (MabThera®) IV	2 doses at fortnightly interval then repeated if necessary every 6-12 months	98 days (3½ months)	Half-life = 20.8 days (Range = 8.58 -35.9 days)	Range 42.9-197.5 days Mean 104 days
Tocilizumab (RoActemra®) IV and SC	Every 4 weeks (IV) Weekly (SC)	56 days (2 months)	8-14 days	40-70 days

\*For the most up-to-date information you should always refer to the full SPC of an individual drug – see [www.medicines.org.uk](http://www.medicines.org.uk)

### 1.1.11 Switching between biologic therapies

Approximately one-third of patients do not respond to the first TNF inhibitor (primary failure) and a significant percentage will also lose efficacy later on during therapy (secondary failure). For both subgroups different treatment options are available, including switching to an alternative TNF inhibitor or changing to an agent with a different mechanism of action. The case for switching to another anti TNF agent can be argued based on their different half-lives and affinities, which might be translated into a different duration of TNF neutralisation and responses at an individual level (EULAR, 2012). However, NICE place restrictions on switching between anti-TNF $\alpha$  therapies (see NICE algorithms).

For example, if rituximab is to be commenced, some units consider a treatment break or 'wash out' period when changing from TNF inhibitors, before starting rituximab. There is no specific guidance on this issue, although rituximab research studies do specify discontinuation of TNF inhibitors before commencing rituximab treatment; in other words, etanercept should be stopped four weeks prior to commencement of rituximab, while both adalimumab and infliximab should be stopped eight weeks prior to the commencement of rituximab (Smolen et al., 2007; BSR/BHPR, 2010).

There is evidence that overlapping therapies, without considering half-life, further increases the risk of infection and adverse effects (golimumab, infliximab), and so care should be taken when switching between biologics. Rescreening, including for infection, between biologics when switching is common practice and local guidelines should be followed.

Individual risks and benefits must be taken into account and discussed clearly with patients

See the NICE treatment algorithm at [www.nice.org](http://www.nice.org) and refer to SPCs, and BSR/BHPR (2011).

## Section 2: Administration of subcutaneous and intravenous biologic therapies

### 2.1 Subcutaneous biologic therapies

This section outlines considerations for the biologic therapies currently administered subcutaneously:

- etanercept
- certolizumab pegol
- adalimumab
- golimumab
- abatacept
- tocilizumab.

This guidance is general only. For additional detail please refer to the SPC, discuss with the medical information department of the manufacturer or your pharmacist.

[Table 1 in Section 1](#) of this document outlines the route of administration, dose and indication for biologic therapies for adult patients.

#### 2.1.1 Home administration

Most people who self-administer biologic therapies will often have their drugs delivered by a home care delivery service. The service should be well-integrated into the care pathways and provide high quality assurance of

safety and quality, and also provide evidence of meeting patients' needs.

Documentation and audit should be an integral aspect of developing a service for patients receiving subcutaneous biologic therapy.

Subcutaneous biologic therapies are available in pre-filled syringes and auto injectors/pens ([See Table 1](#)). These can be issued either from a hospital pharmacy, community pharmacy or via home delivery. Most rheumatology services use a home care delivery service and there are several advantages to this approach:

- patient self-efficacy, independence and convenience
- VAT exemption, making it cost effective
- time-saving for rheumatology services, as home care services can train patients to self-inject, arrange regular delivery of their treatment and collect clinical waste.

These arrangements must be supported by a robust governance framework and agreed service specifications, including information governance, medicines management, quality standards, staff competencies and patient support.

Packaging and transport systems should ensure that adequate protection and storage instructions are adhered to during delivery. Comprehensive information regarding storage and pre-injection considerations and training in self-administration is mandatory before starting treatment.

Training patients to self-administer may be carried out in the health care setting by a specialist practitioner, or by a trained nurse employed by a home delivery company. Practitioners should be guided by local policies.

Supporting a patient to inject in their own home can provide a significant degree of independence and is also a cost-effective treatment pathway, avoiding unnecessary hospital attendances and/or the need for direct health care practitioner support.

Patients should be introduced to the product during the

initial assessment for suitability for biologic therapy so that they can make an informed choice of both treatment and administration technique.

Once a patient has been assessed and fulfils the criteria for treatment with subcutaneous biologic therapy, home care registration consent and a prescription should be completed to enable the patient to receive their first treatment to their home.

### Practitioner training and competence

No specialist training is required – all practitioners should be competent in the subcutaneous injection technique. Specific information describing the use of each pen or pre-filled syringe is available from the manufacturer, and provided with the drug on delivery.

However, practitioners should:

- be knowledgeable and competent in all aspects of administration and risk management, and stay up-to-date with the latest evidence in relation to biologic therapy indications contra-indications, dose, administration and side-effects
- have undertaken appropriate training to educate, support and teach patients in the self-administration of biologic therapy
- ensure appropriate communication and support are available for primary health care teams, home delivery services and patients self-administering in their own homes
- be aware of clinical governance and local policies in relation to the management of patients receiving biologic therapies.

### Checklist for practitioners

All practitioners should adhere to the following checklist prior to administering subcutaneous injections to a patient:

- check the dose, dosage, form (syringe or pen) frequency prescribed and expiry date
- ensure blood monitoring is in place and that blood results are satisfactory

- check there are no contra-indications to administration (as per the SPC)
- ensure the patient has consented to have the injection
- ensure the patient knows the advice line telephone number for support or concerns
- document the injection and site used either on patients injection log or chart
- be aware of protocols relating to the safe disposal of sharps including pens
- note the date and time of next injection
- inform the hospital when the first injection has been given, and if there are any concerns.

See [Appendix 8](#) for an example of a standardised assessment and management template for inclusion in a patient record.

### Training for patients

A patient training check list and competency example can be found at [Appendix 9](#).

Practitioners need to be flexible in their training methods, which should be tailored according to the patient/carer learning needs, and after discussion and assessment of their competence in administration techniques. You should agree a training package with the patient/carer. Some patients/carers will require a greater number of practice sessions, and you will need to modify the level of supervision you give before the patient is confident and competent.

In many cases patients with inflammatory joint disease will already be competent in subcutaneous injections as they will have already been self-administering.

In a very small number of adult cases, patients may be unable to self-administer their treatment. In these circumstances, and with the patients consent, a carer can be taught to administer the injection.

The patient and carer should be aware that the home administration is subject to undertaking a training process and an assessment of their ability to manage

home administration (including appropriate refrigeration facilities if necessary).

For home administration to work efficiently, good communication is vital – not only between primary, secondary, tertiary care and pharmacy services, but also with family members or carers.

A back-up plan must be in place to ensure that in the event of a patient being unable to self-administer (for example, due to limited dexterity) or their trained carer being unavailable, they can call on specialist support or a non-specialist rheumatology practitioner's support (for example home care nurse, practice nurse or district nurse).

Patients should be advised that they can elect not to self-administer and can opt out of treatment. However, should they choose this course of action they must inform their health care team promptly, so their records can be appropriately updated, deliveries cancelled, and alternative treatment be arranged in a timely manner.

Following training and risk assessment the patient or carer must:

- be competent and want to proceed with home administration
- demonstrate a clear understanding of their responsibilities in the safe management of the biologic therapy, including waste and sharps disposal
- agree to undertake regular blood monitoring and attend clinic appointments as needed
- agree to a regular review of home administration risk assessment
- agree a back-up plan in the event of being unable to self-administer.

### Rotating injection sites

Patients or carers who self-administer treatment need to ensure that they rotate the injections sites. If giving two injections (such as MTX and a biologic therapy) these should be given in different sites. For example,

one should be given in the right thigh and the second in the left thigh. The injections should be at least 3cm apart, if given in the same limb. If injecting in the abdomen, injections should be in a 5cm radius away from the navel. Refer to the manufacturer's training guide for further information.

It is suggested that the patient should keep a record of injection sites used. For additional information refer to the SPC or BNF/BNFC.

### Product changes

Patients who self-administer must be told about any product change, as this may result in changes to the volume provided in the syringe or pen, storage conditions, expiry date or appearance of the syringes. In addition, they must also be informed of the potential change in administration technique according to the manufacturer's guidelines and be appropriately retrained. These changes may also require changes in prescription details, requiring renewal, therefore transfer to new applications of drugs must be planned carefully in advance to avoid delays in the administration processes and to reduce the risk of gaps and delays in treatment.

There are a number of patient organisations and websites that the patient can access for additional information and support (see [Appendix 13](#)).

### Contra-indications for patient self-administration

- The patient declines treatment/the training programme.
- Are unable to administer the injection because of poor dexterity as indicated in a practical demonstration to the rheumatology nurse, and if they do not elect to have a carer to administer treatment instead
- Show poor concordance with attendance and monitoring
- Are unable to safely store the injections at home or are unable to demonstrate an understanding of the need for safe storage and sharps/waste disposal



- demonstrate a lack of understanding of the safety and self-care requirements.

### Continuing management

On completion of the training programme and when the patient/carer has demonstrated competence in all aspects of administration, you should inform them of the follow-up arrangements.

If a home care company is taking over delivering the treatment, the home care service should be notified and informed of the patient's progress.

The patient must be provided with the necessary equipment by the department or the home care company.

## 2.2 Intravenous biologic therapies

This section outlines considerations for the intravenous administration of the following biologic therapies:

- abatacept
- infliximab
- rituximab
- tocilizumab.

This guidance is general only. For additional detail please refer to the SPC, discuss with the manufacturer's medical information department, or your pharmacist.

[Table 1 in Section 1](#) of this document outlines the route of administration, dose, regime, NICE appraisal and indication for biologic therapies for adult patients. [Section 1](#) also summarises assessment, screening, contra-indications and monitoring information.

Biologic therapies do not require specialist handling precautions as they are not chemotherapy agents and disposal of equipment and unused medication should be in accordance with local requirements.

See current SPC for specific information.

### 2.2.1 Conditions for administration

#### Delivery setting

A patient's care pathway is led by a specialist multi-disciplinary team of nurses, doctors and health care professionals. This team has traditionally been based in a secondary care setting. However, there has been a considerable increase in the development of services provided by specialist teams in a community setting.

Either community or hospital facilities are suitable for the infusion of intravenous biologic therapy. Risk assessment is an essential part of setting up any facility. Protocols for the administration must take into account the risk of adverse reactions; for example, the administration of the first infusions, and in the case of tocilizumab, risk of infusion reactions up to and including the fifth infusion.

Provision will depend on the demand for and availability of day-case facilities taking into account patient needs, such as providing care close to a person's home where possible. Shared infusion clinics across the range of inflammatory conditions where biologic therapies may be used can help improve efficiency (see examples in NICE 2010 commissioning services). The following support should also be available for administration of intravenous infusions:

- a designated rheumatology practitioner should be available for advice
- a pharmacy or home administration service to reconstitute infusions
- appropriate equipment for infusion and resuscitation
- appropriately trained staff.

Current therapies are being developed to provide subcutaneous versions (for example, tocilizumab has been licensed for use in the UK since May 2014 thus reducing the need for infusion services, and increasing convenience for patients).

### Practitioner competence

Practitioners who are going to administer biologic therapies using intravenous routes should:

- be competent in the management of patients receiving injectable medicines and be skilled in the preparation, administration and management of biologic infusions including cannulation
- be competent in resuscitation procedures and have access to basic life support resuscitation equipment
- have written guidance on the management of preparation and administration of biologics, anaphylaxis and infusion reactions according to local policy.

For more information see *Standards for infusion therapy* (RCN, IV therapy, 2010).

### Vial sharing

The National Patient Safety Agency (NPSA) does not support vial sharing (NPSA/2007/20). NICE has not considered or made recommendations relating to vial sharing.

Standards for the preparation and manufacture of injectable medicines within hospital pharmacies are set out in the Department of Health's Executive Letter EL (97)52 and the EU guide on good manufacturing practice (EC, 2010).

Where clinicians undertake vial sharing, a thorough risk assessment must be undertaken and governance processes followed taking full account of licensing, safety and good manufacturing practice.

### Pre-infusion/injection assessment

You must fully assess patients before administering an infusion. As well as the assessment set out in [Section 1](#) of this document, prior to the infusion you should specifically include:

1. Routine questioning of potential infectious contacts (such as chicken pox, TB). If you suspect an infection, consult the patient's prescribing physician. Caution: varicella immunity should be checked if an infection is suspected – see local trust

or BSR guidance. The patient should confirm that they are not aware of any inter-current infections and that they don't have difficulty in breathing or any shortness of breath.

2. Women of child-bearing age should confirm the date of their last period and confirm that they are using an effective method of contraceptive. Consider pregnancy testing if there is any uncertainty. Re-iterate the risks of a patient receiving these therapies if she could be pregnant.
3. Patients should be prescribed appropriate prophylaxis to treat or prevent infusion reactions.
4. Obtain details of the patient's history of atopic diseases such as asthma, eczema, or allergic rhinitis, known allergies or previous infusion reactions and take these seriously. If necessary review them with the prescribing physician.
5. Baseline observations:
  - check there are no contra-indications to treatment, including any contra-indicated medication
  - check any recent blood tests are within satisfactory parameters
  - record baseline temperature, pulse, blood pressure and O<sub>2</sub> saturation levels if indicated
  - urinalysis – request MSU if infection suspected and consider if infusion should be administered.

## 2.2.2 Treating infusion reactions

Anaphylactic reactions have been reported in all of the biologic drugs given by infusion. The frequency of these reactions is described as uncommon or rare. For example when these drugs are used for RA there are fewer than 1 per 1000 infusions for abatacept and infliximab and fewer than 1 per 100 infusions for rituximab and tocilizumab.

However, onset can be rapid and the condition can be life threatening. Should anaphylaxis occur:

- stop the infusion
- administer as prescribed intravenous hydrocortisone, intravenous chlorpheniramine (or other appropriate antihistamine) and/or any other emergency treatment following your local policy on managing anaphylactic reactions
- contact the doctor or designated specialist practitioner as appropriate but emergency treatment should not be delayed
- record any adverse reaction in the patient's record.

Drugs prescribed for use in the event of an infusion-related reaction:

- chlorpheniramine 10 mg IV tds (or other appropriate antihistamine)
- hydrocortisone 100 mg IV tds
- metoclopramide 10mg IV tds
- paracetamol 1g orally qds (maximum 4g in 24 hours).

Refer to your local policy for infusion reaction management.

Signs and symptoms of anaphylaxis:

- airway swelling (throat/tongue/face)
- difficulty breathing
- hoarse voice
- stridor
- wheeze
- becoming tired
- confusion
- pallor, clamminess
- increased pulse
- low BP
- cyanosis (late sign)
- cardiac arrest.

[www.resus.org.uk](http://www.resus.org.uk)

## 2.2.3 Abatacept administration

### Special equipment

A sterile non-pyrogenic, low-protein-binding filter (pore size 0.2µm to <1.2µm) is essential and a silicone-free disposable syringe is provided with the drug which must be used to reconstitute each vial.

### Preparation of infusion

The preparation of the injection must be undertaken according to the SPC of the drug, and administered within the stipulated timeframe that the drug is stable once reconstituted.

Abatacept is supplied in 250mg vials as a dry powder. Each vial is reconstituted under aseptic conditions with 10mls of sterile water for injection using the silicone-free disposable syringe provided with each vial and an 18-21 gauge needle.

Calculate the dose and the number of vials needed. Calculate the total volume of reconstituted solution required. Immediately after reconstitution, the concentrate must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection. The final concentration will be no more than 10 mg/ml. Dose of infusion is 500mg, 750mg or 1000mg (depending on weight) at week 0, 2, 4 then monthly by intravenous infusion. See table below.

Body weight of patient	Dose	Number of vials
< 60 kg	500 mg	2
≥ 60 kg to ≤ 100 kg	750 mg	3
> 100 kg	1,000 mg	4

Avoid shaking during reconstitution.

### Administering the infusion

Abatacept is infused through a low protein binding filter (see equipment) into a peripheral cannula using an IV pump with a primed line (0.9% sodium chloride).

Abatacept should be administered over 30 minutes.

### Clinical observations during infusions

No routine observations during the infusion are required, however in the event that the patient reports feeling unwell, observations should be taken.

Observe for any signs of respiratory deterioration in those with COPD.

Observe for side effects throughout: and take appropriate action.

Acute infusion-related events (ie those that occur within one hour of the infusion) are most commonly headache and nausea ( $\geq 1/10$  patients). Dizziness and hypertension may also occur. Seek medical advice in the case of hypertension.

hours of reconstitution and dilution. When reconstitution and dilution are performed under aseptic conditions, the infusion solution can be used within 24 hours if stored at 2°C to 8°C.

Do not store any unused portion of the infusion solution for reuse.

Avoid shaking during reconstitution.

### Administering the infusion

The first infusion should be administered over two hours and is repeated at week two and week six, and thereafter every eight weeks.

In carefully selected patients who have tolerated the initial two-hour infusion of standard dose infliximab (3mg/kg), subsequent infusions can be administered over an hour or according to local policy.

## 2.2.4 Infliximab administration

### Equipment

Infliximab is infused through a low protein binding filter giving set into a peripheral cannula using an IV pump with a primed line.

### Preparation of infusion

The preparation of the injection must be undertaken according to the SPC of the drug, and administered within the stipulated timeframe that the drug is stable once reconstituted.

Each vial contains 100 mg of infliximab dry powder. Calculate the dose and the number of vials needed. Calculate the total volume of reconstituted solution required.

Under aseptic conditions, reconstitute each vial with 10 ml of water for injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle.

The reconstituted solution dose is further diluted to 250 ml with sodium chloride 9mg/ml (0.9%) solution.

No preservative is present; it is therefore recommended that the administration of the solution for infusion should be started as soon as possible and within three

### Clinical observations during infusions

Every 30 minutes, temperature, pulse and blood pressure should be recorded for two hours following the first four infusions, and then for one hour following subsequent infusions.

Observe for side effects throughout, taking appropriate action if an adverse event occurs. Record any adverse reactions in the patient's notes.

For full list of administration details, please see drug specific SPC.

## 2.2.5 Rituximab administration

### Drugs prior to infusion

Rituximab is associated with infusion related reactions (IRR), which may be related to release of cytokines and/or other chemical mediators. In rheumatoid arthritis premedication consisting of an analgesic/ anti-pyretic drug and anti-histamine drug, and glucocorticoids should also be administered before each infusion in order to reduce the frequency and severity of IRR.

Standard doses are as follows:

- methylprednisolone 100mg IV (100mgs in 100mls normal saline infused over 30 minutes (the methylprednisolone should be given 60 minutes before rituximab))
- paracetamol 1g orally (30 minutes prior to infusion) if not already taken
- chlorpheniramine 10 mg IV (30 minutes prior to infusion) or an oral anti-histamine according to local protocol
- antihypertensives should also be omitted before the infusion, see SPC for more details.

### Equipment

Rituximab infused through a peripheral cannula using an IV pump with a primed line and with a low protein binding filter.

### Preparation of infusion

The preparation of the injection must be undertaken according to the SPC of the drug, and administered within the stipulated timeframe that the drug is stable once reconstituted. Aseptic precautions must be used. Rituximab is provided in vials of 100mg in 10ml and 500mg in 50ml vials. Rituximab can be diluted to a concentration of between 1-4mgs/ml normal saline.

### Reconstitution

Concentration	1mg/ml	2mgs/ml	4mgs/ml
Volume of fluid	1,000mls	500mls	250mls

### Administering the infusion

Rituximab is infused through a peripheral cannula using an IV pump with a primed line. The following regime is based on a concentration of 2mgs/ml i.e. 1,000mgs in 500mls. The rate of the infusion will depend on the concentration of the rituximab and whether it is the first or second infusion.

#### Infusion rate for day 0

Time	mgs/hour	mls/hour
1st 30 minutes	50mg/hour	25mls/hour
2nd 30 minutes	100mg/hour	50mls/hour
Then the rate can be increased by 50mg/hour (25mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) providing no adverse reactions occur.		

#### Infusion rate for day 14 if the patient had no reaction to the first infusion

Time	mgs/hour	mls/hour
1st 30 minutes	100mg/hour	50mls/hour
2nd 30 minutes	200mg/hour	100mls/hour
The rate can be increased by 100mg/hour (50mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) providing no adverse reactions occur. Note: the SPC has been updated with a new license for a faster infusion rate up to 600mg/hr (RA only). See <a href="http://www.medicines.org.uk">www.medicines.org.uk</a>		

In the event of a reaction to the first infusion, the second infusion should be administered at the same rate as the first. Rituximab treatment (two infusions) is repeated no more frequently than every six months (NICE TA195, 2010).

### Clinical observations during infusions

Every 15 minutes for the first hour, then every 30 minutes and prior to increasing the rate of infusion and until infusion completed. Observations to include:

- blood pressure
- pulse
- temperature
- O<sub>2</sub> saturation levels (if indicated).

Note: It is most important to observe the patient in the first few minutes of the infusion or after any rate change as this is when reactions are most likely to occur.

An example of a rituximab protocol is available on the Rheumatology forum page of the RCN website [www.rcn.org.uk](http://www.rcn.org.uk)



## 2.2.6 Tocilizumab administration

### Equipment

Tocilizumab is infused through a peripheral cannula using an IV pump with a primed line and with a low-protein-binding filter.

### Preparation of infusion

Prepare the infusion according to manufacturer's guidelines. Tocilizumab is supplied in vials containing 20ml/ml concentration of either 4 ml (80mg), 10 ml (200mg) or 20 ml (400mg) concentrate. The recommended posology is 8 mg/kg body weight, given once every four weeks.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended.

Calculate the withdrawal volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of concentrate required for the patient's dose, under aseptic conditions. The required amount of tocilizumab concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml.

To mix the solution, gently invert the infusion bag to avoid foaming.

### Administering the infusion

The infusion should be administered over an hour and repeated monthly.

### Clinical observations during infusions

Every 30 minutes, temperature, pulse and blood pressure, should be recorded.

Observe for side effects throughout, taking appropriate action and recording any adverse reactions in the patient's notes.

## 2.2.7 Post-infusion care and advice to patients

Discharge the patient after the infusion, providing observations taken one hour after the infusion start time are satisfactory.

Before the patient leaves:

- advise them to seek medical advice if they develop any symptoms which suggest an infection (eg fever in the hours or days after the infusion). Provide contact numbers for the rheumatology department or first contact point; for example, GP and/or attendance at the hospital's accident and emergency department (A&E)
- make sure regular MTX monitoring, according to BSR/BHPR and local guidelines is set up if applicable
- make patients who have diabetes aware that they may experience a falsely elevated blood glucose reading on the day of the infusion, if they have had abatacept, as this interferes with blood glucose monitoring strips (glucose dehydrogenase pyroloquinolinequinone – GDH-PHQ)
- ensure follow-up for assessment or next infusion has been arranged
- ensure an understanding of the importance of the need to attend for regular medical/AHP reviews
- ensure patient has a biologics alert card to carry with them (see [www.arc.org.uk](http://www.arc.org.uk)).

For a full list of adverse effects, see the drug's SPC (available at: [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk)).

## 2.2.8 Withdrawal of treatment

Treatment should be withdrawn if an adequate response is not initially achieved or maintained as outlined in [Section 1](#).

Treatment should also be stopped in the following situations:

- any serious/severe adverse reaction, active or serious infection for example any new infections or reactivation of any infections ie TB, VZ, hepatitis etc. until infection has resolved clinically
  - PML immediate withdrawal and no re-treatment with rituximab. Prompt reduction or discontinuation of other immunosuppressants and appropriate investigations should be undertaken.
  - any anaphylactic reaction or other serious allergic reactions. The administration of biologic therapy should be stopped and appropriate therapy given
  - symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations  $\geq 5$  times the upper limit of normal (ULN) develop(s), biologic therapy should be discontinued, and a thorough investigation of the abnormality should be undertaken
  - any confirmed haematological disorders. Also if ANC  $< 0.5 \times 10^9/l$  or a platelet count  $< 50 \times 10^3/\mu l$ . Temporary withdrawal until repeat bloods satisfactory
  - any new or worsening of pre-existing central or peripheral demyelinating symptoms (and appropriate referral to specialist initiated)
  - any symptoms suggestive of a lupus-like syndrome; positive tests for antibodies against ds-DNA and/or other significant autoimmune disease, further treatment should not be given and appropriate interventions initiated
  - any new or worsening skin rashes (ie lupus-like syndrome or psoriasis etc) and appropriate referral to specialist initiated
  - any suspected signs or symptoms and/or confirmation of malignancy
  - any new or worsening symptoms of congestive heart or cardiac disorders (such as hypertension, hyperlipidaemia) and/or angina pectoris, cardiac arrhythmias (such as arterial flutter and fibrillation and/or myocardial infarction). Any new or worsening symptoms of pulmonary/lung disease
  - any uveitis symptoms – consider alternative biologic
  - pending surgery (please refer to section [1.1.10](#) Biologics and surgery section of PART ONE of this document)
  - contraception/pregnancy/breastfeeding (please refer to the safety monitoring section).
- An alternative biologic including rituximab, adalimumab, etanercept, infliximab and abatacept may be considered for patients in whom treatment with anti-TNF is withdrawn due to an adverse event before the initial six-monthly assessment of efficacy, depending on initial treatment choice and contraindications, provided the risks and benefits have been fully discussed with the patient and documented (NICE, CG79, TA195).
- Re-treatment with rituximab in RA should only be considered when initial treatment response has been lost. The frequency of infusion should be not  $< 24$  weeks (note: the NICE recommendation is no more frequently than every six months, while the SPC allows for every 16 weeks). Otherwise treatment should be discontinued.
- The BSR/BHPR (2010) also recommends that repeat treatment with rituximab in RA should be decided on clinical grounds, not on B-cell numbers.
- AS patients can swap to an alternative anti-TNF if intolerant before the 12 weeks response period.
- Elimination and half-life must always be taken into account when swapping between biologic therapies (see [Table 4 in Section 1.1.10 of PART ONE](#) of this document).
- Please refer to: the SPC for each biologic therapy, related NICE guidance and also the BSR/BHPR (2010) RA guidelines on safety of anti-TNF $\alpha$  therapies available at: [www.rheumatology.oxfordjournals.org](http://www.rheumatology.oxfordjournals.org) at the time of writing these guidelines are being updated and due for publication in 2015.

# PART TWO: CHILDREN AND YOUNG PEOPLE

## Introduction

Part two provides guidance for paediatric rheumatology clinical nurse specialists (PRCNS) and community children's nurses (CCNs) caring for children and young people of 18 years of age and younger, who are receiving biologic therapies for Juvenile idiopathic arthritis (JIA). The role of paediatric rheumatology nurses is pivotal in ensuring that children, young people and their families and carers are fully informed about the biologic therapy that the child and young person is receiving.

At the time of publication of the 2009 Royal College of Nursing biologics guidance document, only a few biologics were licensed for use in children and young people.

JIA is a relatively rare disease, with an estimated incidence in the UK of 0.1 per 1,000 children, equivalent to 1,000 new cases per year. The prevalence is in the order of 1 per 1,000 children, so about 8,500 children in England are affected. For a classification of JIA, see [Appendix 10](#).

In this document, the term 'children' refers to those aged between two and 17 years of age; this benchmark does not include the small number of people under two or aged 18 years or older with long-standing JIA, who are receiving treatment with biologic therapies.

Available data suggest that the indicative benchmark rate for the number of children aged 4-17 years with JIA, eligible for and receiving treatment with biologic therapies, is 0.015 per cent, or 15 per 100,000 children per year (NICE, October 2012).

## This guidance

The guidance in part two aims to provide a standardised approach to the care of children and young people when receiving biologic therapies. The experience gained in the assessment and management of children and young people receiving these drugs provides an opportunity for paediatric rheumatology clinical nurse specialists and paediatric rheumatologists to develop a framework for practice and a consensus on management.

The RCN Working Party identified four key national issues relating to the care of children and young people with JIA.

1. Nursing resource implications for biologic therapies: no additional funding has been associated with the endorsement of such therapies and the associated requirements, and the on-going development of British Society of Paediatric and Adolescent Rheumatology (BSPAR) Etanercept Cohort Study (formerly the Biologics and New Drugs Register (BNDR) for Juvenile Idiopathic Arthritis Patients Treated with Biologic Therapies) as mandated in the NICE guidelines for etanercept.
2. The continued need to provide guidance on specific clinical issues in the assessment and management of children and young people receiving biologic therapies.
3. The continued need for consensus and clarity about emerging evidence, and about what can be agreed as best practice.
4. The national service frameworks highlighting the specific needs of children and young people – the NSF (2004) England and Wales, and Specialist Children's Services Framework in Scotland.

In preparing this guidance, the working party found that in some areas of clinical practice the evidence to support best practice remains unclear. In this instance, evidence is provided in a pragmatic way by clinicians experienced in the assessment and management of children and young people receiving biologic therapies.

# Section 1:

## Assessing and managing children and young people needing biologic therapies

### 1.1 The special needs of children and young people

As a specialist practitioner, it is essential that you are aware that the care of children and young people with JIA should be managed according to the Standards of Care for children and young people with juvenile idiopathic arthritis (2010) (ARMA and BSPAR) and the Department of Health (2004) NSF in England and Wales and Specialist Children's Services Framework in Scotland.

Children and young people should be admitted to designated areas in hospital which meet their specific needs with appropriately trained personnel. The Department of Health in England has highlighted the specific needs of adolescents and the need for effective transition from children's to adult services DH (2004) and RCN (2003). Children and young people with JIA require prompt diagnosis and referral to specialist paediatric rheumatology multi-disciplinary team should be made within six weeks of the onset of symptoms (BSPAR, 2010).

Around the UK, there are many centres with specialist paediatric rheumatology teams. They work in multi-disciplinary teams that include paediatric rheumatologists, nurse practitioners, ophthalmologists,

clinical nurse specialists, paediatric physiotherapists, psychologists, podiatrists and occupational therapists.

All these professionals aim to provide high quality clinical care nearer to the child's home and minimise disruption for the family. They also work with schools and social services to support the child and family in the community and throughout the child's education (BSPAR, 2009).

Some rheumatology units work with pharmaceutical companies which provide nurses to support care of children and young people. It is important that such staff are suitably qualified and trained to work with children and young people.

### 1.2 Treating JIA with biologic therapies

Etanercept was licensed for use in JIA in 2000, and in March 2002, NICE published guidance on anti-TNF $\alpha$  treatment etanercept for children and young people with JIA aged 4-17 years. Since this time abatacept, adalimumab and tocilizumab have all been licensed for JIA; tocilizumab received a NICE recommendation (TA 238) for the treatment of JIA in young people aged two years and older whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate.

It is important to acknowledge that in practice, many JIA patients in the UK under the age of 18 are being given other unlicensed biologic therapies as listed in the [table on page 48](#).

It is essential that all children and young people receiving biologic therapies have their care managed by a tertiary paediatric rheumatology service, and these, in turn, may share care with the child or young person's local hospital. Information about accessing tertiary paediatric rheumatology services is available at [www.bspar.org.uk](http://www.bspar.org.uk).

**Table 5. Biologic therapy options for children and young people**

Generic name	adalimumab	etanercept	infliximab	tocilizumab	abatacept	anakinra	canakinumab	rituximab
Brand name	Humira®	Enbrel®	Remicade®	RoActemra®	Orencia®	Kineret®	Ilaris®	MabThera®
Inhibits what?	TNF	TNF	TNF	IL6 receptor	T- cell	IL-1	IL1	CD20 antigen on B cell surface
Type of biologic	Fully human soluble anti-TNF $\alpha$ monoclonal antibody	Soluble TNF receptor fusion protein	Chimeric human murine ant-TNF monoclonal antibody	Humanised anti-IL6 receptor monoclonal antibody	Fusion protein	Human anti-IL1 Receptor antagonist	Fully human monoclonal antibody	Chimeric Mouse human IgG1 monoclonal antibody
Licensed	Yes – Polyarticular JIA from the age of two years	Yes – Polyarticular JIA from the age of two years. Psoriatic arthritis and enthesitis-related arthritis from the age of 12 years	Off label	Yes – Systemic JIA and Poly JIA over the age of two years	Yes – Poly JIA (after insufficient response to other DMARDs including at least one TNF inhibitor in patients six years and older)	Off label	For CAPS	Off label
NICE approval	No	Yes	No	Yes (sJIA only – not polyarticular JIA)	No	No	No	No
Dose	24mg/m <sup>2</sup> up to 40 mgs	0.4mg/kg twice weekly (up to 25mg/dose) or 0.8mg/kg weekly (up to 50mg/dose)	6mg/kg	Dose for sJIA: < 30kg 12mg/kg $\geq$ 30kg 8mg/kg Dose for pJIA: $\geq$ 30kg 8mg/kg or <30kg, 10mg/kg	10mg/kg	2mg/kg Max 100 mgs	2-4mg/kg	750mg/m <sup>2</sup> (max 1g) (BSPAR guidelines)
Given how often	Fortnightly	Every week or twice weekly	At 0, 2 and 6 weeks, then 4 to 6 weeks	Fortnightly for sJIA, 4 weekly for Poly JIA	At 0, 2, 4 weeks, then 4 weekly	Daily	8 weekly	Day 0 and day 14



**Table 5. Biologic therapy options for children and young people continued**

Drug half-life	12-14 days	5 days	9 days	23 days	8 to 25 days	6 hours	22.9 to 25.7 days	32 days
<b>How given</b>	SC	SC	IVI	IVI	IVI	SC	SC	IVI
<b>MTX needed?</b>	Suggested, not required	No	Yes	No	No	No	No	Sometimes (BSPAR recommend monotherapy or cyclophosphamide)
<b>Common adverse events</b>	Injection site reactions Painful injection, upper respiratory infections	Injection site reactions, upper respiratory infections	Infusion reactions, including anaphylaxis, upper respiratory infections	Infusion reactions, upper respiratory infections, changes in blood parameters; especially neutrophils, LFTs and platelets. Normalises ESR and CRP and masks fever, so be alert for covert signs of infection	Low rate of infusion reactions, headaches	Injection site reactions, often appear after initiation, but spontaneously resolve with no intervention, can be very painful Respiratory infections	Neutropenia Localised injection site reactions	Chills or fever Nausea Allergic reactions Headache Dizziness Flushing Blurred vision
<b>Special instructions</b>	Can sting when given as has low PH value	Add reconstitution fluid slowly, best used when removed from fridge for 15 mins before use	Must use 0.4micron low protein binding filter for administration. Infuse over 2 hours Observe post infusion	Use 50ml or 100ml bag of saline depending on which dose bracket used. Infuse over 1 hour	Must use 0.4µm filter and silicone free syringes. Infuse over 30mins Observe post infusion	Should be given at same time daily, due to short half-life Rebound effect can occur with stopping therapy	Vials have special instructions on how to prepare, see package leaflet	Paracetamol and an antihistamine before each dose Close monitoring on first dose for reactions

For more detailed information on immunisation and contra-indications refer to the Department of Health [The Green Book website](#).

### 1.3 The paediatric rheumatology clinical nurse specialist (PRCNS)

Each child or young person with JIA should be referred to a PRCNS within four weeks (ideally two weeks) of their first appointment with a specialist. The role of the PRCNS is to support and guide the child or young person and their family through diagnosis and treatment options, and provide on-going access and information.

The paediatric rheumatology CNS should have a registered children's nursing qualification.

Many families are supported at home by a community children's nurses (CCN) or at their local hospital by ward or day care nurses for the administration of medications by the subcutaneous route and for blood monitoring. These nurses will require education and ongoing support from the PRCNS.

Biologic therapies may also be given at tertiary centres and nurse practitioners may be involved in this care and are experienced in the assessments and safe administration of biologic infusions on the ward.

### 1.4 Shared care arrangements

Due to the distances some children and young people often need to travel to access specialist paediatric rheumatology services, shared care arrangements are often instigated. If GPs are asked to engage in shared care they must fully consent if it's something from a specialist centre that their CCG does not normally endorse. These arrangements must be highly organised and robust to maintain a safe, and effective service, especially when these professionals are directly involved in the administration and support of children and young people receiving biologic therapies.

### 1.5 Biologics registers

1. The BCRD /Biologics for Children with Rheumatic Diseases is the extended biologics study. The study aims to recruit all children with JIA who are being newly (within six months) treated with biologic agents (other than etanercept) or MTX in the UK. The research is being funded by the Arthritis Research UK. See [www.bcrdstudy.org](http://www.bcrdstudy.org)
2. The BSPAR ECS /BSPAR Etanercept Cohort Study, previously known as the Biologics and New Drugs Register (BNDR), aims to recruit all children with JIA who are being newly treated with etanercept or MTX. The study is funded by BSPAR.

### 1.6 Special skills for working with children and young people receiving biologic therapies

Paediatric rheumatology clinical nurse specialists and registered children's nurses who assist in the administration of biologic therapies should work within an appropriate multi-disciplinary team and:

- have specialist expertise in the biologic therapies they are administering and be fully aware of the potential side effects of treatment and of monitoring schedules
- be competent in the administration of subcutaneous injections and have the ability to teach and assess the competence of children, young people and their families/carers in such techniques
- be skilled in teaching children and young people about their treatment, recognising their patient's level of physical and cognitive abilities
- involve other specialists, such as hospital play specialists and psychologists, to support children and young people who require injections, particularly those who have needle aversion.

## 1.7 Assessing and managing patients

To ensure that children and young people receive appropriate biologic therapies, a CNS should ensure that the child/young person and parents/carers are actively involved in decision-making about treatment. This can be achieved by ensuring:

- the child/young person and family/carers are given time with a PRCNS following their initial consultation with medical staff, to allow an opportunity to review information and facilitate informed decision-making
- information is provided in a format and at a level that is understandable to all
- this information includes the risks and benefits of the treatments being offered
- an assessment of the potential for self-administration by the child/young person (or their parents/carers should they decide to administer treatments to their child)
- the provision of support, education and training plans for home administration as necessary.

Assessment of the child and /young person, and accurate data collection about them, is essential both before treatment begins and throughout its course. The BSPAR guidance is set out in [Appendix 11](#).

## 1.8 The use of unlicensed medicines or licensed medicines for unlicensed applications in paediatric practice

Children's medicines are regularly provided off-licence (where the medicine does not have a license for use in children) or off-label (where the medicine is used in a different way than that described in the license). This may include biologic medications as they can be used off label in the treatment of inflammatory arthritis.

A statement produced by the Medicines Committee informs and guides health professionals, health service managers, and parents and carers, who prescribe, dispense, administer or have responsibility for medicines for children (RCPCH, December 2013).

## 1.9 Detailed assessment of patients

**Table 6. Assessment check list prior to starting any biologic therapy for children and young people**

Education for family and child/young people	Side effects, including risk of cancers, route administration, frequency, dose, storage medication at home, no live vaccinations, infection risk and risks of chicken pox/shingles if contracted on treatment – to seek urgent doctor review. Current research studies discussed.
Lifestyle issues	Age appropriate conversation with parent and young person/child, including recreational drugs, alcohol intake, contraception and why pregnancy should be avoided. Tattoos and body piercing should be discouraged.
Blood screening	FBC, ESR, U&E, LFT, CRP, VZV status.
TB screening	QTB or/and T spot, CXR.
Measurements	Height, weight, body surface area, centile recorded.
Psychological support	To prepare for new medication and route of administration, support compliance with parent/self-administration and referral to local community children's nurses for administration if required.
Training for S/C administration	Injection technique, safe storage of medication and sharps at home, carry biologics alert card (this training can be undertaken by anyone proficient in S/C administration).

## 1.10 Vaccinations

### Live vaccines

Live vaccines must not be given during treatment and for six months following the completion of treatment. This includes MMR, and BCG, which should not be administered in patients receiving biologic therapies (see RCPCH, 2002: *Immunisation of the immunocompromised child best practice statement* available at [www.rcpch.ac.uk](http://www.rcpch.ac.uk) and also [Appendix 12](#)).

As with any immune-suppressant therapy, guidelines on immunisation in the immune-compromised child should be followed. Inactivated vaccines can be given, but the child may not build up the appropriate immune response to vaccines.

It is recommended that all children and young people are brought up-to-date with the pneumococcal vaccine for those who have not had it previously and the injectable annual flu vaccines should be given while on treatment.

### 1.11 Varicella in children

All patients should have their varicella antibody status measured at diagnosis and certainly before commencing immunosuppressive treatment (including steroids, MTX and all biologic therapies).

In children and young people who do not have adequate antibodies, this test may be re-checked annually if the child/young person has a negative response.

If siblings/parents have not had chicken pox they can be considered for vaccination.

If a child is exposed to varicella-zoster virus (VZV) in other words, face-to-face contact or 15 minutes in the same room as someone with VZV, prophylaxis should be given:

- zoster immunoglobulin (ZIG) a blood product and can be given to a seronegative patient who has been in contact with chicken pox if given less than 72 hours from contact (it may attenuate infection if

given up to 10 days post exposure); however, this will only provide temporary immunity of approximately four weeks

- aciclovir, either oral or IV is often only given if the child develops VZV. The child should be assessed by a local paediatrician to review their condition and then make a discussion on route of administration.

If either of the above situations occurs, families should be advised to contact their local shared care paediatric consultant, rheumatology team or GP immediately.

A biologic therapy alert card should be given to young people to carry with them to inform others that they are on biologic therapies (these are available from [www.arthritisresearchuk.org](http://www.arthritisresearchuk.org)).

## 1.12 Monitoring

The following monitoring regime is recommended for children/young people who start biologic therapies:

- for the first year of treatment – bloods; FBC, U&E, LFTs, ESR, CRP should be undertaken every three months unless condition necessitates otherwise
- if receiving IV biologic therapies, a blood test should be taken prior to each infusion
- a medical review should be conducted every three months – to include joint count, CHAQ, parental and physician VAS
- any adverse reactions should be reported via the Yellow Card system
- on-going CNS support should be made available via a helpline, especially with infections/chickenpox/shingles.

## 1.13 Malignancy alert/warning

In 2009 the US Food and Drug Administration (FDA) reported and increased risk of malignancies associated with the use of TNF blockers in children and young

people; to date 48 cases of malignancies have been reported of which 15 were cases in children with JIA.

In May 2011 BSPAR issued a position statement on cancer risk in JIA patients treated with etanercept, concluding that an analysis of the reported incidents did not suggest a considerably increased risk of cancer associated with the use of etanercept for this population.

### 1.14 Follow-up care between treatments

Even if families become self-sufficient in the administration of biologic therapies at home, they must continue to be monitored as problems with compliance are not uncommon, particularly with adolescent patients.

After their treatment, ensure that the child/young person and their family are given:

1. Contact details: ensure that the family are given these, both verbally and written, for normal and out of hours queries. Out-of-hours contacts will be dependent upon local services and the on-call arrangements within your paediatric rheumatology team.
2. Next treatment date: the date, and where they need to have drug monitoring/bloods taken.
3. Date for full assessment and review of treatment.
4. An understanding of the importance of the need to attend for regular medical/AHP reviews.
5. Ensure families have a biologic therapy alert card for young people to carry with them to inform others that they are on biologic therapies (these are available from [www.arthritisresearchuk.org](http://www.arthritisresearchuk.org) ).

### 1.15 Transition to adult services

The National Service Framework for children and

young people recommends that young people with long-term health problems are supported to make transition to adulthood and work towards achieving their maximum potential in terms of education, health, development and wellbeing (DH, 2004).

Successful transition depends on good communication and collaboration between agencies, but early discussion with the young person and parents/carers is vital in supporting this outcome.

A checklist for assessing young people during transition is recommended by the RCN guidance for nursing staff-adolescent transition care (RCN, 2013).

The six key areas to cover are:

- self-advocacy
- independent health care behaviour
- sexual health
- psychosocial support
- education and vocational planning
- health and lifestyle.

A child or young person with a JIA or an inflammatory illness will require careful and planned transition to adolescents and /or adult services. On average one-third of children with JIA will have active inflammatory disease into their adult life (Nigrovic and White, 2006). They may be on a biologic therapy and therefore require more consideration to ensure that the supply and administration for this medication is not compromised.

It is important to note that when a child/young person is diagnosed with JIA, their disease remains being JIA even into their adult years. Transition of young people into adult care is profoundly complicated in rheumatology care by different disease measures, for example the Childhood Health Assessment Questionnaire (CHAQ) versus the Health Assessment Questionnaire (HAQ) and the Core Outcome Variables (COV) compared to the Disease Activity Score (DAS). This becomes a problem when collecting data for registries, monitoring disease and even applying for biologics.



# Appendix 1

## Core documents

The first edition of this document was published in 2009. Since then there have been a number of changes including new publications, advisory documents and updated guidance from professional organisations and regulatory bodies. It is vital that practitioners using this document also refer to these core documents which are listed below.

### Professional bodies

BSR guidelines can be accessed at:  
[www.rheumatology.org.uk](http://www.rheumatology.org.uk)

- BSR (2006) *Guidelines for the management of RA* (the first two years)
- BSR (2008) *Guidelines for the monitoring of disease modifying anti-rheumatic drugs*
- BSR (2009) *Guidelines for the management of RA* (after the first two years, pending publication)
- BSR (2009) *RA biologics guidance*
- BSR (2012) *Guidelines for the treatment of psoriatic arthritis with biologics*
- BSR (2012) *Top ten quality standards for RA* (3-5 and 7-10 apply)
- BSR (2012) *Top ten quality standards for spondyloarthritis*
- BSR (2014) *Guidelines for tocilizumab*
- BSR and BHPR (2010) *Rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy*
- BSR/BHPR (2010) *Rheumatoid arthritis guidelines on safety of anti-TNF $\alpha$  therapies*
- BSR/BHPR (2011) *Guidelines on MabThera<sup>®</sup>*

- ARMA (2004) *Standards of care for people with inflammatory arthritis*. Available at [www.arma.uk.net](http://www.arma.uk.net)
- British Thoracic Society (BTS) (2005) *Guidelines: BTS recommendations for assessing risk and for managing mycobacterium tuberculosis infection and disease in patients due to start anti-TNF $\alpha$  – a treatment*.
- EULAR (2010) *Update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis*. Available at [www.eular.org](http://www.eular.org)
- EULAR (2012) Recommendations for the management of psoriatic arthritis with pharmacological therapies, *Annual of Rheumatic Diseases*; 71, pp.4-12.
- EULAR (2013) Recommendations for the management of RA with synthetic and biological disease-modifying anti-rheumatic drugs, *Annual of Rheumatic Diseases*, R9, pp.964-975.
- NASS (2012) *The AS pathway*.
- NRAS (2001-2013) *10 Key standards of care*. Available at [www.nras.org.uk](http://www.nras.org.uk)

### Regulatory bodies: England, Northern Ireland, Scotland and Wales

The National Institute of Health and Clinical Excellence (NICE) is the National Health Service (NHS) regulatory body for England and Wales. It reviews research evidence and undertakes economic modelling to provide guidance to the Department of Health on the benefit of specific treatments.

In Northern Ireland, the Department of Health, Social Services and Public Safety (DHSSPS) has a formal link with NICE, under which all NICE guidance documents published from 1 July 2006 are reviewed locally for their application to Northern Ireland. Guidance documents found to be applicable are endorsed by the DHSSPS for implementation. Arrangements have been put in place for practitioners intending to undertake new interventional procedures to take into account NICE guidance.

In Scotland, there is some recognition of the NICE documents. However, the Scottish Intercollegiate Guidance Network (SIGN) provides a similarly regulatory function, providing guidance to Scottish Parliament on the benefit of specific treatments (see [www.scottishmedicines.org.uk](http://www.scottishmedicines.org.uk)). Patients receiving biologics in Scotland are also included in the BSRBR as for the rest of the UK.

Treatment criteria for biologic therapy have been outlined by NICE for England and Wales and The Scottish Consensus Guidelines (SCG) for Scotland.

### Guidance documents:

- NICE TA130 Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (October 2007).
- NICE TA143 Adalimumab, etanercept, infliximab for the treatment of ankylosing spondylitis (May 2008).
- NICE TA186 Certolizumab pegol for the treatment of rheumatoid arthritis (February 2010).
- NICE TA195 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010).
- NICE TA199 Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (August 2010).
- NICE TA233 Golimumab for the treatment of ankylosing spondylitis (August 2011).
- NICE TA220 Golimumab for the treatment of psoriatic arthritis (April 2011).
- NICE TA225 Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (June 2011).
- NICE TA247 Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198) (2011).
- NICE TA238 Tocilizumab for the treatment of systemic juvenile idiopathic arthritis (December 2011).
- NICE (2012) *Commissioning biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology*.
- NICE RA Management Guidelines CG79 (February, 2009, updated 2013).
- NICE TA280 Abatacept for treating rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (rapid review of technology appraisal guidance 234) (April 2013).
- NICE QS33 Rheumatoid arthritis (August 2013)
- NICE QS40 Psoriasis (2013)
- NICE (2013) *Systemic biologic therapy for psoriasis and psoriatic arthritis*. Available at [www.nice.org.uk](http://www.nice.org.uk).
- In Wales see the All Wales (2013) Best practice recommendation. All Wales Medicines Strategy Group: Final Appraisal Recommendation Advice No: 1513 – adalimumab (Humira®) for use within the NHS Wales for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.

Access to guidance documents: [www.nice.org.uk](http://www.nice.org.uk).

NICE and SIGN require adherence by health care practitioners to their guidance and recommend local and national audits. NHS funders of drug budgets may consider medical exception reports to request treatment for patients who fail to fulfil the treatment criteria but are deemed to have specific clinical need (see [www.nice.org.uk](http://www.nice.org.uk) or [www.sign.ac.uk](http://www.sign.ac.uk)).

### Other core documents:

- The National Patient Safety Agency (NPSA) for guidelines on the administration and management of injectable products. Available at [www.npsa.nhs.uk](http://www.npsa.nhs.uk)
- *Guidelines for the administration of medicines* (NMC, 2004).
- Summary of Product Characteristics (SPC) of each of the therapies discussed. SPCs provide comprehensive information about the specific biologic therapy, and can be accessed at [www.medicines.org.uk](http://www.medicines.org.uk)
- Arthritis Research Campaign ([www.arc.org.uk](http://www.arc.org.uk)) and Skills for Health competency frameworks ([www.skillsforhealth.org.uk](http://www.skillsforhealth.org.uk))
- Yellow card scheme, see [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)
- *Equity and excellence: liberating the NHS: Transparency in outcomes – a framework for the NHS*
- *Operating framework for the NHS in England 2012-13.*
- *NHS Outcomes Framework 2014-15.*
- *Procurement guide for commissioners of NHS funded services 2010.*
- *Innovation for health and wealth: accelerating adoption and diffusion in the NHS.* Available at [www.institute.nhs.uk](http://www.institute.nhs.uk)
- Quality, innovation, productivity and prevention (QIPP). See NICE website [www.nice.org.uk](http://www.nice.org.uk) and [www.evidence.nhs.uk/qipp](http://www.evidence.nhs.uk/qipp)
- Commissioning for quality and innovation (CQUIN) makes a proportion of providers' income conditional on quality and innovation.

We recommend that you also refer to local service provider and NHS Trust policies.

## Appendix 2

# Specialist practitioner competence checklist

Name of practitioner:			
Name of supervisor:			
Element of competence to be achieved	Date of achievement	Practitioner signature	Supervisor signature
Discuss the rationale for the use of subcutaneous biologic therapy in rheumatic conditions			
Discuss potential issues related to treatment including: <ul style="list-style-type: none"> <li>• screening of patients</li> <li>• possible side effects or adverse events</li> <li>• drug interactions</li> <li>• contra-indications to therapy</li> </ul> Discuss the circumstances when subcutaneous biologic therapy should not be administered			
Describe interventions to alleviate side effects			
Discuss the process for assessing the patient's suitability for biologic therapy. For example, medical history, concomitant medications, allergies, level of disease activity, dexterity and attitude to treatment			
Demonstrate the ability to check the validity of the current prescription. This includes expiry date, dose, route by which the drug is to be administered and the checking of the patient identification			
Demonstrate the ability to teach a patient/carer how to administer subcutaneous biologic therapy			
Demonstrate the ability to assess a patient's/carer's suitability for home administration of subcutaneous biologic therapy			
Describe local health and safety guidelines and risk assessment required for providing a subcutaneous biologic therapy service in hospital and in the patient's home. With particular relevance to: <ul style="list-style-type: none"> <li>• storage, handling and hygiene prep (hand washing/clean working area)</li> <li>• safe use and disposal of equipment</li> <li>• ensuring a quiet and safe environment</li> <li>• travelling and transporting biologic therapy</li> </ul>			

Demonstrate the ability to discuss the information/educational needs of the patient/carer in relation to home administration of subcutaneous biologic therapy			
Demonstrate the ability to provide the patient/carer with information about the treatment in order that they are able to give informed consent (written/verbal – in line with local guidelines)			
Demonstrate adherence to information governance policy and procedures, in relation to record sharing and confidentiality			
Describe sites on the body that would be appropriate for subcutaneous injection			
Demonstrate the ability to maintain concise and accurate patient documentation and audit			
Describe the local monitoring requirements and follow up arrangements for subcutaneous biologic therapy			
Identify the ways of maintaining current competency			
<b>Identified areas for further learning:</b>		<b>Date of review:</b>	



## Appendix 3

### Diagnostic criteria

Rheumatoid arthritis (RA)	Psoriatic arthritis (PsA)	Ankylosing spondylitis (AS)
<p>Classification criteria: where patients have at least 1 joint with definite clinical synovitis (swelling) which is not better explained by another disease. Add score of categories A-D</p> <p><b>A. Joint involvement</b></p> <p>1 large joint 0</p> <p>2–10 large joints 1</p> <p>1–3 small joints (with/without involvement of large joints) 2</p> <p>4–10 small joints (with/without involvement of large joints) 3</p> <p>&gt;10 joints (at least one small joint) 5</p> <p><b>B. Serology (at least 1 test result is needed for classification)</b></p> <p>Negative RF and negative ACPA 0</p> <p>Low-positive RF/low-positive ACPA 2</p> <p>High-positive RF or positive ACPA 3</p> <p><b>C. Acute-phase reactants (at least 1 test result is needed for classification)</b></p> <p>Normal CRP and normal ESR 0</p> <p>Abnormal CRP or abnormal ESR 1</p> <p><b>D. Duration of symptoms</b></p> <p>&lt;6 weeks 0</p> <p>≥6 weeks 1</p> <p>A score of ≥6/10 is needed for classification of a patient as having definite RA.</p>	<p>To meet the CASPAR criteria:</p> <p>Presence of inflammatory articular disease (joint, spine, or enthesal) with ≥3 points from the following 5 categories:</p> <ol style="list-style-type: none"> <li>1. Current psoriasis OR history of psoriasis, OR family history of psoriasis.</li> <li>2. Rheumatoid negative (usually).</li> <li>3. Current dactylitis OR a history of dactylitis.</li> <li>4. Juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.</li> </ol> <p>Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.</p>	<p>Modified New York criteria for diagnosis of AS:</p> <p><b>Radiographic criterion:</b></p> <p>Sacroiliitis at least grade 2 bilaterally or grade 3 or 4 unilaterally</p> <p><b>Clinical criteria:</b></p> <ul style="list-style-type: none"> <li>• low back pain and stiffness &gt; 3/12s that improves with exercise but is not relieved by rest</li> <li>• limitation of the lumbar spine in both the sagittal and frontal planes</li> <li>• limitation of chest expansion relative to normal values correlated for age and sex.</li> </ul> <p>Definite ankylosing spondylitis if radiological criterion is present, including at least one clinical criterion.</p> <p>Probable ankylosing spondylitis if three clinical criteria are present, or if the radiological criterion is present, but there are no clinical signs of disease.</p> <p>All reasonable measures should be taken to ensure that symptoms are due predominantly to ankylosing spondylitis and that alternative causes (spinal fracture, disc disease and fibromyalgia) are excluded. All Wales (2013) Best practice recommendation : use of Humira® for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.</p>

## Source documents

ACR-EULAR (2010) revised RA classification criteria:  
[www.rheumatology.org.uk](http://www.rheumatology.org.uk)

See also ACR 1987 diagnostic criteria still commonly used

NICE/RCP (2009) *Rheumatoid Arthritis National clinical guideline for management and treatment in adults* [www.rcplondon.ac.uk](http://www.rcplondon.ac.uk)

NICE (2013) CG79  
[www.nice.org.uk](http://www.nice.org.uk)

SIGN Guideline 121 (2010) *Diagnosis and management of psoriasis and psoriatic arthritis: A national clinical guideline*  
[www.sign.ac.uk/guidelines](http://www.sign.ac.uk/guidelines)

*The Classification criteria for Psoriatic Arthritis* (CASPAR criteria) Taylor et al (2006) *Arthritis Rheum* 2006;54(8):2665-73.

EULAR (2012) *Textbook on Rheumatic Diseases* Chapter 11 Clinical Features pg 255-275

Also see Moll and Wright (1978) criteria which are still commonly used

NICE : 2013) Ankylosing Spondylitis Diagnosis <http://cks.nice.org.uk/ankylosing-spondylitis#!diagnosis>

*Assessment of Spondyloarthritis international Society* (ASAS) criteria Rudwaleit et al (2009) *Ann Rheum Dis* 68:777-83.

MNYC (Modified New York) van der Linden (1984) *Arthritis and Rheumatism* 27, 4, 361-368.

EULAR (2012) *Textbook on Rheumatic Diseases* Chapter 11 Clinical Features pg. 255-275.

## Appendix 4

### Current live vaccines available in the UK

Live vaccine	Brand name
BCG	Bacillus Calmette-Guerin Vaccine
Measles, mumps and rubella combined vaccine (MMR)	MMRvaxPRO®, Priorix®
Poliomyelitis (live oral vaccine)	Poliomyelitis Vaccine, live (oral) GSK OPV
Rotavirus (live oral vaccine)	Rotarix®
Typhoid (live oral vaccine)	Vivotif®
Varicella-Zoster Vaccine	Varilrix®, Varivax®
Shingles	Zostavax®
Yellow fever	Arilvax®, Stamaril®

This is an example of vaccines available. Check [The Green Book](#) and BNF before administration.

## Appendix 5

### Current non-live vaccines available in the UK

Non live vaccine	Brand name
Cholera Vaccine (oral preparation only)	Dukoral®
Diphtheria	Given as combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation.
Hepatitis A	Avaxim®, Epaxal®, Havrix Monodose®, Vaqta Paediatric®
Hepatitis B	Engerix®, Fendrix®, HBvaxPRO®
Hepatitis A and B combined	Ambirix®, Twinrix®
Influenza	Aggrippal®, BegriVac®, Enzira®, Fluarix®, Fluvirin®, Imuvac®, Influvac® Sub-unit, Mastafu®, Optafu® and Viroflu®
Pneumococcal	Pneumovax II® (Adults and Children over 5 years), Prevenar® (Primary childhood immunisation)
Poliomyelitis (injection)	Inactivated poliomyelitis vaccine (non-proprietary) IPV
Meningococcal Group C	Meningitec®, Menjugate Kit®, NeisVac-C®
Meningococcal polysaccharide A,C, W135 and Y vaccine	ACWY Vax®
Rabies	Rabipur®
Tetanus	*Single preparation no longer available. Combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation given.
Tick-borne encephalitis	TicoVac®
Typhoid (polysaccharide injection for vaccination)	Typherix®, Typhim Vi®

## Appendix 6

# Information for patients or carers administering injections of biologic therapies at home

Make sure that this information is always nearby in case you have any queries or problems.

### Advice line telephone number:

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### Home care contact number:

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An answerphone service is available

If the problem is urgent, or it is out of normal working hours, please telephone your own doctor. There will be advice to tell you how to access help out of hours.

### Your GP surgery number:

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### Equipment

The package containing your treatment will come with either:

- syringes or needles for your injection, together with small glass vials containing the medication you have been prescribed
- a pre-filled syringe or pre-filled pen or auto injector that contains your medication.

### Information leaflets

The home care team will provide a patient information leaflet about how to inject yourself using the treatment prescribed for you. This information is included in the package containing your injection and equipment. Please read the details carefully in addition to any extra information provided about your treatment. If you have queries, contact your specialist nurse/practitioner or the home care service.

### Supplies of treatment and equipment

Make sure you know when and how your treatment will be delivered to you at home. You also need to know how the sharps box and other clinical waste will be disposed of. Do not put the sharps box into the dustbin – used needles and syringes are a hazard. The sharps box is usually collected by your home care team.



## How to give biologic therapies by subcutaneous injection

(Subcutaneous means under the skin)

You will be trained by a practitioner or nurse either at the rheumatology service you attend or by a nurse provided by the home care service. You should not self-inject or inject your family member without training.

Do not give the injection if you have any signs of infection or if you feel unwell or if there are any other reasons (such as imminent surgery) not to give it without contacting either your GP or rheumatology service for advice.

### Getting ready

- Don't rush – make sure you have plenty of time. As you get used to giving the injection, you will find it much easier. Make sure that there are no distractions, such as children or animals in the room.
- Always wash your hands and dry them.
- Prepare your equipment before your start. Take your injection pack or auto-injector or pen from the fridge. Put it on a clean, flat surface. You should leave the auto-injector flash pen to reach room temperature before injecting, this helps reduce the risk of reactions.
- Decide where you will put the injection – either under the skin of your tummy or in the front of your thigh. Choose a different side of your tummy or opposite thighs each time you inject.
- Read and check the label, dosage and expiry date on the bottle. If the expiry date has passed, do not inject the drug but contact your pharmacist or specialist nurse/practitioner to arrange replacement supplies.
- The area of skin you are going to inject should be clean and dry.

### Giving the injection

- Do not shake the syringe/auto-injector or pen.
- If the liquid in the syringe has particles or is not clear, do not inject the fluid. Contact the pharmacy or specialist nurse/practitioner about it.

### Giving the injection using a syringe and needle

- Remove the sheath from the needle. Make sure that you do not touch any part of the needle while you are preparing the injection.
- Pinch the skin around the area you will be injecting. Insert the needle into the skin, at a right angle directly into the skin. The needle is only half an inch (about 1.5cm) long, and will deliver the injection just below the skin. Push the plunger gently all the way down, whilst keeping the needle still and then hold the syringe in that position for a couple of seconds until you see all the fluid has left the syringe.

### Giving the injection using an auto-injector pen

- Remove the cap(s) from the pen as instructed in your packaging.
- Pinch the skin around the area you will be injecting. Place the injection end of the auto injector pen against the skin, at right angle (90 degrees) pointing the injecting end straight down onto the skin. There may be a window on the auto injector so you can see it change colour when you have successfully given the medication.

- Push down on the plunger or button section of the device as you have been instructed. This will activate the injector and may be accompanied by a click. You will experience a sharp prick in the skin. Hold in position for a few seconds.

### After you've given the injection

- Withdraw the needle and syringe/auto-injector/pen and cover the injection site with a cotton wool swab.
- After a few seconds remove the swab, and cover the injection site with a plaster if needed.
- To avoid pricking yourself unintentionally do not put the cover back on the needle or auto-injector pen. Discard the auto-injector or syringe and needle into the sharps box, along with any the alcohol wipe and cotton wool swab if used. DO NOT PUT ANY EQUIPMENT INTO THE HOUSEHOLD RUBBISH.
- You may notice bleeding or bruising at the injection site. Don't worry; this happens when a small blood vessel is punctured by a needle. If there's bleeding, apply a cotton wool swab and maintain gentle pressure for a minute or two until bleeding stops. The bleeding will soon stop and any bruising will disappear.
- Make a note of when your next injection will be due – and ensure that you have enough of the treatment available.

**If you experience a rash or discomfort around the injection area** Sometimes when people receive a subcutaneous injection, some of the injected fluid may leak into the surrounding skin and cause irritation around the injection area. This will normally settle in a few days. If you have a severe rash or it doesn't settle or you are concerned, seek advice from your specialist team.

**If your carer accidentally pricks themselves with the needle after they have given you the injection**, they must make the injury area bleed as much as possible while running it under a cold tap for at least 10 minutes. It is advisable for them to seek guidance from your GP's surgery or telephone advice line. You and your carer may need to answer a few questions to help the doctor or nurse decide if any treatment is needed.

For additional information/guidance and pictures to show your patients, refer to the specific product information patient information leaflets. There are also useful pictures in the *Administering subcutaneous methotrexate guidelines* (RCN, 2013).

## Appendix 7

### Safety monitoring summary

See summary of product characteristics (SPC) for each drug for more detailed information, and references in the main body of this document.

<b>Infections</b>	<p><b>Patients</b> must be advised to self-monitor for any infection, including for example primary varicella (chickenpox), shingles or TB etc, before, during and after (six months) biologic therapy.</p> <p><b>Practitioners</b> should be aware of the risk of opportunistic infections in order to minimise delays in diagnosis and treatment. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy in accordance with local recommendations.</p>
<b>Hepatitis B and C reactivation</b>	<p>Cases of hepatitis and reactivation of hepatitis B and worsening hepatitis C have been reported therefore monitoring for signs and symptoms, liver function tests, HBV DNA load should be considered.</p> <p><b>Specialist physician input is recommended.</b> Patients with serological evidence of cleared past infection [HBsAg negative/core antibody (anti-HBcAb) positive] should have their HBV serology monitored during therapy and may require concomitant anti-viral treatment if detrimental changes develop (BSR/BHPR, 2010).</p>
<b>Allergic reactions</b>	<p><b>Injection site</b> reactions to s/c biologic injections are usually mild and resolve without treatment. The most commonly reported are bleeding, bruising, erythema, itching, pain and swelling). Between 6-25 per cent, of those receiving subcutaneous biologic injections report these.</p> <p><b>Allergic reactions</b> have been reported to include pruritus, though some serious anaphylactic reactions have also been reported with adalimumab and golimumab.</p> <p>Infusion reactions: serious hypersensitivity reactions have been reported in association with:</p> <p><b>Tocilizumab</b> – reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous infusions even if they have received premedication with steroids and antihistamines.</p> <p><b>Infliximab</b> – acute infusion reactions including anaphylactic shock and delayed hypersensitivity reactions have been reported. <b>Treatment should be stopped immediately and emergency treatment given.</b></p> <p><b>Rituximab</b> – reactions reported are usually reversible with a reduction in rate, or interruption of rituximab infusion and administration of an anti-pyretic, an antihistamine and occasionally oxygen, IV saline or bronchodilators and glucocorticoids if required. Premedication of an analgesic/antipyretic drug, an antihistamine drug, plus methylprednisolone, should always be administered before each infusion of rituximab.</p>
<b>Active hepatic disease/hepatic impairment</b>	<p>Have been reported with tocilizumab and infliximab:</p> <p>Monitoring recommendations include:</p> <p>LFTs: 4-8 weeks for first six months of treatment and then three monthly thereafter and when clinically indicated other liver function tests including bilirubin (amalgam of both SPCs' recommendations).</p>

<b>Haematological disorders</b>	<p>All patients on anti-TNF<math>\alpha</math> therapy, including those not on concomitant DMARDs, FBCs should be monitored regularly.</p> <p><b>Tocilizumab</b> monitoring recommendations include: FBC: 4-8 weeks after treatment initiation and thereafter, according to standard practice.</p> <p><b>Golimumab</b> has been very rarely associated with disorders, cytopenias and malignancies, including lymphomas.</p> <p>In practice FBC is repeated every six months, or according to DMARDs and remind patients to report signs of haematological disorders – such as bruising bleeding tiredness or pallor.</p>
<b>Glycaemic control and sodium levels</b>	<p><b>Tocilizumab</b> and <b>infliximab</b>: caution in those patients who are on a controlled sodium diet, as both of these contain sodium.</p> <p><b>Etanercept</b>: hypoglycaemia (in diabetic patients) has been reported therefore patient education and monitoring needs to be considered, as clinically indicated.</p>
<b>Neurological disorders</b>	Symptoms potentially indicative of new/worsening demyelinating disorders. Cases of PML have been reported with <b>rituximab</b> (and other biologics) and so patients and practitioners need to be vigilant regarding this.
<b>Auto-antibody formation</b>	<p>Need to monitor for lupus-like symptoms during treatment, and if patients develop such symptoms, and ds-DNA test prove positive – respective biologic therapy should be discontinued and expert advice sought. Also HAAA (human antihuman antibodies) may be associated with a greater risk of infusion/allergic reactions or a reduced treatment benefit.</p> <p>The potential for the HAAA anti-bodies to develop must be considered in all treatments that have a chimeric monoclonal antibodies component – in other words <b>infliximab</b> and <b>rituximab</b>. The co-prescription of MTX can significantly reduce the incidence of antibodies developing.</p>
<b>Malignancies</b>	Monitor and exercise vigilance for any possible signs of malignancies during biologic therapy. Appropriate skin protection and periodic skin examination is recommended.
<b>Cardiac Disorders</b>	<p>Patients with a history of cardiac disease should be monitored closely Cardiovascular risk factors should be managed as part of a patient's care i.e. hypertension / hyperlipidaemia – in particular with <b>tocilizumab</b>: Lipid parameters: 4-8 weeks after treatment initiation. (Patient should be managed according to local clinical guidance for management of hyperlipidaemia).</p>
<b>Pulmonary symptoms</b>	<p><b>Patients</b> should be monitored (lung function tests) for any new or any worsening of pre-existing <b>pulmonary</b> symptoms (<b>interstitial lung disease (ILD)</b>) and encouraged to promptly report these to their <b>GP</b> and <b>specialist practitioners</b> – so that appropriate assessment, <b>investigations</b> and advice can be given – which may include the cessation of the therapy, until full investigations have been completed.</p>
<b>Skin rashes</b>	Practitioners should monitor and be observant and vigilant regarding the development of any skin rashes whilst receiving any biologic therapy. Be aware of <b>lupus-like syndrome</b> or other significant autoimmune disease or psoriasis.
<b>Uveitis</b>	Monitor for the development of any uveitis type symptoms that patients may develop whilst receiving any biologic therapy. An <b>alternative anti-TNF<math>\alpha</math></b> agent could be considered.
<b>Surgery</b>	Monitor patient's post-operative surgery progress and provide appropriate advice, as and when required.

<b>Pregnancy breastfeeding and contraception</b>	<p>Patients (of both sexes) and women of child-bearing age should be advised to use appropriate contraception to avoid becoming pregnant and not breastfeed during therapy or for specific time periods following therapy depending on the biologic therapy.</p> <p>There is at present no evidence to the contrary of this advice however, the continuation of anti-TNF<math>\alpha</math> therapy could be considered in patients wishing to conceive/father a child or if a woman conceives if the risks of stopping treatment are perceived to be high.</p> <p>The pros and cons of breastfeeding in patients treated with anti-TNF<math>\alpha</math> therapies should be considered on an individual basis.</p>
<b>Post treatment monitoring</b>	<p>Infliximab the elimination of infliximab may take up to six months – monitoring once treatment has been stopped monitoring should continue accordingly.</p>



## Appendix 8

### Example of a standardised assessment and management template for inclusion in patient records

Assessment check list	
Section 1: eligibility criteria	
Ensure fulfils medication criteria and clinical classification of condition	
yes/no	
Ankylosing spondylitis criteria 12 weeks apart	
Date:	Date:
BASDAI 1	BASDAI 2
Spinal pain VAS 1	Spinal pain VAS 2
Psoriatic arthritis 68 tender /66 swollen joint count 1 month apart	
Date:	Date:
1st: Tender joint count	2nd: Tender joint count
1st: Swollen joint count	2nd: Swollen joint count
1st: Patient global	2nd: Physician global
Rheumatoid arthritis DAS 28 score assessment 1 month apart	
Date:	Date:
Tender joints	Tender joints
Swollen joints	Swollen joints
ESR/CRP	ESR/CRP
Global health VAS	Global health VAS
DAS 1	DAS 2
Baseline HAQ	

Section 2: Exclusion criteria		
Tick when checked and refer to prescribing practitioner if any exclusion criteria identified	Tick box	
Known sensitivity to therapy or component parts (eg murine products)		
Pregnant or breastfeeding (effective contraception must be used)		
History of or suspicion of malignancy – requires further investigation Type: _____ Date: _____		
Moderate or severe congestive heart failure (New York Heart Classification (NYH) III or IV)		
Family history or previous diagnosis or suspicion of demyelination (eg MS)		
Active infection of patients at high risk of infection. Examples include:		
• chronic leg ulcers		
• previous tuberculosis or risk factors or suspicion of TB (see section below, TB assessment)		
• septic arthritis of a native joint within the last 12 months or sepsis		
• prosthetic joint within the last 12 months: excluded indefinitely if the joint remains in situ		
• persistent or recurrent chest infections		
• other infections: acute or chronic hepatitis B or C, or HIV		
• Chronic respiratory conditions including: interstitial lung disease, chronic obstructive pulmonary disease (COPD) or abnormal chest x-ray		
• History of pneumocystis pneumonia (PCP) and taking high dose steroids		
<b>Cautions:</b> Evidence of any pre-malignant conditions including: Barrett's oesophagus, cervical dysplasia, large bowel polyps, non-melanoma skin cancer; signs of heart failure (CCF)		
Patient eligible for treatment?      Yes      No		
If NO, state reason for exclusion:		
If YES complete all screening below before continuing		

Section 3: Screening prior to treatment			Tick box
<b>Tuberculosis assessment of immunity/risk</b>			
BCG scar	YES	NO	
Mantoux	YES	NO	
Quantiferon or T-Spot test	YES	NO	
Chest x ray			
Results:	Date:		
Signature:			
NOTE: chest x-ray should be taken as close as possible to the time before starting treatment			
<b>Tuberculosis risk factors/additional respiratory factors to consider</b>			
Note: specific respiratory symptoms, eg cough productive of blood stained sputum, or any signs of respiratory infection:			
TB travel risk factors for individual or close relatives			
(for example, frequent travel and residency in areas of high prevalence for TB)			
If increased risk factors identified, discuss with clinician regarding additional screening			
Referred to TB clinic	YES	NO	
Result:			
Check result of TB testing before proceeding			
<b>Immunisation</b>			
Influenza vaccination	YES	NO	
Pneumovax immunisation	YES	NO	
Varicella zoster status			
Exposure to recent infections (shingles/chicken pox)	YES	NO	
Hepatitis B assessment required	YES	NO	
Hepatitis C assessment required	YES	NO	
<b>Other:</b>			
Skin check (PsA)			
Throat lymphadenopathy			
BP	pulse	weight	height
urinalysis			
Blood tests checked:			
Abnormalities checked:			
Note any attendance for regular health checks and results if appropriate. For example, cervical screening for women.			
Note any investigations pending with other specialist areas: eg dermatology for skin investigations			
<b>Specify further investigations required:</b>			
Review date:			
<b>Review of infection:</b>			
Type:			
Date of last infective episode:			
Treatment:			
(Review with prescribing practitioner)			

<b>Section 4: Patient guidance and shared decision making:</b>		<b>Yes</b>
Has the patient been fully informed about treatment options including risks and benefits of each option, and likelihood of these?		
Has the patient had an opportunity to ask questions?		
Has the patient been provided with written information?		
Informed consent to join BSR Biologics Register given?		
If required, has the BSR Biologics Register data been collected?		
Are all the pre-treatment screening tests completed?		
Drug prescribed:		
Dosage, route and frequency:		
Combination therapy prescribed:	Dosage, route and frequency:	
Start date:	Review date:	

## Appendix 9

### Training checklist for home administration of subcutaneous biologic therapy by a patient (adult, young person or child) or carer/parent

Patient name:	
Person taught:	
Trainer name:	
Name of drug: (note pre-filled syringe or PEN)	

Skill	Training date	Date completed	Patient/ carer's signature	Trainer's signature
Demonstrates understanding of verbal and written information.				
Describes why biologic therapy is given.				
Describes potential side-effects and how to deal with them (such as injection site reaction).				
Can discuss when not to give the injections (such as infection or surgery).				
Knows the correct hand washing techniques.				
Knows how to check the equipment and drug.				
Can give the injection using a safe technique and can identify where the injection can be given.				
Disposes of the pen or syringe appropriately.				
Knows how to deal with a needle stick injury.				
Knows who and when to contact in case of any problems or uncertainty.				
Understands blood test requirements and follow up arrangements.				
Understands storage requirements.				
Demonstrates understanding of travelling instructions for biologic therapy.				
Describes the organisation of delivery and delivery and waste removal.				
Patient/carers agrees and is competent to self-inject at home (copy for patient)				



## Appendix 10

# International League of Associations for Rheumatology (ILAR): 2001 classification of juvenile idiopathic arthritis (JIA), updated 2004

The following can only be diagnosed after six weeks:

1	Oligoarticular onset	Four or fewer joints involved.
	Extended oligoarticular	More than four joints involved after the first six months of disease.
2	Polyarticular onset Rheumatoid factor –ve	Five or more joints during the first six months of disease with no detectable rheumatoid factor.
3	Polyarticular onset Rheumatoid factor +ve	Five or more joints during the first six months of disease and when rheumatoid factor is detected on at least two occasions, at least three months apart.
4	Systemic onset	Arthritis of any number of joints with a documented typical high quotidian spiking fever of at least two weeks duration and one or more of the following: <ul style="list-style-type: none"> <li>• transient episodic erythematous rash</li> <li>• enlargement of liver or spleen</li> <li>• serositis.</li> </ul>
5	Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of the following: <ul style="list-style-type: none"> <li>• dactylitis</li> <li>• nail abnormalities (pitting)</li> <li>• family history of psoriasis confirmed by a dermatologist in at least one first-degree relative.</li> </ul>
6	Enthesitis-related arthritis	Previously known as juvenile spondyloarthropathy. <ol style="list-style-type: none"> <li>1) Arthritis and enthesitis, or</li> <li>2) Arthritis or enthesitis plus two of the following:               <ul style="list-style-type: none"> <li>• sacroiliac joint tenderness, inflammatory spinal pain, or both</li> <li>• HLA-B27</li> <li>• family history in first-, or second-degree relative of medically confirmed HLA B27+ve associated disease</li> <li>• acute anterior uveitis</li> <li>• onset of arthritis in a boy after the age of eight years.</li> </ul> </li> </ol>
7	Other arthritis	Any form of idiopathic chronic arthritis which does not fit into the above categories.

(Petty, et al., 2001)

# Appendix 11

## BSPAR guidelines for prescribing biologic therapies in children and young people with JIA

Taken from the BSPAR (formerly British Paediatric Rheumatology Group) Guidelines for prescribing biologic therapies in children and young persons with juvenile idiopathic arthritis (BPRG, 2002).

### Eligibility for treatment with etanercept in children and young people (BPRG, 12 April 2002).

#### Inclusion criteria

JIA of the following types:

- systemic
- polyarticular (seronegative or positive for rheumatoid factor)
- extended oligo-articular
- psoriatic
- enthesitis-related.

And the following features:

- five or more swollen joints
- three or more joints with limitation of motion and pain, tenderness or both.

The measurement of disease activity must be strictly defined, objective and robust.

The standard core set data will be used to assess response to therapy:

- number of active joints
- number of joints with loss of range of movement
- physicians global assessment
- patient or parents global assessment
- Childhood Health Assessment Questionnaire
- ESR.

Measurements should be made at two points one month apart.

### Failure of standard therapy

Patients must have had an adequate therapeutic trial of MTX. An adequate therapeutic trial would be defined as:

- treatment for at least three months at a dosage of parenteral MTX of 15 mg/m<sup>2</sup> weekly (unless significant toxicity limited the dose tolerated)
- $\geq 5$  active joints and  $\geq 3$  joints with loss of motion plus pain/tenderness
- the disease is only controlled by unacceptable side effects of high doses of corticosteroids ( $>0.25$  mg/kg daily) and has active disease as defined above in the last six months.

### Exclusion criteria

Reference should be made to the drug data sheet (SPC), but important exclusions include:

- young women who are pregnant or breastfeeding or who are sexually active without adequate contraception
- any infection
- current or previous TB
- previous or present sepsis of a prosthetic joint still in situ
- malignancy or pre-malignancy states
- immuno-deficiency.

### Criteria for withdrawal of therapy (adverse events)

- malignancy
- severe drug related toxicity
- pregnancy (temporary withdrawal)
- severe inter-current infection (temporary withdrawal). Response should be assessed at six months core set outcomes and reference made to the current guidelines on continuing treatment.

### Prescribing centres

It is recommended that paediatric consultants or paediatricians/rheumatologists with appropriate training should only prescribe etanercept if they regularly see children and young people with JIA.

They must have expertise in the use of parenteral MTX at the dosage described in this guidance. They must also be willing to take part in future studies of biologic agents.

In addition, the centre must have a nurse specialist who is able to teach children and parents injection techniques and does this regularly.

A condition of the drug licence is that all patients should be entered into the BPRG biologic registry. This reflects good practice for novel therapy.

## Appendix 12

# Testing for varicella antibodies in children

All patients should have their varicella antibody status measured at diagnosis and certainly before commencing immuno-suppressive treatment (including steroids, MTX and all biologic therapies).

In children and young people who do not have adequate antibodies, this test may be re-checked annually if the child/young person has a negative response. If it is possible to delay commencement of immuno-suppressive therapy (only in mild disease), children/young people should be considered for varicella immunisation, if appropriate prior to starting immunosuppressive therapy. This does not always give full immunity and may need to be repeated.

If siblings/ parents have not had chicken pox they too should be considered for vaccination.

There are several issues to consider when children and young people following the administration of a live vaccine:

- the risk of clinically developing the illness from the vaccine
- the immune response being modified such that the vaccine will be less effective
- the timing of the commencement of treatment should be discussed with the prescribing physician
- if a child is exposed to VZV (face-to-face contact or 15 minutes in the same room), prophylaxis should be given
- zoster immunoglobulin (ZIG), a blood product, can be given to a sero-negative patient who has been in contact with chicken pox if given less than 72 hours from contact (it may attenuate infection if given up to 10 days post exposure); however, this will only provide temporary immunity of approximately four weeks
- aciclovir, either oral or IV, is only given if the child develops VZV; the child should be assessed by a local paediatrician to review their condition and then make a discussion on route of administration. If either of the above situations occurs, families should be advised to contact their rheumatology team or GP immediately.

All live vaccines are contra-indicated; for example, inhaled flu, oral polio, BCG, MMR, oral typhoid and yellow fever vaccines.

Injectable flu and pneumovax vaccines are recommended in immuno-compromised patients.

# Appendix 13

## Websites and resources for patients and further information

### **Arthritis Care** [www.arthritiscare.org.uk](http://www.arthritiscare.org.uk)

Arthritis Care offers practical and emotional support to help people learn to manage their condition more effectively, including guidance for adults and children receiving treatment with biologic therapies.

Professional confidential helpline offering information and support:

Freephone: 0808 800 4050 (weekdays 10am-4pm)

Email: [helplines@arthritiscare.org.uk](mailto:helplines@arthritiscare.org.uk)

The Source – Arthritis Care's helpline for young people aged 25 and under: Freephone helpline 0808 808 2000 (weekdays 10am-4pm)

Email: [thesource@arthritiscare.org.uk](mailto:thesource@arthritiscare.org.uk)

Online discussion forums offer peer support and the opportunity to share experiences:  
[www.arthritiscare.org.uk/forums](http://www.arthritiscare.org.uk/forums)

Write to: Arthritis Care, 18 Stephenson Way, London NW1 2HD.

### **National Ankylosing Spondylitis Society (NASS)** [www.nass.co.uk](http://www.nass.co.uk)

NASS provides information and advice for people with AS who are on a biologic therapy or being considered for one. This covers eligibility, information on particular drugs and lifestyle issues. NASS can also put people in touch with others who are already taking a biologic therapy for reassurance and support. Specific medical questions are referred to those NASS trustees who are clinicians or to other health professionals.

Contact NASS on 0208 948 9117.

Email: [nass@nass.co.uk](mailto:nass@nass.co.uk)

Write to: NASS, Unit 0.2, 1 Victoria Villas, Richmond, Surrey TW9 2GW.

### **National Rheumatoid Arthritis Society (NRAS)** [www.nras.org.uk](http://www.nras.org.uk)

The NRAS helpline team is fully conversant with all patient issues relating to biologic therapies and can provide detailed, written information to callers on a variety of subjects, from eligibility criteria to individual drug details. The website also has information. There is a nationwide network of NRAS medical advisers who can answer specific, detailed medical queries. Patients can also speak to volunteers who are successfully benefitting from different biologic therapies, which can help reassure people about to start treatment.

NRAS helpline

Freephone: 0800 298 7650 Monday to Friday, 9.30am – 4.30pm.

Email: [helpline@NRAS.org.uk](mailto:helpline@NRAS.org.uk)

Write to: NRAS, Unit B4 Westacott Business Centre, Westacott Way, Littlewick Green, Maidenhead SL6 3RT.

### **NHS Confederation** [www.nhsconfed.org](http://www.nhsconfed.org)

Member organisations can access publications at:  
[www.nhsconfed.org](http://www.nhsconfed.org)

### **Psoriatic Arthropathy Alliance and the Psoriasis Support Trust (PAPAA)** [www.papaa.org](http://www.papaa.org)

PAPAA was formed in 2007 from two existing charities, the Psoriatic Arthropathy Alliance (PAA) and the Psoriasis Support Trust (PST). It aims to become a principle resource of information and help for people with psoriasis and psoriatic arthritis in the UK.

## Patient information leaflets

Information for patients on biologics is provided at the following sites.

### Adults:

Arthritis Care: [www.arthritiscare.org.uk](http://www.arthritiscare.org.uk)

Arthritis Research UK:  
[www.arthritisresearchuk.org](http://www.arthritisresearchuk.org)

Juvenile SLE group: [www.liv.ac.uk/ukjsle](http://www.liv.ac.uk/ukjsle)

Lupus UK: [www.lupusuk.org.uk](http://www.lupusuk.org.uk)

National Ankylosing Spondylitis Society:  
[www.nass.co.uk](http://www.nass.co.uk)

National Rheumatoid Arthritis Society:  
[www.nras.org.uk](http://www.nras.org.uk)

Psoriatic Arthritis: [www.papaa.org](http://www.papaa.org)

British Thoracic Society: [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)  
(tuberculosis treatment)

### Children and young people:

Arthritis Research UK, including: *Arthritis: A guide for teenagers* [www.arthritisresearchuk.org](http://www.arthritisresearchuk.org)

Children's arthritis: [www.ccaa.org.uk](http://www.ccaa.org.uk)

Adolescent arthritis: [www.dreamteam-uk.org](http://www.dreamteam-uk.org)

Kids with Arthritis:  
[www.arthritiscare.org.uk](http://www.arthritiscare.org.uk)

Lupus UK: [www.lupusuk.org.uk](http://www.lupusuk.org.uk)

National Ankylosing Spondylitis Society:  
[www.nass.co.uk](http://www.nass.co.uk)

National Rheumatoid Arthritis Society:  
[www.NRAS.org.uk](http://www.NRAS.org.uk)

Paediatric Rheumatology International Trials  
Organisation: [www.pediatric-rheumatology.printo.it](http://www.pediatric-rheumatology.printo.it)

Patient held record:  
[www.sickkids.on.ca/myhealthpassport](http://www.sickkids.on.ca/myhealthpassport)

Medicines for Children  
[www.medicinesforchildren.org.uk](http://www.medicinesforchildren.org.uk)

British Society for Rheumatology guidelines:  
[www.rheumatology.org.uk](http://www.rheumatology.org.uk)

British Society for Paediatric and Adolescent  
Rheumatology (BSPAR): [www.bspar.org.uk](http://www.bspar.org.uk)

## Manufacturers' websites

UCB UK [www.ucbpharma.co.uk](http://www.ucbpharma.co.uk)

Pfizer (formerly Wyeth) [www.pfizer.co.uk](http://www.pfizer.co.uk)

Schering Plough (MSD) [www.msd-uk.com](http://www.msd-uk.com)

Bristol-Myers Squibb UK [www.b-ms.co.uk](http://www.b-ms.co.uk)

Roche Products Ltd: [www.roche.co.uk](http://www.roche.co.uk)

Blueteq Ltd: [www.blueteq.com](http://www.blueteq.com)

Healthcare at Home: [www.hah.co.uk](http://www.hah.co.uk)

## Useful websites

National Electronic Library for Medicines:  
[www.evidence.nhs.uk](http://www.evidence.nhs.uk)

National Patient Safety Agency: [www.npsa.nhs.uk](http://www.npsa.nhs.uk)

NHS Quality Improvement for Scotland:  
[www.healthcareimprovementscotland.org](http://www.healthcareimprovementscotland.org)

Paediatric Rheumatology European Society (PReS):  
[www.pres.org.uk](http://www.pres.org.uk)

RCN for members-only access to rheumatology forum  
website and online guidance, some available for  
non-members: [www.rcn.org.uk](http://www.rcn.org.uk)

Subcutaneous injections information:  
[www.bddiabetes.co.uk](http://www.bddiabetes.co.uk)

You can find full texts of all UK government legislation  
at: [www.legislation.gov.uk](http://www.legislation.gov.uk)



# References

## PART ONE: Adult patients

All SCPs accessed via [www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)

[Cimzia® \(certolizumab pegol\)](#)

[Enbrel® \(etanercept\)](#)

[Humira® \(adalimumab\)](#)

[MabThera® \(rituximab\)](#)

[Orencia® \(abatacept\)](#)

[Remicade® \(infliximab\)](#)

[Roactemra® \(tocilizumab\)](#)

[Simponi® \(golimumab\)](#)

All Wales Medicines Strategy Group (June 2013) *Final appraisal recommendation advice No: 1513 – adalimumab Humira®) 40 mg prefilled pen or 40 mg prefilled syringe*, Penarth: AWMMSG.

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Arthritis Research UK patient information leaflets on etanercept, infliximab, adalimumab, certolizumab pegol, rituximab, golimumab and tocilizumab. Available from: [www.arthritisresearchuk.org](http://www.arthritisresearchuk.org)

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British Society for Rheumatology (BSR) (2011) *BSR statement on vaccination in adult patients with rheumatic diseases*, London: BSR. Available from: [www.rheumatology.org.uk](http://www.rheumatology.org.uk)

British Society for Rheumatology (BSR) (2012) *Guidelines for the treatment of psoriatic arthritis with biologics*, London: BSR. Available from: [www.rheumatology.org.uk](http://www.rheumatology.org.uk)

British Society for Rheumatology (BSR) (2012) *Quality standards – top ten quality standards for RA (3-5 and 7-10 apply)*, London: BSR. Available from: [www.rheumatology.org.uk](http://www.rheumatology.org.uk)

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